The Use of Biomarkers in Prostate Cancer Screening and Treatment

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Prostate cancer screening and diagnosis has been guided by prostate-specific antigen levels for the past 25 years, but with the most recent US Preventive Services Task Force screening recommendations, as well as concerns regarding overdiagnosis and overtreatment, a new wave of prostate cancer biomarkers has recently emerged. These assays allow the testing of urine, serum, or prostate tissue for molecular signs of prostate cancer, and provide information regarding both diagnosis and prognosis. In this review, we discuss 12 commercially available biomarker assays approved for the diagnosis and treatment of prostate cancer. The results of clinical validation studies and clinical decision-making studies are presented. This information is designed to assist urologists in making clinical decisions with respect to ordering and interpreting these tests for different patients. There are numerous fluid and biopsy-based genomic tests available for prostate cancer patients that provide the physician and patient with different information about risk of future disease and treatment outcomes. It is important that providers be able to recommend the appropriate test for each individual patient; this decision is based on tissue availability and prognostic information desired. Future studies will continue to emphasize the important role of genomic biomarkers in making individualized treatment decisions for prostate cancer patients.


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KEY WORDS
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Prostate cancer (PCa) screening and diagnostic methods have been guided by prostate-specific antigen (PSA) levels for over 25 years, yet PSA screening has become controversial due to increasing rates of overdiagnosis and overtreatment. The lifetime risk of an American man developing PCa is 1 in 6, whereas the lifetime risk of a man dying from PCa is 1 in 35.1 This discrepancy has led to questions regarding the value of diagnosing low-grade, indolent PCa and has called into question the utility of PSA as a screening tool.

In 1986, the US Food and Drug Administration (FDA) approved PSA as an adjunctive test to the digital rectal examination (DRE) for PCa diagnosis in men aged 50 years. Subsequently, between 1985 and 1995, the PCa incidence in the United States doubled from 55 cases per 100,000 men to 110.2 In addition, the rate of radical prostatectomy (RP) increased sixfold from 1984 to 1990.3 More men were diagnosed with lower-grade, clinically indolent cancer while they were asymptomatic, leading to criticisms of overdiagnosis in 1.7% to 40%.13 Several modifications including bleeding, urinary retention, infection, and sepsis. In addition to the anxiety associated with such a procedure, these risks present a significant burden to any man considering biopsy. The decision to proceed with biopsy must be weighed against the high likelihood that low-grade disease will be detected, as well as the possibility of undergrading due to biopsy sampling error. Patients who require repeat biopsy after initial

In an effort to improve PCa screening methods, a new wave of PCa biomarkers has emerged that have higher PCa specificity than PSA and its isoforms. Biomarkers are molecules whose detection or evaluation provides information about a disease beyond standard clinical parameters.15 They can be detected in a variety of settings, including tissue samples, blood, and urine. Biomarkers can provide diagnostic as well as prognostic information, assisting providers in making disease predictions designed to guide treatment decisions on an individualized basis.

Here we present a nonsystematic review of 12 commercially available markers and tests for PCa. This review is intended to guide clinicians in the utilization of these tests in the appropriate clinical space. These tests have either been approved by the FDA or are offered under a laboratory’s Clinical Laboratory Improvement Amendments (CLIA) certificate.

Decision: To Proceed With Biopsy?

Presently, 1.3 million men undergo biopsies annually in the United States, more than 85% of whom will not have significant PCa. Prostate biopsy is an invasive procedure with the resultant possibility of complications including bleeding, urinary retention, infection, and sepsis. In addition to the anxiety associated with such a procedure, these risks present a significant burden to any man considering biopsy. The decision to proceed with biopsy must be weighed against the high likelihood that low-grade disease will be detected, as well as the possibility of undergrading due to biopsy sampling error. Patients who require repeat biopsy after initial
negative biopsy can also use various genomic tests to help consider the likelihood of finding cancer in the setting of persistent symptoms or elevated PSA levels.

4Kscore
Kallikreins are a family of 15 related serine proteases that are known to alter cell growth regulation, increase extracellular matrix remodeling and degradation, and promote cell invasion and angiogenesis. Human kallikrein-3 (PSA) and human kallikrein-2 (hK2) are the dominant forms and normally function to liquefy the contents of the vas deferens. They are formed as proproteins (pro-PSA and pro-hK2) and are cleaved to generate enzymatically active forms that can act on seminogelins. If they enter the circulation, they are rapidly bound by antichymotrypsin (ACT) or inactivated through proteolytic cleavage. The levels of both kallikreins increase in circulation as the tumor becomes more poorly differentiated, perhaps due to loss of tissue architecture. Level of hK2 expression has been found to adequately discriminate between low-grade and high-grade disease, as well as organ-confined and non–organ-confined disease. Analysis of the various forms of available PSA/hK2 (pro-PSA, active PSA, ACT-bound PSA and cleavage-inactivated PSA) in the circulation can suggest altered prostate biology.

The 4Kscore® Test (OPKO Health, Miami, FL) measures the plasma levels of the four different prostate-derived kallikrein proteins. Levels of these biomarkers are combined with certain clinical characteristics (age, DRE, prior biopsy status) to predict the risk of finding Gleason ≥7 disease on biopsy. It is designed for use in men with an elevated PSA level or abnormal DRE result who are considering an initial prostate biopsy, as well as in men with prior negative biopsy results and presently elevated PSA levels.

Multiple validation studies using the ERSPC cohort have shown significant discrimination of high-grade disease with incorporation of the 4Kscore as compared with a base model of age, total PSA (tPSA) level, and DRE result alone (area under the curve [AUC] 0.77, 0.81, 0.87 in the base model to 0.87, 0.84, 0.90 with 4Kscore). In addition, the 4Kscore decreases the number of unnecessary biopsies by 49% to 57% among men being screened for the first time. Among men who have had prior negative biopsy results, a similar increase in detection of high-grade disease and decrease in biopsy number was identified (AUC 0.71, 0.72 in the base model to 0.80, 0.83 with 4Kscore). A validation trial in the United States by Parekh and colleagues reported an AUC for predicting Gleason score of ≥7 of 0.82. The authors also showed that using a cutoff of 9% risk of high-grade disease on biopsy would result in a 43% reduction in the number of biopsies, while only conferring a 2.4% delay in diagnosis of high-grade cancer.

The 4Kscore is not appropriate for men who have received a DRE in the previous 96 hours, men on a 5α-reductase inhibitor, or men who have undergone any therapy or procedure for symptomatic BPH, thereby limiting its utility in a large portion of the urologic population.

Use of Biomarkers in PCa Screening and Treatment

Prostate Health Index
The Prostate Health Index (PHI; Beckman Coulter, Brea, CA) is a blood test that analyzes levels of fPSA, tPSA, and [-2]proPSA (p2PSA) using the equation ([p2PSA/fPSA] × tPSA)1/2 to predict risk of Gleason ≥7 disease on biopsy. Here, p2PSA refers to a proprotein isoform of PSA with 2 amino acid proleader peptide sequence (normally pro-PSA has 7 amino acid leader amino acids), which was shown to have the most concentration in tumor tissues. It reports risk of aggressive cancer as a four-tiered probability based on various score cutoffs. PHI is intended for use in men aged ≥50 years with serum PSA 4 to 10 ng/mL and negative DRE findings; it was approved by the FDA in 2012. PHI scores of 0 to 26.9, 27.0 to 35.9, 36.0 to 54.9, and ≥55.0 correlate with probabilities of Gleason ≥7 cancer on biopsy of 9.8%, 16.8%, 33.3%, and 50.1%, respectively.

At PSA levels of 4.0 to 10.0 ng/mL, measuring the ratio of fPSA to tPSA significantly improves discrimination between PCa and benign conditions. p2PSA has been identified as the most PCa-specific isoform of PSA, and a higher percentage of p2PSA is associated with more aggressive PCa. In 2011, Catalona and colleagues published the results of a large, multicenter trial of 892 men with tPSA levels 2 to 10 ng/mL and normal DRE results. They found that the PHI assay as a whole has an AUC of 0.703. They also report a fivelfold increased risk of PCa in patients with a PHI value >55. A meta-analysis of 16 studies reported sensitivity of 0.85, specificity of 0.45, and an AUC of 0.70 in detecting PCa. Stephan and associates showed a 49% to 57% decrease in biopsy number as compared with a base model of age, total PSA (tPSA) level, and DRE result alone (area under the curve [AUC] 0.77, 0.81, 0.87 in the base model to 0.87, 0.84, 0.90 with 4Kscore). In addition, the 4Kscore decreases the number of unnecessary biopsies by 49% to 57% among men being screened for the first time. Among men who have had prior negative biopsy results, a similar increase in detection of high-grade disease and decrease in biopsy number was identified (AUC 0.71, 0.72 in the base model to 0.80, 0.83 with 4Kscore). A validation trial in the United States by Parekh and colleagues reported an AUC for predicting Gleason score of ≥7 of 0.82. The authors also showed that using a cutoff of 9% risk of high-grade disease on biopsy would result in a 43% reduction in the number of biopsies, while only conferring a 2.4% delay in diagnosis of high-grade cancer.

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Use of Biomarkers in PCa Screening and Treatment continued

reported increasing rates of PCa-positive biopsy results with increasing PHI scores, but do not offer a cutoff PHI score for detection of aggressive PCa. In addition, PHI has also been found to be a significant predictor of pT3 disease and Gleason score ≥7 at time of RP.36

Apifiny

Apifiny (Armune Bioscience, Kalamazoo, MI) is a blood test that measures the expression of eight PCa-specific autoantibodies. It is marketed for men with PSA >2.5 ng/mL who are considering initial biopsy, reporting a score on a scale of 1 to 100 that reflects risk of Gleason ≥7 on biopsy. A score of ≥59 reflects increased risk.

The humoral immune response to cancer consists of the production of autoantibodies against a number of tumor antigens. In 2005, Wang and associates37 identified a panel of 22 autoantibody biomarkers that, when present, were highly diagnostic of prostate malignancy, citing 88.2% specificity, 81.6% sensitivity, and an AUC of 0.93.37 They used a T7-phage peptide display library to screen for biomarkers using 62 peptides against 96 biopsy tissues (48 positive and 48 negative for cancer). The Apifiny test incorporates detection of antibodies to 8 of these 22 identified biomarkers (CSNK2A2, centrosomal protein 164 kDa, NK3 homeobox 1, aurora kinase interacting protein 1, 5′ UTR BMI1, ARF6, chromosome 3′ UTR region Rapporin/RhoEGF, and desmocollin 3) that have roles in androgen response regulation, cellular structural integrity, and cell cycle regulation.38 With this eight-autoantibody panel, Apifiny has reported to have an AUC of 0.69 for men with PSA >4 ng/mL, sensitivity of 0.603, specificity of 0.69, PPV of 0.299, and negative predictive value (NPV) of 0.888.38

**Progensa PCA3 Assay**

Progensa PCA3 assay (Hologic, Marlborough, MA), a long noncoding RNA also referred to as DD3, was identified as overexpressed in 53 out of the 56 tumor tissues analyzed and absent from the 18 control samples.39 Follow-up studies showed it to have elevated expression in >90% of PCa.40 Mechanistic studies identified its role in PCa cell survival, in part through its ability to regulate androgen receptor signaling.41 The PCA3 assay was approved by the FDA in 2012 as a diagnostic test for PCa in the setting of a prior negative biopsy result. The assay is an in vitro nucleic acid amplification test measuring concentration of PCA3 and PSA messenger RNA (mRNA) molecules in a first catch post-DRE urine specimen. It uses the ratio of the levels of these two markers (eg, to negate the effect of increased PSA due to BPH and age) to calculate the PCA3 score, which is directly correlated with likelihood of positive biopsy result. It is designed for use in men aged ≥50 years who have had one or more negative biopsy results and who are considering a repeat biopsy.

Men with a score <25 are 4.56 times more likely to have a negative biopsy result than men with a score >25,42 and lower PCA3 scores are associated with low-volume and low-grade disease.43,44 Marks and associates45 first evaluated the use of PCA3 in 226 patients undergoing repeat biopsy. At a score cutoff of 35, the group demonstrated a sensitivity and specificity of 0.58 and 0.72, respectively (AUC 0.68). Using a PCA3 score cutoff of 20, Wei and coworkers46 reported a sensitivity of 0.775, a specificity of 0.571, and an NPV and PPV of 90% and 33.6%, respectively.

PCA3 level is not elevated in acute inflammatory or infectious states, and is independent of prostate size. In addition, the PCA3 assay maintains its predictive power in men with BPH who are on long-term treatment with 5α-reductase inhibitors with nearly no loss of specificity over 4 years.47 PCA3 expression level has been found in many studies to independently correlate with biopsy outcome45,48–50 and tumor aggressiveness, as measured by tumor volume, tumor grade, and Gleason score.43,48,51 However, other studies have found no significant correlation between PCA3 score and Gleason grade at biopsy.45,52

The current assay is approved for men undergoing repeat biopsy, although evidence is mounting that the PCA3 assay may have utility as a screening tool in men with elevated PSA values. However, the relation of PCA3 score with tumor aggressiveness and thus true prognostic value remains controversial. It is also important to note that the optimal PCA3 cutoff score is still subject to debate; Leyten and colleagues53 showed an increase in sensitivity from 0.68 to 0.83 when lowering the cutoff from 35 to 25, and a corresponding decrease in specificity from 0.58 to 0.51.

**Michigan Prostate Score**

The Michigan Prostate Score (MiPS) was released in 2013 and is an assay that incorporates serum
use in men with an elevated PSA level who are considering initial biopsy, or in men with previous negative biopsy results who are considering a repeat biopsy. A score of 1 to 100 reflects the percent chance of finding any PCa on biopsy, and the score report also provides a risk estimate for detecting cancer of Gleason score \(\geq 7\).

Tomlins and colleagues\(^56\) found that the level of \(\text{TMPRSS2:ERG}\) transcript in the urine is associated with the presence of PCAs, tumor volume, and Gleason score \(\geq 7\) both at biopsy and in prostatectomy specimens. Specificity of \(\text{TMPRSS2:ERG}\) is very high, at 93.2%\(^63\). Salami and colleagues\(^57\) report an improved discriminatory ability for the combination of PSA, PCA3, and \(\text{TMPRSS2:ERG}\), as opposed to each alone (AUC 0.88 for the combined test vs 0.72 for PSA, 0.65 for PCA3, and 0.77 for \(\text{TMPRSS2:ERG}\)). In a cohort study by Leyten and associates\(^53\), knowledge of MPS score prior to biopsy would avoid 35% of biopsies. Tomlins and colleagues\(^58\) also reported that using various percent cutoffs would avoid 35% to 47% of biopsies, while delaying diagnosis in only 1.0% to 2.3% of high-grade cancers.

\(\text{TMPRSS2:ERG}\) has not been found to correlate significantly with long-term risk of biochemical recurrence or PCa-specific mortality.\(^59\) Although \(\text{TMPRSS2:ERG}\) gene fusions are reported to be associated with high-risk tumors, a more recent study reported no strong correlation between these fusions and long-term patient outcome.\(^60\)

In addition, the \(\text{ERG}\) rearrangements are less prevalent in men of African descent when compared with white men, 27% versus 54%, respectively. Finally, the report does not offer a low-risk/high-risk cutoff score.

**SelectMDx**

SelectMDx (MDx Health, Irvine, CA) provides the likelihood of detecting any PCa on prostate biopsy, as well as the probability for high-grade versus low-grade disease. The test measures mRNA levels of distal-less homeobox 1 (\(\text{DLX1}\)) and homeobox C6 (\(\text{HOXC6}\)) in a post-DRE urine specimen and combines this with serum PSA, PSA density, DRE status, age, and family history of PCAs.

\(\text{HOXC6}\) regulates genes with both oncogenic and tumor suppressor activities, as well as several genes important for prostate morphogenesis and metastasis to the bone.\(^61\) It is frequently overexpressed in patients with PCa, indicating an oncogenic role, and the degree of overexpression is directly associated with Gleason score.\(^62,63\) \(\text{DLX1}\) is involved in neuroendocrine-epithelial differentiation, a characteristic associated with aggressive PCa.\(^64\) Both the \(\text{HOXC6}\) and \(\text{DLX1}\) biomarkers have been shown to have independent value in predicting Gleason \(\geq 7\) PCa on biopsy, and are potentially involved in the onset of PCa.\(^65\) In predicting the risk of high-grade PCa in men with PSA \(\geq 4\) ng/mL, Van Neste and colleagues\(^66\) found that \(\text{HOXC6}\) and \(\text{DLX1}\) independently have an AUC of 0.73 and 0.65, sensitivity of 91% and 83%, and specificity of 33% and 16%, respectively. Together they have an AUC of 0.76, sensitivity of 91%, and specificity of 36%. When combined with the clinical parameters mentioned above, the AUC increases to between 0.86 and 0.90.\(^66\)

**Detection of the novel biomarkers \(\text{HOXC6}\) and \(\text{DLX1}\) in a post-DRE urine sample allows for individualized decision making according to probability of high-grade disease.**

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ConfirmMDx (MDxHealth) is designed as a risk stratification tool for men with a negative prostate biopsy result and aims to reduce the number of repeat biopsies. It is a unique assay in that it analyzes epigenetic changes in DNA methylation patterns of key tumor suppressor genes such as \(\text{GSTPI}, \text{RASSFI},\) and \(\text{APC}\) in a prostate tissue sample. \(\text{GSTPI}\) is involved in DNA detoxification, \(\text{RASSFI}\) is involved in cell cycle regulation, and \(\text{APC}\) is involved in apoptosis, cell migration, and cell adhesion.\(^67\) Hypermethylation of \(\text{CpG}\) islands in the promoter regions of these

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PSA level, urine PCA3 mRNA, and urine \(\text{TMPRSS2:ERG}\) mRNA. More than 50% of PCAs harbor fusions between \(\text{TMPRSS2:ERG}\), and multiple studies have shown that \(\text{TMPRSS2:ERG}\) fusions are more common in young men with early-stage PCAs and in men presenting with low serum PSA values.\(^54,55\) The MiPS test utilizes a urine sample, which must be taken no more than 1 hour after DRE. It is designed for use in men with an elevated PSA level who are considering initial biopsy, or in men with previous negative biopsy results who are considering a repeat biopsy. A score of 1 to 100 reflects the percent chance of finding any PCa on biopsy, and the score report also provides a risk estimate for detecting cancer of Gleason score \(\geq 7\).

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Decision: Active Surveillance Versus Intervention?

Active surveillance (AS) has now become a standard of care in the treatment of very low-risk and low-risk PCa. However, AS tends to be underutilized, and most men with low-risk disease eventually receive surgical or radiation treatment. The rate of progression necessitating intervention of men on AS protocols is approximately 40% over a 10-year period. Epstein and colleagues conducted a literature review of studies with >100 patients and found presence of Gleason score upgrading after RP from 6 to 7 in 35% of patients. Such data underscore the need to appropriately risk stratify patients after biopsy.

The following biomarker tests are designed to guide management decisions and appropriately counsel postbiopsy patients regarding AS versus intervention.

Oncotype DX

The Oncotype DX assay (Genomic Health, Redwood City, CA) uses a fixed, paraffin-embedded prostate needle biopsy tissue sample to predict the aggressiveness of an individual patient’s tumor, as reported by a Genomic Prostate Score (GPS) of 1 to 100. The test was approved for use in PCa in 2013, joining previous variations that were marketed for breast cancer and colon cancer. The quantitative reverse transcriptase-polymerase chain reaction assay measures the RNA expression levels of 5 reference genes (ARF, ATP5E, CLTC, GSI, PGKI) and 12 genes representing 4 biologic pathways with known roles in PCa tumorigenesis: the androgen pathway (AZGPI, KLK2, SRD5A2, and FAM13C), cellular organization (FLNC, GSN, TPM2, and GSTM2), proliferation (TPX2), and stromal response (BGN, COL1A1, and SFRP4). These are combined to generate a GPS ranging from 0 to 100; a higher GPS score is concordant with a higher chance of adverse pathology (primary Gleason pattern of 4-5 or disease that is no longer organ confined) after RP. It is designed to assist with risk stratification and further treatment decisions in clinically low- and low-intermediate-risk patients, specifically the decision to undergo AS or further treatment.

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In analysis of adverse pathology, incorporation of the GPS improved the AUC of NCCN by 90%.79 Due to the long-term follow-up of this study, the authors were also able to conclude that GPS is also a strong predictor of biochemical recurrence (BCR) and future metastases. A study by Klein and colleagues80 found that addition of the GPS score to existing clinical and pathologic factors expanded the low-risk population from 10% to 26%, and reclassified 35% of NCCN low-risk men to the very low-risk category, and 10% to the intermediate-risk category. With regard to clinical decision making, Badani and colleagues81 found an overall 18% change in treatment recommendations after receiving GPS results in a cohort of 158 patients at 3 clinical institutions, a 19% to 21% decrease in RP recommendation, and a 33% decrease in RT recommendation. These changes in treatment decisions were found over all NCCN risk groups, but the NCCN low-risk group showed the greatest absolute recommendation change after a GPS of 37%. However, GPS score led to change in NCCN category in 39% of patients (lower in 35%, higher in 4%).

**ProMark**
The quantitative multiplex proteomic-based test, ProMark (Metamark, Waltham, MA) predicts potential cancer aggressiveness in patients with Gleason 3+3 or 3+4 disease on biopsy by measuring direct levels of eight proteins (DERL1, CUL2, SMAD4, PDSS2, HSPA9, FUS, pS6, and YBOX1) in a biopsy specimen through quantitative immunofluorescence. All of these proteins have roles in cell proliferation, stress response, and signaling pathway activities. ProMark reports individualized risk of Gleason ≥4+3 disease and/or non–organ-confined disease on a scale of 1 to 100, were an RP to be performed, and combines this with the patient’s NCCN risk category. In 2014, Shipitsin and colleagues82 first reported a set of 12 protein biomarkers that were predictive of PCA aggressiveness and PCa-specific mortality despite sampling error. The AUC for the assay was reported at 0.72 for predicting lethal outcome, and 0.71 for predicting aggressive cancer. Further clinical validation was achieved by Blume-Jensen and associates,83 who used 8 of the 12 candidate proteins and defined endpoints of “favorable” versus “nonfavorable,” and “Gleason 6” versus “non-Gleason 6” in biopsy and prostatectomy specimens from 276 patients. The analysis for “favorable” pathology yielded an AUC of 0.68, and “Gleason 6” pathology yielded an AUC of 0.65. When combining the assay results with NCCN classification, AUC increased to 0.75. Similarly, when taking into account PSA, the percentage of positive cores and biopsy Gleason pattern, AUC for “favorable” pathology increased to 0.71. A risk score of 0.33 is recommended (on a scale of 0-1) as a cutoff for unfavorable pathology, with sensitivity of 90%, PPV of 83.6%, and a false-negative rate of 10%.

**PTEN/TMPRSS2:ERG**
The PTEN/TMPRSS2:ERG (Metamark) molecular assay is for use in men with Gleason 3+3 or 3+4 disease on biopsy, as well as those with an atypical/high-grade prostatic intraepithelial neoplasia (HGPIN) diagnosis on biopsy. It helps to predict PCA aggressiveness by measuring the presence or absence of both the fusion gene TMPRSS2:ERG and the tumor suppressor gene PTEN in a biopsy; the presence of TMPRSS2:ERG and/or the absence of PTEN indicates a more aggressive cancer.

PTEN is a tumor suppressor gene that is known to modulate a number of downstream targets with important roles in apoptosis and cell cycle progression. Specifically, it dephosphorylates the membrane lipid phosphatidylinositol-3,4,5 phosphate (PIP3) to phosphatidylinositol-4,5 phosphate (PIP2) thereby abrogating Akt membrane binding and its subsequent activation.84 PTEN inactivation in cancer cells has been shown to be associated with high Gleason score and tumor progression.85,86 Yoshimoto and colleagues87 found that hemizygous PTEN deletion was found in 39% and homozygous deletion in 5% of tumor samples. Those samples with a homozygous deletion were more likely to have late biochemical recurrence (P = .005). Similarly, Schmitz88 reported complete loss of PTEN expression in prostate cancer cells both in situ and metastatic to lymph nodes in 59% of cases.

The PTEN/TMPRSS2:ERG assay is reported in terms of binary results, and has not been shown to be significantly correlated with Gleason score at biopsy, pathologic stage, or other factors that indicate more aggressive disease at the time of surgery.87 It is unique, however, in that it can be used in men with atypia or HGPIN on biopsy, and may lead to earlier diagnosis of potentially aggressive PCa.

**Prolaris**
The Prolaris (Myriad Genetics, Salt Lake City, UT) score is a quantitative measure of the average expression of 31 cell cycle progression (CCP) genes and 15 reference genes in either a biopsy specimen or an RP specimen to predict tumor aggressiveness and recurrence. The test was originally developed for breast cancer risk analysis. According to the NCCN guidelines, it is recommended for patients with very low- and
Cuzick and colleagues reported a clinically localized PCa on biopsy, risk. In a study of 585 men with a 10-year PCa-specific mortality and AUA risk category to report positive cores, Gleason score, age, PSA, clinical stage, percent positive cores, Gleason score, and AUA risk category to report a 10-year PCa-specific mortality risk. In a study of 585 men with clinically localized PCa on biopsy, Cuzick and colleagues reported that CCP score, which reflects tumor aggression and recurrence, and can also provide information on the risk of death due to PCa.

**Decipher**
The Decipher test (GenomeDx, San Diego, CA) is a genomic classifier that measures RNA expression of 22 different genes (LASPI, IQGAP3, NFIB, SITR4, THBS2, ANO7, PCDH7, MYBPC1, EPPK1, TSBP, PBX1, NUSAP1, ZWILCH, UBE2C, CAMK2N1, RABGAP1, PCAT-32, GLYATL1P4, PCAT-80, and TNFRSF19), identified through extensive literature survey, in either a biopsy specimen or an RP specimen. These 22 genes encompass several important biologic pathways such as cell proliferation, differentiation, cell motility and cell adhesion, cell cycle progression, immune modulation, and androgen receptor pathway. The Decipher score represents a continuous risk score called a genomic classifier and ranges from 0 to 1; a low risk score is 0 to 0.45, an average risk score is 0.46 to 0.6, and a high-risk score is 0.61 to 1.0. According to NCCN guidelines, it is recommended for patients with adverse pathology after RP. Decipher reports 5-year risk of metastases, 10-year PCa-specific mortality, and risk of high-grade disease for men with any PCa on biopsy. Much of the data to support Decipher comes from studies done in prostatectomy specimens. Decipher score after prostatectomy conveys information to help with making decisions about adjuvant radiation therapy or observation after RP. It can also guide decisions regarding the use of hormone deprivation therapy in patients with biochemical recurrence. Its intended use is in men with high-risk pathology or high-risk clinical features after RP, reporting 5-year risk of metastases and 10-year PCa-specific mortality. Klein and colleagues reported that in 337 Gleason 3+3 prostatectomy specimens, 20% had intermediate or high-risk Decipher scores, indicating a potentially more aggressive cancer in a low-risk biopsy. A 2016 report by Ross and colleagues significantly and independently correlates Decipher score with incidence of BCR, metastasis, and PCa-specific mortality ($P < .01$). Five-year metastasis rate in a cohort of post-RP, clinically high-risk patients (PSA > 20 ng/mL, Gleason 8, pT3b, or GPSM score 10) has been reported to be 2.4%, 6.0%, and 22.5% for patients with low Decipher scores (< 0.4), intermediate scores (0.4-0.6), and high scores (>0.6), respectively ($P < .001$). In addition, Den and coworkers found that Decipher scores can help guide timing of post-RP radiation therapy in men with high-risk pathology. Alshalalfa and coauthors observed a distinct...
# TABLE 1

## Summary of Available Tests and Indications

<table>
<thead>
<tr>
<th>Test</th>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>Initial Biopsy</strong></td>
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<tr>
<td>PHI (Beckman Coulter, Brea, CA)</td>
<td>Blood</td>
<td>Levels of tPSA, fPSA, p2PSA (p2PSA/fPSA) × tPSA¹/²</td>
<td>Risk of HG cancer on biopsy (score 1-100)</td>
<td>Men ≥50 y with PSA 4-10 ng/mL and negative DRE result who are considering initial biopsy</td>
<td>Score 0-26.9: 9.8% risk of HG disease</td>
<td>Catalona WJ et al²⁹</td>
</tr>
<tr>
<td>Apifiny (Armune Bioscience, Kalamazoo, MI)</td>
<td>Blood</td>
<td>Circulating levels of 8 PCa-specific autoantibodies</td>
<td>Risk of HG cancer on biopsy (score 1-100)</td>
<td>Men with PSA ≥2.5 ng/mL who are considering initial biopsy</td>
<td>Score 1-58: low risk of HG disease</td>
<td>Schipper M et al³⁸</td>
</tr>
<tr>
<td>SelectMDx (MDx Health, Irvine, CA)</td>
<td>Urine</td>
<td>Expression of DLX1 and HOXC6</td>
<td>Percent risk of Gleason 6 disease on biopsy</td>
<td>Men with elevated PSA value who are considering initial prostate biopsy</td>
<td>Low risk: routine follow-up and screening</td>
<td>Van Neste L et al⁶⁶</td>
</tr>
<tr>
<td><strong>Repeat Biopsy</strong></td>
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<tr>
<td>PCA3 (Hologic, Marlborough, MA)</td>
<td>Urine</td>
<td>Ratio of PCA3 and PSA expression</td>
<td>Risk of Gleason 6 disease on biopsy (score 1-100)</td>
<td>Men age ≥50 y who are considering repeat biopsy after initial negative biopsy</td>
<td>Score 1-25: low risk of cancer, safe to defer biopsy</td>
<td>Gittelman MC et al⁴²</td>
</tr>
<tr>
<td>ConfirmMDx (MDxHealth)</td>
<td>Biopsy</td>
<td>Hypermethylation intensity of tumor suppressor genes GSTP1, RASSF1, and APC</td>
<td>Risk of PCA on repeat biopsy</td>
<td>Men who are considering a repeat biopsy after initial negative biopsy result</td>
<td>Negative: safe to defer biopsy</td>
<td>Stewart GD et al⁵⁰; Partin AW et al⁵¹; Van Neste L et al⁷²</td>
</tr>
<tr>
<td><strong>Initial or Repeat Biopsy</strong></td>
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<tr>
<td>4Kscore (OPKO Health, Miami, FL)</td>
<td>Blood</td>
<td>Levels of tPSA, fPSA, intact PSA, and human kallikrein-related peptidase 2</td>
<td>Percent risk of HG cancer on biopsy</td>
<td>Men with an elevated PSA or abnormal DRE result who are considering initial or repeat biopsy</td>
<td>Low risk (1%-7.5%): safe to defer biopsy with follow-up of PSA</td>
<td>Vickers AJ et al²¹,²³,²⁵,²⁶; Parekh DJ et al²⁷</td>
</tr>
</tbody>
</table>

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### Use of Biomarkers in PCa Screening and Treatment continued

<table>
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<tr>
<th>Test</th>
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</thead>
<tbody>
<tr>
<td>MiPS</td>
<td>Urine</td>
<td>Expression of PCA3 and TMPRSS2:ERG Combined with serum PSA</td>
<td>Percent risk of Gleason ≥6 disease on biopsy</td>
<td>Men with elevated PSA value who are considering initial biopsy or repeat biopsy after initial negative result</td>
<td>Does not provide low- and high-risk cutoffs</td>
<td>Salami SS et al(^{52}); Leyten G et al(^{53}); Tomlins SA et al(^{58})</td>
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<tr>
<td><strong>After Biopsy: Active Surveillance vs Intervention</strong></td>
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<tr>
<td>Oncotype DX (Genomic Health, Redwood City, CA)</td>
<td>Biopsy</td>
<td>Expression of 12 PCa-related genes</td>
<td>Percent likelihood of Gleason 3+3 or 3+4 disease on RP</td>
<td>Men with very low- and low-risk PCa based on NCCN risk group</td>
<td>Does not provide low- and high-risk cutoffs</td>
<td>Cullen J et al(^{79}); Klein EA et al(^{80})</td>
</tr>
<tr>
<td>ProMark (Metamark, Waltham, MA)</td>
<td>Biopsy</td>
<td>Quantitative levels of 8 PCa-related proteins</td>
<td>Percent risk of developing aggressive disease (Gleason ≥4+3, non-organ-confined disease) based on ProMark score alone and when combined with NCCN category</td>
<td>Men with Gleason 3+3 or 3+4 on biopsy</td>
<td>Does not provide low- and high-risk cutoffs</td>
<td>Shipitsin M et al(^{82}); Blume-Jensen P et al(^{83})</td>
</tr>
<tr>
<td><strong>PTEN/TMPRSS2:ERG (Metamark)</strong></td>
<td>Biopsy</td>
<td>Presence or absence of PTEN deletion</td>
<td>Cancer aggressiveness</td>
<td>Men with Gleason 3+3 or 3+4 on biopsy</td>
<td>Negative (intact PTEN, no ERG rearrangement): active surveillance</td>
<td>Yoshimoto M et al(^{87})</td>
</tr>
<tr>
<td>ProLaris</td>
<td>Biopsy</td>
<td>Expression levels of 31 genes associated with cell cycle progression</td>
<td>Cancer aggressiveness (score 1-10) 10-y PCa-specific mortality risk</td>
<td>Men with PCa on biopsy</td>
<td>Does not provide low- and high-risk cutoffs</td>
<td>Cuzick J et al(^{90})</td>
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### Use of Biomarkers in PCa Screening and Treatment

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<tr>
<td>Decipher</td>
<td>Biopsy</td>
<td>Expression levels of 22 genes associated with high-risk PCa</td>
<td>5-y metastasis risk</td>
<td>Patients with localized disease on biopsy</td>
<td>Does not provide low- and high-risk cutoffs</td>
<td>Cooperberg MR et al92; Klein EA et al95; Ross AE et al96</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Likelihood of HG disease on RP</td>
<td></td>
<td>Low risk: active surveillance</td>
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<td></td>
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<td></td>
<td>10-y PCa-specific mortality risk</td>
<td></td>
<td>High risk: consider further treatment</td>
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</table>

### After RP: Secondary Treatment vs Observation

<table>
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<tr>
<td>Prolaris</td>
<td>Prostate</td>
<td>Expression levels of 31 genes associated with cell cycle progression</td>
<td>Risk of biochemical recurrence within 10 y (score 1-10)</td>
<td>Men who have undergone RP</td>
<td>Does not provide low- and high-risk cutoffs</td>
<td>Cuzick J et al91; Cooperberg MR et al92</td>
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<td>Provides score relative to others in the same AUA risk category</td>
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</tr>
<tr>
<td>Decipher</td>
<td>Prostate</td>
<td>Expression levels of 22 genes associated with high-risk PCa</td>
<td>5-y metastasis risk</td>
<td>Men with high-risk pathology or high-risk clinical features after RP</td>
<td>Low risk: observe with PSA monitoring, RT if PSA value rises</td>
<td>Karnes RJ et al97; Den RB et al98</td>
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<tr>
<td></td>
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<td></td>
<td>10-y PCa-specific mortality risk</td>
<td></td>
<td>High risk: adjuvant or early RT with further intensification of treatment as needed</td>
<td></td>
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</tbody>
</table>

AUA, American Urological Association; DRE, digital rectal examination; GPS, Genomic Prostate Score; HG, high-grade (Gleason $\geq 7$); fPSA, free prostate-specific antigen; NCCN, National Comprehensive Cancer Network; p2PSA, [-2]proPSA; PCa, prostate cancer; PHI, Prostate Health Index; PSA, prostate-specific antigen; RP, radical prostatectomy; tPSA, total prostate-specific antigen.

The most recent update to the NCCN Guidelines for Prostate Cancer Early Detection includes the addition of various biomarkers to treatment algorithms. As reflected in the guidelines, one biomarker cannot be recommended over another at this time. Additionally, these markers should not be used as first line in the diagnosis of PCa. Although many of these biomarkers offer valuable information on a case-by-case basis, they should be considered as one piece of the puzzle in counseling patients regarding their specific prostate malignancies.

Although we have come a long way in elucidating the underlying genetic changes in PCa and how they can guide management decisions, there is still much room for discovery and improvement. Genomic sequencing efforts over the past few years have shown the development of PCa to be driven additionally though copy number variations (CNVs). CNVs have also been shown to be associated with aggressive disease and survival; however, none of the genomic tests that are currently commercially available take CNVs into account when predicting aggressive disease or disease outcomes. In addition, a confounding factor in the general applicability and utility of these assays is the inherent intratumor heterogeneity and multifocality of PCa, which is not accounted for in any of the tests developed so far.

Currently available targeted therapy for PCa consists of mechanisms...
Use of Biomarkers in PCa Screening and Treatment

of attack on the prostate cell mem-
brane (prostate-specific membrane
antigen [PSMA], prostatic acid
phosphatase [PAP], and prostate
stem cell antigen [PSCA]), tumor
angiogenesis (bevacizumab, thal-
 lidomide, sunitinib), the androgen
receptor pathway, and other cell
proliferation pathways (mamma-
lia target of rapamycin [mTOR]
inhibitors).106 As our knowledge of
the general biology and immunol-
ogy of PCa—as well as what geneti-
cally differentiates low-risk and
high-risk cancers—increases, it is
reasonable to predict that a greater
number of targets will become avail-
able for increasingly specific cancer
treatment, as well as improved pre-
diction of tumor response to these
targeted therapies.

Recent studies out of The Cancer
Genome Atlas have led to the clas-
Sification of PCa into different sub-
types, yet the utility of this in the
clinical setting awaits further eva-
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epigeneic changes that have been
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References
Cancer Society Prostate Cancer Advisory Commit-
tee. American Cancer Society guideline for the early
detection of prostate cancer: update 2010. CA Cancer
J Clin. 2010;60:70-98.
2. Potolsky AL, Feuer EI, Levin DL. Impact of screening
on incidence and mortality of prostate cancer in the
assessment of radical prostatectomy: time trends, geo-
graphic variation, and outcomes. The Prostate Patient
Outcomes Research Team. JAMA. 1993;269:2633–
2636.
2014;65:304-315.
Cancer Project Team. Mortality results from a random-
2009;360:1310-1319.
Cancer Project Team. Mortality results from a random-
2009;360:1310-1319.
Investigators. Screening and prostate-cancer mortal-
2009;360:1320-1328.
Screening for prostate cancer: U.S. Preventive Services
Task Force recommendation statement. Ann Intern
characteristics of prostate-specific antigen in men
with an initial PSA level of 3.0 ng/ml or lower. JAMA.
10. Reddan AJ, Duffy MJ, Handy FC, et al. Use of pro-
estatic-prostatic antigen (PSA) isoforms for the detec-
tion of prostate cancer in men with a PSA level of 2-10
ng/ml systematic review and meta-analysis. Eur Urol.
testing for early diagnosis of prostate cancer. N Engl J
time and overdiagnosis in prostate-specific anti-
gen screening: importance of methods and context. J
prostate cancer in 2008 II: the importance of mole-
cular subforms of prostate-specific antigen and tissue
15. Prensner JR, Rubin MA, Wei JT, Chinnaiyan AM.
Genome Atlas have led to the clas-
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Outcomes Research Team. JAMA. 1993;269:2633–
2636.
2014;65:304-315.
5. Androule GD, Crawford ED, Grubb RL, et al; Pro-
estatic-cancer Screening, Rotterdam. Clin Cancer
screening on predicting the outcome of prostate
cancer biopsy in men with elevated prostate-specific
antigen: data from the European Randomized Study of
institutional prospective trial in the USA confirms
that the 4Kscore accurately identifies men with
high-grade prostate cancer. Eur Urol. 2015;68:464-
470.
8. Chiu TY, Mikolajczyk SD, Lenskis K, et al. Immuno-
chemical staining of prostate cancer with mono-
clonal antibodies to the precursor of prostate-specific
percentage of free prostate-specific antigen to enhance
differentiation of prostate cancer from benign pros-
tatic disease: a prospective multicenter trial. JAMA.
1998;279:1542-1547.
10. Mikolajczyk SD, Catalona WJ, Evans CL, et al. Pro-
enzyme forms of prostate-specific antigen in serum
pro-psa antigen predicts preferentially detects
aggressive prostate cancers in men with 2 to 4 ng/ml
prostate specific antigen. J Urol. 2004;171(6 Pt
1):2239-2244.
multicenter, National Cancer Institute Early Detection
Research Network study of [-2]proPSA: improving prostate
sampling and correlating with cancer aggressiveness.
S-P2PSA and prostate health index for aggressive
center evaluation of [-2]prostate-specific antigen and
the prostate health index for detecting prostate
prostate-specific antigen isoform p2PSA and its de-
rivatives, S-p2PSA and Prostate Health Index, predict
pathologic outcomes in patients undergoing radical
prostatectomy for prostate cancer: results from a
1233.
prostate cancer biomarkers derived from autoan-
DD3: a new prostate-specific gene, highly overex-
pressed in prostate cancer. Cancer Res. 1999;59:5975-
5985.
19. de Kok JH, Verhaegh GW, Roelfs RW, et al. DD3(PCAC3), a very sensitive and specific marker to
detect prostate tumors. Cancer Res. 2002;62:2695-
2700.
noncoding RNA is involved in the control of prostate-
continued


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