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Whom to Biopsy: Pre-Diagnostic Risk Stratification with Biomarkers, Nomograms and Risk Calculators

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SYNOPSIS

This article describes markers used for prostate biopsy decisions, including PSA, free PSA, the Prostate Health Index, 4K Score, PCA3, and ConfirmMDx. We also summarize the use of nomograms combining multiple variables for prostate cancer detection.

Keywords

prostate cancer; PSA; biomarkers; prostate biopsy; nomograms

Introduction

Historically, prostate biopsy was performed due to a PSA level exceeding a specific threshold or suspicious findings on digital rectal examination. However, this approach lacks specificity and more recently there has been an expansion in the availability of new blood, urine and tissue tests that can be used to help with prostate biopsy decisions. In addition, the movement toward personalized medicine has led to an effort to develop prediction tools that can incorporate multiple variables together to provide more individualized risks of detecting prostate cancer on biopsy.

The purpose of this review is to describe currently available marker tests and multivariable nomograms that can be used in prostate biopsy decisions. This is a critical issue in patient management since prostate biopsy is an invasive procedure with potential associated risks,

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such as infection, hematuria, hematospermia, pain, and lower urinary tract symptoms.[1] Further downstream, a critical issue is the overdiagnosis of clinically indolent prostate cancer resulting in unnecessary decrement in quality of life for a tumor that would not have caused harm. These considerations highlight the importance of using the best possible information to help patients and physicians make decisions about prostate biopsy.

Blood Biomarkers

Total PSA

The majority of prostate cancer is currently diagnosed through screening with prostate-specific antigen (PSA). The PSA test was initially used in forensics and was subsequently found to be elevated in the blood from men with prostatic disease. It is approved by the US Food and Drug Administration (FDA) for monitoring of prostate cancer after diagnosis and as an aid to early prostate cancer detection.

There have been several randomized trials of PSA-based screening. The largest studies of these trials, the European Randomized Study of Screening for Prostate Cancer (ERSPC), showed that screened men have a lower risk of metastatic disease and prostate cancer death, but this comes at a cost of unnecessary biopsies and overdetection of indolent tumors.[2] In the core age group of 55 to 69 years, PSA screening reduced PCa-specific mortality by 21% after 13 years of follow-up. This study primarily used a PSA level of 3 ng/ml as the threshold for performing prostate biopsy.

By contrast, the US Prostate, Lung, Colorectal and Ovarian (PLCO) screening trial found no significant difference in prostate cancer death between the screening and usual care arms.[3] However, more than 90% of men in the usual care arm received PSA tests before or during the trial, due to the widespread use of PSA screening in the US already during the time of the study.[4] This study used a PSA of 4 ng/ml as the threshold for biopsy, although there were issues with biopsy compliance.

Although the initial FDA approval of PSA used a threshold of 4 ng/ml, there are a substantial proportion of cancers found at lower PSA levels. In practice, PSA is a continuous variable and the selection of any particular cutoff involves a trade-off between sensitivity and specificity. Data from the Prostate Cancer Prevention Trial (PCPT) indicated that the risk of clinically significant cancer (i.e. Gleason ≥ 7) with a PSA between 2.1 and 3.0 ng/mL and 3.1 and 4.0 ng/mL was 4.6% and 6.7%, respectively.[5] The PCPT also demonstrated that a PSA level greater than 10 ng/mL has a specificity of 99.5% for Gleason ≥ 7 PCa.[6] These findings suggest that PSA is an excellent tool for biopsy decisions in men with significantly elevated PSA (i.e. greater than 10 ng/mL) but further risk stratification may be necessary prior to biopsy in men with moderately elevated PSA (i.e. 2 to 10 ng/mL).

PSA values may also be confounded by numerous benign conditions and instrumentation of the urinary tract. Previous studies have shown that even assay standardization can have a substantial impact on the results, presenting a “pseudo-acceleration” or “pseudo-deceleration” that could potentially falsely influence clinical decisions.[7] Important recommendations to reduce confounding are to avoid checking PSA in the setting of recent

urinary tract infections or procedures, to use the same lab for serial measurements and to repeat abnormal values after a short period of observation, which itself can reduce unnecessary biopsies. Despite these efforts, however, there remain drawbacks to basing prostate biopsy decisions exclusively on total PSA values, and there has been intensive investigation into alternative markers that can be used in prostate cancer detection.

Free PSA (fPSA)

PSA circulates in two forms, either complexed to proteins or free (unbound) PSA. The percent of free PSA (%fPSA) is a way to distinguish benign from malignant conditions, wherein a higher %fPSA indicates a lower risk of significant prostate cancer.[8] A prospective, multicenter study of men with PSA levels of 4 to 10 ng/mL found that using a 25% fPSA cutoff would detect 95% of prostate cancers and avoid 20% of unnecessary biopsies.[9] Other studies have shown that %fPSA can also help distinguish benign versus malignant disease in men with PSA levels less than 4 ng/ml.[10,11]

Free PSA is approved by FDA, and it is widely available in clinical practice. In the 2016 National Comprehensive Cancer Network Guidelines, %fPSA is listed among the reflex testing options for men with a PSA greater than 3 ng/mL considering initial prostate biopsy, and for men with previous negative biopsy considering re-biopsy.[12] Free PSA is also a component of two other new markers used as reflex tests, the Prostate Health Index (phi) and 4Kscore.

Prostate Health Index (phi)

Phi is a newer prostate cancer marker test that measures three different forms of PSA: total PSA, free PSA, and [−2]proPSA, which is an isoform that is more specific for prostate cancer. It is calculated using the following formula: $([-2]proPSA/fPSA) \times \sqrt{PSA}$. Phi improves the specificity of prostate cancer detection, and it was approved by the FDA in 2012 for men with PSA levels between 4 and 10 ng/mL. The current NCCN guidelines offer phi as an optional reflex test to help decide on initial or repeat prostate biopsy.[12] Phi has been validated in high-risk populations including men who are obese, African American men, or have a positive family history.[13–16]

Multiple prospective studies have shown that phi outperforms total and free PSA for prostate cancer detection on biopsy.[17–21] It is also associated with prostate cancer aggressiveness. In 658 men with PSA levels between 4 and 10 ng/mL, phi was compared with its individual variables for the prediction of clinically significant cancer.[18] Phi was the most accurate predictor with an area under the curve (AUC) of 0.707 for Gleason ≥ 7 cancer (versus AUC 0.661, 0.558, and 0.551 for %fPSA, [−2]proPSA, and PSA, respectively) and AUC of 0.698 for Epstein significant cancer (versus AUC 0.654, 0.550, and 0.549 for %fPSA, [−2]proPSA, and PSA, respectively). By reducing the number of unnecessary biopsies, phi as a reflex test prior to prostate biopsy can improve cost-effectiveness of PCa screening.[22]

Higher phi levels also predict a greater risk of adverse pathology at radical prostatectomy, including high-grade disease, larger tumor volume, extracapsular extension and seminal

vesicle invasion.[23] Phi has also been shown to predict biopsy reclassification during active surveillance.[24,25]

Recent studies have explored different methods of employing phi. Like PSA, phi can be considered in the context of other variables such as prostate volume (i.e. to calculate a phi density). One study evaluated phi density in 118 men with PSA greater than 2 ng/mL that were undergoing prostate biopsy.[26] For the detection of clinically significant PCa, phi density demonstrated a higher AUC than PSA, PSA density, %fPSA, the product of %fPSA and prostate volume, and phi. Other studies have evaluated phi in conjunction with multiparametric MRI (mpMRI), with one finding a negative predictive value of 97% for clinically significant PCa in men undergoing repeat biopsy.[21,27] This suggests that phi remains useful in an MRI-based detection paradigm.

4Kscore

The 4Kscore is a new marker test that combines 4 kallikrein markers (tPSA, fPSA, intact PSA, and human kallikrein 2) along with age, DRE, and prior biopsy results into a proprietary algorithm to predict the risk of high-grade PCa on biopsy. The 4Kscore is a CLIA-certified test that is commercially available in multiple countries. In the NCCN guidelines, it is also an optional second-line test to help with initial or repeat prostate biopsy decisions.[12]

The 4Kscore has been shown consistently to improve the specificity of screening for both initial biopsy and repeat biopsy. [28–32] The 4-kallikrein panel was measured in 6129 men with elevated PSA undergoing biopsy in the ProtecT trial.[29] Performance of the base model including age and PSA was compared with that of the base model with %fPSA and the base model with the 4-kallikrein panel. The model incorporating the 4-kallikrein panel had an AUC of 0.820 for high-grade PCa (versus 0.799 and 0.738 for %fPSA and PSA models, respectively; $p < 0.001$). One head-to-head study by Nordström *et al* demonstrated that the 4-kallikrein panel and phi had similar performance for identifying high-grade prostate cancer on biopsy.[33]

The 4Kscore has also been shown to predict aggressive pathology at prostatectomy[34] and future risk of metastatic disease.[35] The baseline 4Kscore also predicts reclassification on the first biopsy during active surveillance, although it did not add incremental value for prediction of subsequent surveillance biopsy outcomes.[36]

Urine Biomarkers

Prostate Cancer Antigen 3 (PCA3)

PCA3 is a prostate-specific, noncoding mRNA that is overexpressed in PCa tissue relative to benign tissue.[37] In clinical practice, PCA3 is measured in the urine following a vigorous digital rectal examination (DRE) in men suspected of harboring PCa.

A well-supported indication for PCA3 is in the setting of repeat biopsy. Several studies have demonstrated that PCA3 is a stronger predictor of PCa on repeat biopsy than either PSA or %fPSA.[38–41] Such evidence has led to approval by the FDA in 2012 and its inclusion in the

NCCN guidelines as a testing option for men with a prior negative biopsy and continued suspicion of PCa.[12]

Some studies suggest that PCA3 in conjunction with PSA prior to initial biopsy improves overall PCa detection,[41–43] but its value is less evident for the detection of high-grade cancer.[43,44] A large multicenter study measured PCA3 levels in men scheduled for either initial or repeat biopsy.[44] Using PCA3 to determine need for repeat biopsy would avoid a substantial number of unnecessary biopsies while rarely missing the diagnosis of a high-grade PCa. In contrast, applying that same PCA3 cutoff for initial biopsy would significantly underdiagnose high-grade cancer.

The relationship between PCA3 score and clinically significant cancer detected on needle biopsy has not been clearly established.[38,40,43,45] However, several studies suggest that higher PCA3 does not predict disease progression on active surveillance, and there are conflicting data on its relationship to aggressive pathology at radical prostatectomy.[46–49] In fact, a recent study of 10,382 radical prostatectomy specimens and 1,694 samples from initial biopsy suggested that more aggressive tumors have lower tissue PCA3 expression.[50] In this large sample of prostate tumors, Alshalalfa *et al* found a bimodal expression of PCA3. Analysis of PCA3 expression in specific Gleason score subgroups revealed that Gleason 9 and 10 tumors had predominantly low PCA3 expression, whereas Gleason 3+3 and 3+4 tumors had predominantly high PCA3 expression. Low PCA3 expression was associated with high Gleason scores on initial biopsy and radical prostatectomy specimens. Furthermore, low PCA3 expression predicted increased likelihood of adverse pathological features at radical prostatectomy, biochemical recurrence, metastatic disease at 5 years, and PCa-specific mortality at 10 years. Although this study examined PCA3 expression in tissue, other studies have similarly provided conflicting data on the performance of the urinary PCA3 assay to predict clinically significant prostate cancer.

Head-to-head comparisons of phi and PCA3 indicate that phi more accurately identifies clinically significant PCa on biopsy and radical prostatectomy pathology.[51,52] Another study demonstrated that pre-operative MRI and phi predicted clinically significant PCa in patients undergoing radical prostatectomy, but PCA3 held no predictive value.[53] These findings suggest that PCA3 alone may be insufficient to select patients at risk for high-grade disease.

PCA3 appears most valuable when used alongside other available tools. Its use with either MRI or real-time elastography has demonstrated increased accuracy in detecting clinically significant PCa.[54,55] Multivariable nomograms that incorporate PCA3 have been internally and externally validated and are discussed in further detail in the nomogram section.[44,56–59]

PCA3 and TMPRSS2:ERG (T2:ERG)

T2:ERG is a gene fusion that is commonly found in PCa.[60] Like PCA3, its mRNA can be detected in urine after DRE.[61] Urinary T2:ERG levels predict clinically significant PCa on both core needle biopsy and radical prostatectomy pathology.[62] Although T2:ERG has a high specificity for PCa, it is present in only 50% of localized PCa. Thus, it has been combined with PCA3 to improve its sensitivity.[63]

Mi-Prostate Score (MiPS) is a commercially available tool that combines serum PSA and urinary PCA3 and T2:ERG. A prospective study by Tomlins et al evaluated MiPS in 1244 men undergoing initial or repeat prostate biopsy.[64] Specifically, they compared the prediction of high-grade PCa by MiPS, PCA3 with PSA, T2:ERG with PSA, and PSA alone. MiPS was the most accurate predictor with an AUC of 0.772 versus 0.747, 0.729, and 0.651 for PSA+PCA3, PSA+T2:ERG, and PSA, respectively.

SelectMDx

Another recently developed tool is SelectMDx, which measures mRNA of PCa-associated genes (HOXC6 and DLX1) in urine collected after a DRE. It incorporates age, family history, DRE findings, history of prostate biopsy, PSA, and PSA density with urinary mRNA levels to predict a patient's risk of low-grade and high-grade PCa.

In a multicenter, prospective study of men undergoing initial or repeat biopsy, this model was developed and validated in consecutive cohorts of 519 and 386 men, respectively.[65] The model demonstrated an AUC of 0.90 (95% CI 0.85–0.95) in the validation cohort; it outperformed the base model of only clinical parameters, the Prostate Cancer Prevention Trial (PCPT) risk calculator, and the PCPT risk calculator with PCA3. Subgroup analysis in men with PSA less than 10 ng/mL revealed that SelectMDx remained a strong predictor for high-grade PCa. If SelectMDx were used to select which patients to biopsy in the validation cohort, 42% of biopsies would be avoided while missing the diagnosis of 2% of high-grade PCa.

ExoDx Prostate IntelliScore

Present in blood and urine, exosomes are vesicles that contain RNA, proteins, and other molecules derived from their cell of origin. ExoDx Prostate(IntelliScore) is a urine-based test that analyzes exosomal RNA of three genes associated with PCa (ERG, PCA3, and SPDEF). This assay predicts risk of high-grade PCA in men undergoing their first biopsy and can also be used in a multivariable approach with clinical variables such as PSA, age, race and family history. In a validation study of 519 men age ≥50 with PSA 2-10 ng/ml undergoing initial biopsy, the urine exosome gene expression assay outperformed the base model of clinical variables alone (AUC 0.71 exosome alone; AUC 0.73 exosome + clinical variables vs 0.63 clinical variables alone, P<.001).[66] An advantage of this test is that it does not require a DRE prior to collecting urine. AUC's are not comparable across marker studies in different populations, and future studies are needed to directly evaluate the comparative performance of the multiple new urine-based markers.

Tissue Biomarkers

ConfirmMDx

Prostate biopsy samples a very small fraction of the total prostate tissue. For men with a previous negative biopsy, the tissue from that biopsy can be examined for epigenetic changes suggestive of a nearby occult prostate cancer that was not sampled. This is the basis behind the ConfirmMDx test which specifically examines hypermethylation of GSPT1, APC, and

RASSF1. ConfirmMDx is commercially available and suggested as an optional test by the NCCN guidelines for men under consideration for repeat biopsy.[12]

In the MATLOC study, 498 subjects from the United Kingdom and Belgium underwent repeat prostate biopsy, and the epigentic assay was a significant independent predictor of biopsy outcome.[67] The assay demonstrated a negative predictive value of 90%. A multicenter validation study (DOCUMENT) tested the epigenetic assay in 350 patients with prior negative biopsy from five US institutions.[68] Similarly, they found that the epigenetic assay was a significant independent predictor of biopsy outcome, with a negative predictive value of 88%.

Nomograms and Risk Calculators

There is increasing recognition that prostate biopsy decisions are not one-size-fits all and that a multivariable approach is important. Multiple guidelines now recommend using this type of approach to prostate biopsy decisions. The Melbourne Consensus Statement recommends that PSA testing should not be considered on its own, but rather as part of a multivariable approach to early prostate cancer detection.[69] The statement mentions 3 different risk calculators that may be used for this purpose: the ERSPC, PCPT and Canadian risk calculators.

The ERSPC risk calculator was first developed in 2006 based on data from Dutch men participating in the European Randomized Study of Screening for Prostate Cancer. Currently, multiple versions are available online for men at different stages of the screening process and with different types of information available. Risk calculator 1 is for men who do not have a PSA result available, and provides an estimate of general prostate cancer risk based on age, family history and urinary symptoms. Risk calculator 2 uses PSA levels to estimate prostate cancer risk. Whereas these are meant to be used by laypeople, risk calculators 3 and 4 were designed for healthcare professionals to help with decision-making by estimating the risk of biopsy-detectable and significant prostate cancer. The risk calculator has also been updated to include new markers such as phi, which improved its detection of clinically significant PCa. This calculator is available in an smartphone application format for ease of use.[70]

The PCPT risk calculator was initially developed in 2006 based on data from American men from the placebo group of the Prostate Cancer Prevention Trial. The first version included PSA, family history, DRE and history of a prior negative biopsy, which together were used to estimate the risk of prostate cancer detection on biopsy. The PCPT risk calculator was subsequently updated to also include an estimate of the risk of high-grade cancer on biopsy. Recently, urinary biomarkers have been incorporated into the PCPT risk calculator in an effort to increase its predictive accuracy for high-grade PCa. Wei *et al* demonstrated that addition of PCA3 to the PCPT risk calculator improved its detection of high-grade PCa on both initial and repeat biopsies.[44] Similarly, MiPS was added to the PCPT risk calculator and compared to PCPT+PCA3, PCPT+T2:ERG, and PCPT alone.[64] For the detection of high-grade cancer, both PCPT+PCA3 and PCPT+T2:ERG outperformed the PCPT risk

calculator, and MiPS+PCPT was superior to the other three models. Similarly, the addition of phi to the PCPT improves its prediction of aggressive PCa.[71]

Finally, the Sunnybrook prostate cancer risk calculator was based on data from Canadian men undergoing prostate biopsy. It uses age, urinary symptoms, PSA, free PSA, ethnic background, family history and DRE findings to provide an estimate of prostate cancer risk. Performance of nomograms across different populations may vary, making external validation of these tools essential.

It is noteworthy that several of the new marker tests discussed above already incorporate a multivariable approach by combining the marker results with clinical variables directly in their algorithms. Examples of such tests include the 4Kscore, MiPS, and SelectMDx. By contrast, other tests like phi, PCA3, and ExoDx Prostate (IntelliScore “EPI”) do not include clinical variables into their formula, but the results of these tests can be incorporated into external nomograms. In addition to the risk calculators described above, several other groups have created different nomograms using phi to predict overall or clinically significant prostate cancer on biopsy.[72,73] For example, a new nomogram combining continuous values of phi with age, prior biopsy, prostate volume, and PSA was shown to outperform the PCPT and ERSPC risk calculators for predicting aggressive disease on biopsy.

Conclusion

For both initial and re-biopsy decisions, there are now multiple second-line tests available that outperform PSA for the prediction of detecting any prostate cancer and/or high-grade disease. A multivariable approach is also recommended that combines each patient’s risk factors together to help inform more personalized biopsy decision-making.

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KEY POINTS

- Free PSA, phi and the 4K score are blood tests that are more specific than PSA and can be used as reflex tests prior to initial or repeat biopsy decisions.
- PCA3 is an FDA-approved and widely available urinary marker to aid in repeat biopsy decisions, but is inferior to several new markers for predicting clinically significant prostate cancer.
- ConfirmMDx is a tissue marker using epigenetic changes to predict the risk of occult cancer that was not sampled on previous biopsy.
- A multivariable approach to prostate cancer detection is recommended that combines multiple clinical variables to provide patients with more individualized risk estimates.