HHS Public Access

Author manuscript

Urol Pract. Author manuscript; available in PMC 2018 July 01.

Published in final edited form as:

Urol Pract. 2017 July ; 4(4): 315–321. doi:10.1016/j.urpr.2016.08.001.

Biomarkers for Prostate Biopsy and Risk Stratification of Newly Diagnosed Prostate Cancer Patients

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Abstract

Introduction—Many new markers are now available as an aid for decisions about prostate biopsy for men without prostate cancer, and/or to improve risk stratification for men with newly diagnosed prostate cancer.

Methods—A literature review was performed on currently available markers for use in decisions about prostate biopsy and initial prostate cancer treatment.

Results—Although total prostate-specific antigen cutoffs were traditionally used for biopsy decisions, PSA elevations are not specific. Repeating the PSA test, and adjusting for factors like age, prostate volume and changes over time can increase specificity for biopsy decisions. The Prostate Health Index (phi) and 4K Score are new PSA-based markers that can be offered as second-line tests to decide on initial or repeat prostate biopsy. The PCA3 urine test and ConfirmMDx tissue test are additional options for repeat biopsy decisions. For men with newly diagnosed prostate cancer, genomic tests are available to refine risk classification and may influence treatment decisions.

Conclusions—Numerous secondary testing options are now available that can be offered to patients deciding whether to undergo prostate biopsy and those with newly diagnosed prostate cancer.

Introduction

Approximately 1.1 million men were diagnosed with prostate cancer globally in 2012, and there were an estimated 307,000 deaths.[1] In the United States, an estimated 180,890 men will be diagnosed with prostate cancer in 2016 along with 26,120 deaths.[2]

There is strong evidence that early detection and curative treatment improve outcomes for men with clinically significant prostate cancer, but many prostate cancers have a prolonged natural history and are not destined to cause harm during the man's lifetime. Identifying

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which cancers are destined to progress and would benefit from early radical treatment is one of the most critical questions in urologic oncology.

Markers for Prostate Biopsy

The majority of prostate cancers are diagnosed through prostate-specific antigen (PSA)-based screening. Historically, decisions about prostate biopsy were based on a single threshold PSA value, as was the case in the major randomized trials of PSA screening. For example, the European Randomized Study of Screening for Prostate Cancer (ERSPC) primarily used a threshold of 3 ng/ml to recommend biopsy and the US Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial used a cutoff of 4 ng/ml.[3, 4] However, data from empiric prostate biopsies in the Prostate Cancer Prevention Trial showed that there is no single PSA threshold that can reliably exclude prostate cancer or high-grade disease.[5]

Furthermore, many non-malignant conditions and other exposures can influence PSA levels, ranging from body mass index to various medications and benign disorders of the urinary tract. The limited specificity of PSA testing leads to unnecessary biopsies with associated risks, including an increasing risk of infectious complications.[6] Further downstream, PSA screening also causes harm by leading to the detection of indolent tumors.

Several options have been proposed to aid in prostate biopsy decisions and reduce downstream harms. One very simple method to avoid unnecessary prostate biopsy is to repeat an abnormal PSA measurement. A recent study from the Ottawa Regional Prostate Cancer Assessment Center examined the utility of repeating the PSA test within 3 months for men with levels of 4–10 ng/ml.[7] Overall, 25% of the men had a normal result (defined as a PSA <4 ng/ml) on repeat testing. These men were significantly less likely to undergo a prostate biopsy or to be diagnosed with prostate cancer. Of note, the same laboratory should be used for repeat PSA measurements when possible due to differences in measured PSA between assays, which could result in pseudo-acceleration or pseudo-deceleration.[8]

There are also several variations on the use of PSA that can improve specificity, such as applying different thresholds based on age.[9] For example, Oesterling et al. recommended thresholds of 2.5, 3.5, 4.5, and 6.5 ng/ml in the 40's, 50's, 60's and 70's as a means to improve specificity. More recently, the American Urological Association encouraged increasing the threshold for biopsy to 10 ng/ml for men over 70 years who choose to continue screening[10], based on data from the PIVOT randomized trial.[11]

Changes in PSA over time, or PSA velocity (PSAV), is another way to increase the specificity of PSA for prostate cancer.[12] Although PSA levels do increase with age and benign prostatic hyperplasia (BPH), these changes are typically insidious. For example, in a trial of men with moderately to severely symptomatic BPH, the average PSA velocity was 0.15 ng/ml/year.[13] A PSA velocity >0.4 ng/ml/year is a significant predictor of prostate cancer risk[14], and higher PSA velocity (>2 ng/ml/year) has been associated with life-threatening prostate cancer.[15]

However, there are several limitations to using PSAV. First, a very high PSA velocity (>3 ng/ml/year) may represent prostatitis so the clinical history and context is important for the proper interpretation of PSA trends.[16] Also, an adequate PSA history is necessary to calculate PSAV and it is not informative with an insufficient number or frequency of tests (<3 tests or interval >2 years in between the tests).[17]

An alternate method of evaluating changes in PSA over time is the PSA velocity risk count, proposed by Carter et al in 2007.[18] This involves calculating the number of times in a row that PSAV exceeds 0.4 ng/ml/year, as a way to evaluate for sustained increases. In a large validation study, men with a risk count of 2 (meaning 2 successive PSAV measurements >0.4 ng/ml/year) had a significantly greater risk of high-grade prostate cancer, and the PSAV risk count provided incremental predictive value above PSA and age alone.[19]

Another option is to divide PSA by volume to calculate the PSA density (PSAD), which is a robust predictor of significant prostate cancer.[20] For men with prostate imaging prior to biopsy (such as those undergoing repeat biopsy or biopsy-naive men who had an MRI), PSAD can be readily calculated. For men undergoing initial biopsy without previous imaging, even a broad, categorical estimation of prostate volume from DRE can be incorporated with other clinical variables into a nomogram for risk stratification.[21]

Another option to improve the specificity of PSA-based screening is to determine the amount of PSA that is circulating complexed to proteins (complexed PSA) versus the unbound or “free” form (percent free PSA).[22] For men with total PSA levels >3 ng/ml, the 2016 National Comprehensive Cancer Network (NCCN) Guidelines state that percent free PSA is potentially informative regarding the need for initial or repeat prostate biopsy.[23] A lower percent free PSA also predicts a higher risk of aggressive prostate cancer.[24]

Two other PSA-based marker tests offered in the 2016 NCCN guidelines for initial and repeat biopsy decisions are the Prostate Health Index (phi) and the 4K Score.[23] Phi is a blood test that uses a mathematical calculation to weigh the concentration of total, free and -2proPSA.[25] Large prospective studies globally have shown that phi outperforms PSA and free PSA for prediction of prostate biopsy outcome.[25, 26] Numerous studies have consistently shown that phi more specific for clinically significant disease compared its individual components.[27, 28] It was FDA approved in 2012 as a reflex test in prostate cancer detection and has regulatory approval in >50 other countries. Phi can also be used in combination with other variables as part of a nomogram[29, 30], including the Rotterdam risk calculator app for smartphones.[31]

The 4K Score is another PSA-based marker test, combining 4 different kallikrein markers (total PSA, free PSA, intact PSA and hK2) along with age, DRE findings (nodule or no nodule) and biopsy history (yes or no prior biopsy) into a proprietary algorithm.[32] A higher score indicates a greater likelihood of finding high-grade prostate cancer on biopsy. As with phi, this test has been validated in large studies from the US and Europe, showing that it is more specific for high-grade prostate cancer than total PSA or the multivariable PCPT risk calculator.[33, 34] This test is not FDA approved and is offered as a Laboratory Developed Test

through the CLIA-accredited OPKO laboratory. A head-to-head study showed similar performance of the 4K Score and phi.[35]

For men with a previous negative biopsy, the 2016 NCCN guidelines also offer the PCA3 urine test as an option.[23] PCA3 mRNA was initially found to be overexpressed in prostate cancer tissue[36, 37], and subsequently assays were developed to measure it in urine after vigorous digital rectal examination.[38] The PCA3 urine test received FDA approval in 2012 for men ≥50 with previous negative biopsy and other indications for repeat biopsy. Numerous studies have shown that PCA3 is more specific than PSA for prostate cancer detection particularly on repeat biopsy,[39, 40] and it can be combined with other clinical factors into multivariable nomograms to predict prostate cancer detection.[41] However, the ability of PCA3 to predict aggressive disease is controversial, and head-to-head studies have shown that phi outperforms PCA3 for the identification of clinically significant prostate cancer on biopsy.[42]

A tissue test called ConfirmMDx is another new option that can be used for men with a negative prostate biopsy. This test evaluates for hypermethylation of 3 markers (GSTP1, APC, and RASSF1) associated with the presence of occult prostate cancer. Studies in both Europe and the United States have confirmed a high negative predictive value for this test (88–90%).[43, 44] Therefore, the results of ConfirmMDx may also be used to help decide on repeat prostate biopsy. Similar to imaging, ConfirmMDx has the added advantage of providing some information on localization, so that additional sampling can be targeted at the region with hypermethylation.

Finally, multiparametric MRI (mpMRI) is increasingly being used for prostate cancer localization and targeted prostate biopsy. A recent systematic review by Futterer et al. reported that mpMRI had a negative predictive value of 63 to 98% for clinically significant prostate cancer.[45] More data are needed on the effectiveness and costs of combining markers and imaging for prostate cancer detection.

Biomarkers for Prostate Cancer Staging

Traditionally, PSA, clinical stage and biopsy Gleason score were the main parameters used for prognostication and prostate cancer management decisions. These three variables form the basis for the D'Amico risk classification scheme, Partin tables and Kattan nomograms.[46–48] Many other nomograms have been developed incorporating other clinical and pathologic variables, such as the CAPRA score which also includes age and percent positive biopsy cores.[49] All of these tools have been used as an aid for patients with newly diagnosed prostate cancer making decisions about treatment.

The identification and commercialization of several new markers has raised the possibility to perform risk stratification with greater precision. One such test is the Prostate Health Index, a blood test combining total, free and -2proPSA,[25] as described above. In addition to its established role in prostate biopsy decisions for at-risk men, phi has also been evaluated in men diagnosed with prostate cancer. Independent studies from the United States and Japan of men on active surveillance showed that phi measurements at baseline predicted

subsequent progression.[50, 51] In the Johns Hopkins program, longitudinal measurements of phi during active surveillance also predicted subsequent biopsy reclassification.[50] Phi has also been shown to predict adverse pathology and biochemical recurrence among men undergoing radical prostatectomy.[52–54] These results confirm a role for phi in risk stratification and decisions about the need for interventional management in prostate cancer patients.

Similarly, the 4K score has been shown to predict the presence of significant prostate cancer at surgery. [55] It has also been shown to predict the long-term risk of metastatic disease[56], suggesting that the pre-diagnostic value can be used to help inform decisions about treatment for newly diagnosed patients.

The PCA3 urinary test has also been evaluated in groups of men diagnosed with prostate cancer. Several studies have evaluated PCA3 as a predictor of pathology features at radical prostatectomy with conflicting results. Nakanishi et al. found a direct relationship between PCA3 scores and tumor volume at prostatectomy, and that PCA3 results could be used to predict small volume disease.[57] Other studies have similarly found that PCA3 could be used to predict insignificant disease.[58] By contrast, there are also multiple reports of no association between PCA3 with adverse tumor features[59], and it was not an independent predictor of short-term biopsy progression during active surveillance.[60]

Several tissue tests are also available as an aid to risk stratification for men with a prostate cancer diagnosis, and have been recently reviewed.[61] The 2016 NCCN guidelines state that tumor-based molecular tests may be considered by men with clinically localized disease. The Prolaris test examines a panel of cell cycle progression genes, and has been shown to predict 10-year prostate cancer-specific mortality among men undergoing conservative management.[62] Another genomic tissue test, OncotypeDx, examines several different gene pathways involved in prostate cancer, and can be used to improve the prediction of adverse pathology at prostatectomy.[63] Finally, Decipher is a panel of 22 RNA expression markers, previously shown to predict metastasis after prostatectomy and which can also be measured in biopsy specimens.[64] All of these tests are commercially available to assist in the initial treatment selection, although they are expensive and data on long-term comparative effectiveness are currently lacking.

Finally, mpMRI may also be used for staging for men with newly diagnosed prostate cancer, and can predict the risk of adverse features at prostatectomy. The NICE guidelines in the UK have already incorporated an upfront MRI for men considering active surveillance,[65] although this has not yet been formally incorporated into surveillance guidelines elsewhere. Additional study is needed on the use of serial MRI during active surveillance to predict progression[66], and how to combine this with other noninvasive markers as a potential way to reduce the frequency of repeat biopsy.

Conclusion

PSA screening has been the subject of intense controversy due to its limited specificity for clinically significant prostate cancer, with unnecessary biopsies triggered by false positive

tests as well as overdiagnosis with subsequent overtreatment of indolent tumors. There are many ways to use the PSA measurement itself more effectively, and several other new markers with greater specificity for clinically significant that can be used for prostate biopsy decisions such as phi and the 4K Score. Tissue markers are also available as an aid for repeat biopsy and prostate cancer treatment decisions. Future studies are needed on the most cost-effective selection of tests in each clinical scenario and the optimal combination of markers with imaging.

Acknowledgments

Funding: This work was supported by the Laura & Issac Perlmutter NYU Cancer Center (P30CA016087), the Louis Feil Charitable Lead Trust, and the National Cancer Institute at the National Institutes of Health (Award Number K07CA178258 to SL). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Abbreviation key

PSA	prostate-specific antigen
PLCO	Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial
ERSPC	European Randomized Study of Screening for Prostate Cancer
PSAV	prostate specific antigen velocity
PSAD	prostate specific antigen density
NCCN	National Comprehensive Cancer Network
phi	prostate health index
mpMRI	multiparametric MRI

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