Whom to Biopsy
Prediagnostic Risk Stratification with Biomarkers, Nomograms, and Risk Calculators

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KEYWORDS

• Prostate cancer • Prostate-specific antigen • Biomarkers • Prostate biopsy • Nomograms

KEY POINTS

- Free prostate-specific antigen (PSA), phi, and the 4Kscore are blood tests that are more specific than PSA and can be used as reflex tests prior to initial or repeat biopsy decisions.
- Prostate cancer antigen 3 (PCA3) is a US Food and Drug Administration-approved and widely available urinary marker to aid in repeat biopsy decisions, but it 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.

INTRODUCTION

Historically, prostate biopsy was performed because of a prostate-specific antigen (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 article 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, because prostate biopsy is an invasive procedure with potential associated risks, 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.

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BLOOD BIOMARKERS

Total Prostate-Specific Antigen

Most prostate cancer is currently diagnosed through screening with 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 United States 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 (ie, Gleason $\geq$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 greater than or equal to 7 PCA.[6] These findings suggest that PSA is an excellent tool for biopsy decisions in men with significantly elevated PSA (ie, >10 ng/mL), but further risk stratification may be necessary prior to biopsy in men with moderately elevated PSA (ie, 2–10 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 pseudoacceleration or pseudodeceleration 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 laboratory 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 Prostate-Specific Antigen

PSA circulates in 2 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 repeat biopsy.[12] Free PSA is also a component of 2 other new markers used as reflex tests, the prostate health index (phi) and 4Kscore.

Prostate Health Index

Phi is a newer prostate cancer marker test that measures 3 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: $([-2]proPSA/fPSA)x\sqrt{PSA}$. 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 National Comprehensive Cancer Network (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