Regence

Medical Policy Manual Laboratory, Policy No. 69

Protein Biomarkers and Multi-analyte Biomarker Tests for Screening, Detection, and/or Management of Prostate Cancer

Effective: February 1, 2025

Next Review: October 2025
Last Review: December 2024

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Protein biomarkers and multi-analyte biomarker tests have been proposed as a method for risk-stratifying patients with, or at risk for prostate cancer to inform decisions related to biopsy/rebiopsy and treatment.

MEDICAL POLICY CRITERIA

Protein biomarkers and multi-analyte biomarker tests for the screening, detection, and management of prostate cancer are considered **investigational**. These include, but are not limited to the following:

A. Autoantibody markers (e.g., Apifiny®)
B. Kallikrein markers (e.g., 4Kscore™ Test)
C. Immunofluorescence markers (e.g., Promark™)
D. Oncotype DX® AR-V7 Nucleus Detect
E. PanGIA Prostate (Genetics Institute of America)
F. IsoPSA®

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

CROSS REFERENCES

1. Gene-Based Tests for Screening, Detection, and/or Management of Prostate Cancer, Genetic Testing, Policy No. 17
2. Analysis of Proteomic Patterns for Early Detection or Assessing Risk of Cancer, Laboratory, Policy No. 41
3. Urinary Biomarkers for Cancer Screening, Diagnosis, and Surveillance, Laboratory, Policy No. 72
4. Investigational Gene Expression, Biomarker, and Multianalyte Testing, Laboratory, Policy No. 77

BACKGROUND

Prostate cancer is a complex, heterogeneous disease. At the extremes of the spectrum, if left untreated, some prostate cancers behave aggressively, metastasize quickly, and cause mortality, while others are indolent and never progress to cause harm. Current challenges in prostate cancer care are risk assessment; early and accurate detection; monitoring low-risk patients undergoing surveillance only; prediction of recurrence after initial treatment; detection of recurrence after treatment; and assessing efficacy of treatment for advanced disease.

In response to the need for better biomarkers for risk assessment, diagnosis, prognosis and management, a variety of exploratory research is ongoing. Some products of this work have already been translated or are in the process of being translated into commercially available tests, including:

- Apifiny® (Armune BioScience®), a cancer-specific non-PSA blood test. This test measures eight specific biological markers that are associated with immune response to prostate cancer; therefore, is proposed for early detection of prostate cancer. According to the manufacturer, based on early clinical studies, a cut point of 59 indicates patients at lower risk, and scores of 59 and above indicates additional evaluation.
- 4Kscore™ Test (OPKO Lab), a blood test that measures four prostate-specific kallikreins which are combined into an algorithm to decide whether a patient should proceed to prostate biopsy.
- Promark™, a protein biomarker test that uses immunofluorescence and automated quantitative images in intact biopsy tissue to risk stratify patients to active surveillance or therapeutic intervention.
- Oncotype DX® AR-V7 Nuclear Detect (Genomic Health, Epic), a test to detect nuclear-localized AR-V7 protein in CTCs of men with metastatic castration-resistant prostate cancer who have failed first-line therapy and are considering additional androgen receptor signaling (ARS) inhibitor therapy.
- PanGIA Prostate (Genetics Institute of America), is a multi-analyte urine assay with algorithmic analysis that estimates an individual's risk of having prostate cancer. The test is marketed as a method to determine whether a patient should undergo a biopsy.

While studies using these tests generate information that may help elucidate the biologic mechanisms of prostate cancer and eventually help design treatments, the above-mentioned tests are currently in a developmental phase, with insufficient evidence of clinical utility.

REGULATORY STATUS

None of the tests addressed in this policy have been submitted to the U.S. Food and Drug Administration (FDA) for marketing clearance but, if available, are offered as laboratory-

developed tests by Clinical Laboratory Improvement Amendments (CLIA) licensed laboratories.

EVIDENCE SUMMARY

In general, the evidence for biomarker tests related to prostate cancer screening, detection, and management addresses either preliminary clinical associations between protein expression and disease states or, in some cases, the clinical validity of these tests, i.e., the association of the test result with outcomes of interest, expressed in terms of clinical performance characteristics such as sensitivity, specificity, predictive value, and comparisons to current standards using receiver-operating curve (ROC) analysis and/or logistic regression. There is limited evidence of clinical utility, i.e., that using a protein biomarker test will change treatment decisions and improve subsequent outcomes that matter to the patient such as mortality, morbidity, or quality of life.

Promotion of greater diversity and inclusion in clinical research of historically marginalized groups (e.g., People of Color [African-American, Asian, Black, Latino and Native American]; LGBTQIA (Lesbian, Gay, Bisexual, Transgender, Queer, Intersex, Asexual); Women; and People with Disabilities [Physical and Invisible]) allows policy populations to be more reflective of and findings more applicable to our diverse members. While we also strive to use inclusive language related to these groups in our policies, use of gender-specific nouns (e.g., women, men, sisters, etc.) will continue when reflective of language used in publications describing study populations.

4KSCORE™ TEST (OPKO LAB)

The 4Kscore™ test, also referenced in the literature as the four-kallikrein panel, is a blood test that generates a risk score for the probability for finding high-grade prostate cancer (defined as Gleason score ≥7) if a prostate biopsy were performed. The intended use of the test is to aid in the decision of whether or not to proceed with a prostate biopsy. The test algorithm combines the measurement of four prostate specific kallikreins (total prostate-specific antigen [tPSA], free PSA [fPSA], intact PSA [iPSA] and human kallikrein 2 [hK2]), which are combined in an algorithm with patient age, digital rectal exam (DRE) (nodules or no nodules), and whether the patient has had a prior negative prostate biopsy. A kallikrein is a subgroup of enzymes that cleave peptide bonds in proteins. The iPSA and hK2 tests are immunoassays that employ distinct mouse monoclonal antibodies. The test is not intended to be used in patients with a previous diagnosis of prostate cancer, a patient who has had a DRE in the previous four days, a patient who has received 5-alpha reductase inhibitor therapy in the previous six months, or a patient who has undergone any procedure or therapy to treat symptomatic benign prostatic hypertrophy in the previous six months.

Mi (2021) performed a systematic review and meta-analysis of studies reporting the diagnostic accuracy of the 4K score to detect high-grade prostate cancer using cutoff values of 7.5% to 10%.[1] Pooled analysis found acceptable diagnostic accuracy, with a sensitivity of 90% (95% confidence interval [CI] 86% to 92%), specificity of 44% (95% CI 36% to 52%) and an area under the curve (AUC) of 0.81 (95% CI 0.77 to 0.84). However, significant heterogeneity among the included studies lowered confidence in the results.

Russo (2017) performed a systematic review of studies that evaluated the diagnostic accuracy of the 4Kscore™ test in patients undergoing biopsy with a PSA level between 2 ng/mL and 20 ng/mL.[2] Twenty-eight studies were included. Results of the DRE were not described. The

negative predictive value (NPV) to exclude any type of cancer ranged from 28% to 64%. The NPV of the 4Kscore™ test to exclude high-grade (Gleason score ≥7) cancer ranged from 95% to 99%.

Vickers (2017) reported results from an individual patient data meta-analysis from 2,891 men from eight cohorts previously using the four-kallikrein panel.[3] The authors evaluated the predictive value for high grade (Gleason 7+) cancer in a subgroup of men with either positive digital rectal exam or prostate-specific antigen (PSA) 10 to 25 ng/mL. The fixed-effects discrimination of the kallikrein model was 0.84 vs 0.69 (difference 0.128, 95% CI 0.098 to 0.159) and 0.82 vs 0.72 (difference 0.092, 95% CI 0.069 to 0.115) for the DRE and PSA groups, respectively. The authors described clinical net benefit with reduction in biopsy rates, and small number of high-grade cancers.

Verbeek (2019) conducted a retrospective comparison of the discriminatory ability of the 4Kscore™ compared to the Rotterdam Prostate Cancer Risk Calculator (RPCRC).[4] The cohort included 2,872 men with PSA >3.0 from the European Randomized Study of Screening for Prostate Cancer Rotterdam. The 4K panel was measured in frozen serum samples. The AUCs were similar, with an AUC of 0.88 for the 4K score and 0.87 for the RPCRC (p=0.41). Addition of the 4K score to the RPCRC had a modest, though statistically significant improvement in discriminatory ability with an AUC of 0.89. A limitation of this study is that men were included who had PSA outside of the levels of interest, which would be between 3 and 10 ng/ml.

A 2015 study by the 4Kscore™ investigators assessed the ability of the four-kallikrein panel to predict high-grade cancer at ten-core prostate biopsy in 4,765 men in the ProtecT study.[5] Cryopreserved blood from men with elevated PSA (≥3.0ng/mL) was tested to predict any-grade or high-grade (Gleason score≥7) prostate cancer. AUC for the four kallikreins was 0.72 (95% CI 0.70 to 0.73) vs 0.63 (95% CI 0.62 to 0.65, p<0.001) for PSA and age alone for any-grade cancer, and 0.82 (95% CI 0.80 to 0.84) vs 0.74 (95% CI 0.72 to 0.76, p<0.001) for high-grade cancer. Using a cutoff of 6% risk of high-grade cancer, the study determined that 428 out of 1000 men could avoid biopsy. The clinical utility of this test, i.e. if the results influenced treatment decisions was not addressed. The authors concede that further evaluation of this panel is needed in prospective studies that test fresh samples in a clinical setting (as opposed to a research lab as performed in this study). Other recent European retrospective studies have found similar results in terms of the ability of the 4Kscore™ test to predict high grade cancer when the referral criteria were expanded to men who had elevated PSA (≥3 ng/ml), low %free PSA (<20%), or suspicious DRE.[6]

The performance of the 4Kscore™ test was validated in a total of 1,012 patients who were enrolled from October 2013 to April 2014 in a blinded, prospective study at 26 urology centers in the United States.[7] Enrollment into the study was open to all men who were scheduled for a prostate biopsy, regardless of age, PSA level, DRE or prior prostate biopsy. Each patient underwent a TRUS-guided prostate biopsy of at least 10 cores. A blinded blood sample that was collected prior to biopsy was sent to OPKO Lab for measurement of the four kallikrein markers. The results of the kallikrein markers, prostate biopsy histopathology, patient age, DRE and prior biopsy status were unblinded and analyzed. The biopsy was negative in 54% of cases (n=542), showed low-grade (all Gleason grade 6) prostatic cancer in 24% (n=239) and high-grade cancer in 23% (n=231). The statistical analysis of the 4Kscore™ test clinical data had an AUC of 0.82 for the detection of high-grade prostate cancer; the AUC for all patients

using tPSA, age, DRE and prior biopsy was 0.76. Limitations of the study include lack of standard criteria for biopsy referral and lack of central laboratory used for histopathology.

Based on the US trial, OPKO has established assay specifications, available on the company website, for two of the four proteins, iPSA and hK2 for biopsy negative (median 0.416ng/mL and 0.069ng/mL, respectively), low-grade disease (Gleason=6) (median 0.469ng/mL and 0.081ng/mL, respectively) and high-grade disease (Gleason ≥ 7) (median 0.511 and 0.107ng/mL, respectively). They also have published precision values for iPSA (0.01 to 0.10 ng/mL coefficient of variation [CV] ≤ 15%, 0.11 to 1.0 ng/mL CV ≤ 8%, 1.1 to 15 ng/mL CV ≤ 5%) and hK2 (0.01 to 0.10 ng/mL CV ≤ 10%, 0.11 to 1.0 ng/mL CV ≤ 8%, 1.1 to 8 ng/mL CV ≤ 10%), thereby demonstrating the analytic validity of the test. These values have been previously determined for the other two prostate-specific kallikreins, tPSA and fPSA, with commercial assays approved for use in human diagnostics by the FDA. Based on the US prospective trial and several retrospective European trials, the test has demonstrated the ability to detect high-grade cancer in specific populations (i.e., men with high PSA and/or men already scheduled for biopsy). The potential of the 4Kscore™ test to reduce biopsy in patients whose biopsy samples did not indicate high-grade cancer was also evaluated. The investigators reported sensitivity, specificity, positive and negative predictive value for four different thresholds investigated for biopsy reduction: ≥6.0%, 9%, 12% and 15% probability of high-grade cancer, thereby demonstrating the test's clinical validity. Additional prospective studies are needed to establish the clinical utility of this test.

Prior to the US trial, this group had conducted multiple studies predicting the use of the test in patient cohorts from the European Randomized Study of Prostate Cancer (ERSPC).[8-12] The majority of these studies were retrospective in nature, mainly assaying cryopreserved blood samples previously collected. In one of the studies, 392 men with high PSA (≥3.0 ng/mL) who underwent radical prostatectomy were screened for the four kallikrein markers to see if the test could distinguish between pathologically insignificant and aggressive disease when used in conjunction with clinical predictors (age, stage, PSA, biopsy findings). The AUC for the clinical predictors alone was 0.81, while using the clinical predictors in conjunction with the 4Kscore™ test improved the AUC to 0.84. Both of which are significantly better at predicting aggressive cancer than total PSA alone (AUC 0.68).[13] The limitations of this study are mainly in its design: retrospective in nature, using cryopreserved sample and relying on six-core biopsies, and not the 10- to 12-core currently recommended for grading accuracy.

Konety (2015) reported on the results of a survey of 35 U.S. urologists identified through the 4Kscore™ database at OPKO Lab as belonging to practices that were large users of the test.[14] All 611 patients of participating urologists to whom men were referred for abnormal PSA level or DRE and had a 4Kscore™ test were included. Urologists, who received the 4Kscore™ as a continuous risk percentage, were retrospectively asked about their plans for biopsy before and after receiving the test results and whether the 4Kscore™ test results influenced their decisions. The physicians reported that the 4Kscore™ results influenced decisions in 89% of men and led to a 64.6% reduction in prostate biopsies. The 4Kscore™ risk categories (low-risk: <7.5%, intermediate risk: 7.5%-19.9%, high-risk: ≥20%) correlated highly ($p<0.001$) with biopsy outcomes in 171 men with biopsy results.

Bhattu (2021) conducted a retrospective exploratory analysis using data from the two previously published validation studies to determine test performance with a cut-off of 7.5% as the indication to proceed with biopsy.[15] A major limitation of the validation studies was the inclusion of patients outside the indeterminate range of PSA. Although this study reported test

characteristics in the subgroup of patients with PSA between 3 and 10, it was limited by its retrospective design.

Punnen (2018) reported on a second prospective validation study of the 4Kscore test conducted at eight US Veterans Affairs hospitals from July 2015 to October 2016.[16]https://www.evidencepositioningsystem.com/mpp_meeting/mpp_pub_final/_blank One aim of the study was to evaluate test performance in African American men; of 366 men enrolled and evaluated, 205 (56%) were African American. In a comparative analysis, there was no difference in test performance in African American and non-African American men (p=0.32).

A small retrospective study in Spain has also evaluated the 4Kscore™, along with the Prostate Cancer Prevention Trial Risk Calculator 2.0 and the European Research Screening Prostate Cancer Risk Calculator in 51 patients undergoing a prostate biopsy.[17] According to the authors, all of the models assessed showed good discriminative ability for high-grade prostate cancer, but this study was limited by the retrospective design and small sample size.

Another study examined the use of the 4Kscore™ in higher-risk patients with either a positive DRE or PSA 10-25 ng/ml.[18] This was a meta-analysis of individual patient data from 2,891 subjects, collected from eight cohorts. The authors reported that the addition of the kallikrein test added to the discriminative power of their model, but this has not been replicated and the clinical utility of using the test in this manner has not been assessed prospectively. A similar study evaluated the use of the four kallikrein markers to predict recurrence after prostatectomy in very-high-risk men and did not see a significant association after adjustment for Kattan risk, and GPSM (Gleason, PSA, seminal vesical, and margin status) score.[19]

AUTOANTIBODIES AND APIFINY® (ARMUNE BIOSCIENCE)

Nakajima (2017) reported results from a blind, prospective, single institution, pilot study comparing levels of serum PSA, PSA autoantibodies (AAPSA), Gal-3, and Gal-3 autoantibodies (AAGal-3).[20] The authors sought to 1) determine the expression levels of AAPSA, Gal-3, and AAGal-3 as diagnostic accompaniments of the PSA test, and 2) examine the relationship between PSA and AAPSA and between Gal-3 and AAGal-3 along with the clinical status the study participants. Ninety-five men ≥18 were classified into five groups: healthy controls with no history of invasive cancer (Group 1); newly diagnosed patients with intact prostate cancer (Group 2); patients who had no evidence of disease recurrence post local therapy (Group 3); patients with rising PSA after local therapy (Group 4); or patients with metastatic prostate cancer (Group 5). Customized ELISA plates were developed for autoantibody detection. Using Spearman's rank correlation (rho), negative correlations were observed between PSA and AAPSA levels among all 95 men combined (rho -0.321, p=0.0021, fitted slope -0.288, p=0.0048), and in metastatic patients (rho -0.472, p=0.0413, fitted slope -1.145, p=0.0061). Results from least squares linear regression modeling indicated that AAPSA and AAGAL-3 are prevalent in men. Given the relationship observed, PSA level of expression by AAPSA may influence PSA testing accuracy. Overall, this evidence suggests larger diagnostic trials are needed to further evaluate the importance of these potential autoantibody markers.

Schipper (2015) identified eight autoantibodies associated with prostate cancer in a case-control study of men 40 to 70 years old with prostate cancer and PSA levels between 2.5 ng/mL and 20 ng/mL, compared to healthy men 25 to 40 years of age with PSA levels less

than 1.0 ng/mL.[21] When the algorithm was applied to an independent validation set, the AUC was 0.69 (95% CI, 0.62 to 0.75).

Wang (2005) suggested that autoantibodies against peptides derived from prostate-cancer tissue could be used as the basis for a screening test for prostate cancer.[22] The authors developed and used phage protein microarrays to analyze serum samples from 119 patients with prostate cancer and 138 controls. The training set was additionally validated against an independent group of 128 serum samples (60 from prostate cancer patients, and 68 from controls). Using a 22-phage-peptide detector, 88.2 percent specificity (95% CI 0.78 to 0.95) and 81.6 percent sensitivity (95% CI 0.70 to 0.90) discriminated between the group with prostate cancer and the control group. Against PSA, the panel of peptides performed better at distinguishing between the group with prostate cancer and the control group (AUC for the autoantibody signature 0.93, 95% CI 0.88 to 0.97; AUC for PSA 0.80, 95% CI 0.71 to 0.88). Logistic-regression analysis determined that the phage-peptide panel provided additional discriminative power over PSA ($p<0.001$). The authors concluded this early phase validation can be used to detect prostate cancer, however, additional multi-institutional studies are needed.

EXODX PROSTATE (INTELLISCORE)

Tutrone (2020) reported a trial that evaluated the effect of ExoDx Prostate on the decision to biopsy.[23] Thise multicenter, prospective, blinded RCT was conducted in partnership with CareFirst BlueCross/BlueShield of Maryland and included 1094 men with a PSA 2 to 10 ng/ml who were considered for prostate biopsy based on clinical criteria. All patients had the test, but only patients randomized to the ExoDx Prostate arm received the test results. The primary outcome of the study was to determine if ExoDX Prostate could reduce initial biopsies. The secondary endpoint was the successful diagnosis of high-grade prostate cancer. A total of 942 patients (86.1%) had complete data and usable samples. In the ExoDx Prostate arm, 93 patients received low risk test results and 106 patients (23%) received recommendations to defer biopsy. High risk ExoDx Prostate scores led to a recommendation for biopsy in 87% of the 365 ExoDx Prostate positive patients. Compliance with a recommendation for biopsy was 72% in the ExoDx Prostate arm compared to about 40% in the control arm, leading to increased biopsy rates in the ExoDx Prostate arm (58%) compared to controls (39%). In African-American patients, who represented 23% of the patient population, 91% had high risk scores. The study did not meet its primary endpoint. The main effect of the test was to increase biopsies with an increase in the number of at least Grade Group 2 cancers, but there was also an increase in the number of men biopsied who had no cancer or low grade cancer compared to the control arm. Additional limitations of the study are the inclusion of men with very low PSA (2 ng/ml) and the lack of information on what screening had preceded the referral for biopsy. It is unclear if the standard of care of repeat PSA and percent free PSA (%fPSA) were assessed prior to the decision to biopsy, if controls received this standard of care, or if the test was intended as a replacement for repeat PSA and %fPSA.

Tutrone (2023) reported on a retrospective outcome analysis follow-up study two and one-half years after the initial 2020 study reported above.[24] Of the original 1094 cohort, 833 patients had complete follow-up data at 2.5 years. In this analysis, patients returned to routine standard of care after enrollment in the clinical utility trial, and a retrospective outcome analysis was conducted. The average time from ExoDX Prostate testing to the first biopsy was significantly longer in the low-risk ExoDX Prostate arm (216 days) compared to high-risk ExoDX Prostate arm (68.7 days; $p <.001$) and when compared to low-risk ExoDX Prostate patients in the

standard of care arm (79.4 days; p <.001). In the ExoDx Prostate arm, low-risk patients had significantly fewer biopsies than high-risk patients (44.6% vs 79.0%, p<.001); in the standard of care arm the decision to defer was independent of ExoDx Prostate score and, as a result, did not differ between low-risk and high-risk scores. Patients in both arms with low-risk ExoDx Prostate scores had lower rates of high-grade prostate cancer at 2.5 years than high-risk ExoDx Prostate score patients (7.9% vs. 26.8%; p<.001), and the ExoDx Prostate arm discovered 21.8% (106 vs 87) more high-grade prostate cancer than the standard of care arm. Limitations of this interim analysis mimic limitations that were described in the above study; the study was also retrospective in nature.

DECIPHER BIOPSY AND DECIPHER PROSTATE RP

The Decipher Biopsy test evaluates malignant prostate tissue for the expression of 22 RNA biomarkers to predict the risks of high-grade disease, metastasis in 5 years, and death from prostate cancer in 10 years. Decipher Prostate RP test evaluates tumor tissue for the expression of 22 RNA biomarkers in order to predict the 5-year risk for metastasis after radical prostatectomy.

Clinical Validity

Nguyen (2023) published a validation study to determine the independent prognostic ability of Decipher on 265 malignant prostate specimens for distant metastasis, prostate-cancer specific mortality, and overall survival.[25] The specimens were from patients enrolled in any of three Radiation Therapy Oncology Group (RTOG) randomized controlled trials. After a median follow-up of 11 years, Decipher scores were an independent predictor of distant metastasis (sHR, 1.22; 95% CI, 1.09-1.36), prostate-cancer specific mortality (sHR, 1.23; 95% CI, 1.09-1.39), and overall survival (HR, 1.12; 95% CI, 1.05-1.20) after adjusting for age PSA, Gleason score, cT stage, and randomized treatment arm. Limitations of the study include the specimens represent a minority of the participants in the three RCTs. Additionally, the quality of the specimens may have been compromised to their age (15-25 years).

Spratt (2023) applied the Decipher Biopsy test to analyze pre-treatment biopsy samples in men with intermediate-risk prostate cancer who were enrolled in an RTOG clinical trial.[26] After a median follow-up of 12.8 years analysis of 215 samples found that the Decipher Biopsy test was independently prognostic of disease progression (p=0.04), biochemical failure (p<0.001), distant metastasis (p=0.01), and prostate cancer-specific mortality (p<0.001).

ONCOTYPE DX® AR-V7 NUCLEAR DETECT

The Oncotype DX® AR-V7 Nuclear Detect is a liquid biopsy test that measures androgen receptor gene activity in circulating tumor cells to assess whether resistance to endocrine therapy is present in the setting of metastatic castration resistant prostate cancer.

Clinical Validity

Two clinical validity studies were identified that did not include the test's developmental cohort. Scher (2018) reported results of a blinded validation study including 142 samples from patients with histologically confirmed, progressing metastatic castration-resistant prostate cancer (mCRPC) from three centers in the U.S. and the United Kingdom from 2012 to 2016.[27] The samples were collected prior to the administration of second-line or greater ARS inhibitors or taxanes. Armstrong (2019) reported results of the PROPHECY trial, a prospective validation

study of AR-V7 detection in 107 samples from men with high-risk mCRPC starting abiraterone or enzalutamide treatment.[28]

In the study by Scher (2018), the median follow-up time in surviving men was not provided. Sixty-eight men were still in the risk set at 12 months.[27] Numerically, men treated with ARS inhibitors had the longest overall survival (OS) if they were AR-V7-negative and had the shortest OS if they were AR-V7-positive. The unadjusted hazard ratio for OS for ARS inhibitors vs taxanes was statistically significantly greater than one (favoring ARS inhibitors) in the AR-V7-negative men, while there was no statistically significant difference in OS (but with an unadjusted HR favoring taxanes) in AR-V7-positive men. A test of interaction for AR-V7 status by treatment was not provided. The analysis was further stratified by a binary prognostic risk score (high vs low) developed from the training cohort and including clinical biomarkers. However, the additional stratification resulted in the group that was AR-V7-positive and receiving ARS inhibitors including fewer than ten men for both high- and low-risk.

In the study by Armstrong (2019), detection of AR-V7 in circulating tumor cells was associated with shorter progression-free survival and OS.[28] However, patients that were positive for AR-V7 still received a clinical benefit from taxane chemotherapy.[29]

Clinical Utility

Graf (2019) published an industry-sponsored study evaluating the potential clinical utility of the test using 255 samples from 193 patients with mCRPC.[30] Physicians were blinded to the AR-V7 status and treated patients with either an ARS inhibitor or a taxane. Physicians tended to choose a taxane over an ARS inhibitor when patients had more advanced disease or had received an ARS inhibitor as a first-line treatment. After accounting for this, there was no significant difference in OS based on the treatment. Patients that had a positive AR-V7 test were reported to have superior survival with taxane treatment compared to ARS inhibitor treatment (p=0.041), while AR-V7-negative patients had superior survival with ARS inhibitor treatment. However, the authors noted that overlapping survival curves limited the interpretation of these results. A significant interaction was seen between AR-V7 status and treatment for survival in multivariable models.

ONCOTYPE DX PROSTATE

The Oncotype DX Prostate assay includes 5 reference genes and 12 cancer genes that represent 4 molecular pathways of prostate cancer oncogenesis: androgen receptor, cellular organization, stromal response, and proliferation. The assay results are combined to produce a Genomic Prostate Score (GPS), which ranges from 0 to 100. Higher GPS scores indicate more risk. The evidence from 5 studies on clinical validity for Oncotype DX Prostate has suggested the GPS can reclassify a patient's risk of recurrence or risk of adverse pathology at RP based on a biopsy specimen.[31-33] One study provided a figure with data on the reclassification of disease-specific survival using NCCN and GPS.[34]\\slcnas10\datapdx7\groups\1. Policy Work\Laboratory\lab69\Policy drafts\2023 10_blank Ten-year prostate cancer death appears to be close to zero for men who are NCCN low-risk regardless of GPS score, indicating little useful reclassification of NCCN low-risk men based on GPS. For NCCN intermediate-risk, the risk of prostate cancer death ranges from approximately 0 for a GPS of less than 40 to close to 40% for a GPS of 100. It is unclear how many of the men with a GPS less than 40 were NCCN favorable intermediate-risk. Moreover, generalizing this evidence to a true active surveillance population, for which most in the study would be otherwise eligible, is difficult because all patients had elective RP. Thus, the findings do not reflect a clinical scenario of predicting the

risk of 10 year disease-specific survival in untreated patients under active surveillance. Some publications also lacked precision estimates for important variables such as risk estimates for recurrence or AUC estimates.

No direct evidence of clinical utility was found. The chain of evidence is also incomplete. Klein (2014) decision-curve analyses have suggested the potential for the combined GPS and CAPRA score data to help patients make decisions based on relative risks associated with immediate treatment or deferred treatment (ie, active surveillance).[31] This would reflect the clinical utility of the test. However, it is difficult to ascribe possible clinical utility of Oncotype DX Prostate in active surveillance because all patients regardless of clinical criteria elected RP within 6 months of diagnostic biopsy. Moreover, the validity of using tumor pathology as a surrogate for cancer-specific death is unclear. Reports from validation studies lack precision estimates for important variables such as risk estimates for recurrence.

The ProtecT trial showed 99% 10-year disease-specific survival in all 3 treatment groups: active surveillance, RT, and RP, including predominately low-risk but also some intermediate-risk men.[35] AUA has recommended active surveillance in low-risk men. The low mortality rate estimated with tight precision makes it unlikely that a test intended to identify a subgroup of low-risk men with a net benefit from treatment instead of active surveillance would find such a group.

The PIVOT trial preplanned subgroup analysis showed a reduction in mortality for RP compared with observation for men at intermediate-risk; AUA has recommended RT or RP for such men.[36] For intermediate-risk men, a test designed to identify men who can receive active surveillance instead of RP or RT would need to show very high NPV for disease-specific mortality at 10 years and improvement in prediction compared with existing tools used to select such men. For these men to forgo evidence-based beneficial treatment, there would have to be a very high standard of evidence for the clinical validity of the test.

PROMARK™ (METAMARK GENETICS)

The protein biomarker test, Promark™ (Metamark Genetics, Cambridge, MA), is an automated quantitative imaging method to measure protein biomarkers by immunofluorescent staining in defined areas in intact formalin-fixed paraffin-embedded biopsy tissue, in order to provide independent prognostic information to aid in the stratification of patients with prostate cancer to active surveillance or therapy.

Analytic Validity

Shipitsin (2014) reported on the analytic validity of the automated quantitative multiplex immunofluorescence in situ imaging approach assessing: the ability of the test to quantitate markers in a defined region of interest (tumor vs surrounding benign), tissue quality control, assay staining format and reproducibility.[37] To evaluate tissue sample quality, they assessed the staining intensities of several protein markers in benign tissue and using these, categorized prostate cancer tissue blocks into four quality groups, of which the best two groups were used to generate tumor microarray blocks; 508 prostatectomy specimens were used and of these, 418 passed quality testing and were used for the tumor microarray blocks. For intra-experiment reproducibility, two consecutive sections from a prostate tumor test microarray block were stained in the same experiment and scatter plots compared the mean values of the staining intensities; signals from consecutive sections showed R^2 correlation values above 0.9 and differences in absolute values typically less than 10%.

Clinical Validity

Blume-Jensen reported on a study of 381 biopsies matched to prostatectomy specimens which were used to develop an eight-biomarker proteomic assay to predict prostate final pathology on prostatectomy specimen using risk scores.[38] Biomarker risk scores were defined as favorable if less than or equal to 0.33 and nonfavorable if greater than 0.80 with a possible range between 0 and 1 based on false negative and false-positive rates of 10% and 5%, respectively. The risk score generated for each patient was compared with two current risk stratification systems, National Comprehensive Cancer Network (NCCN) guideline categories and the D'Amico system. Results from the study showed that, at a risk score of less than or equal to 0.33, the predictive value of the assay for favorable pathology in very low- and low-risk NCCN and low-risk D'Amico groups were 95%, 81.5%, and 87.2%, respectively, while the NCCN and D'Amico risk classification groups alone had predictive values of 80.3%, 63.8%, and 70.6%, respectively. The positive predictive value for identifying favorable disease with a risk score of less than or equal to 0.33 was 83.6% (specificity, 90%). At a risk score of greater than 0.80, 77% had nonfavorable disease. Overall, 39% of the patients in the study had risk scores less than or equal to 0.33 or greater than 0.8, 81% or which were correctly identified with the eight-biomarker assay. Of the patients with intermediate risk scores (>0.33 to ≤0.8), 58.3% had favorable disease. The performance of the assay was evaluated on a second blinded study of 276 cases to validate the assay's ability to distinguish "favorable" pathology (defined as Gleason score on prostatectomy less than or equal to 3+4 and organ-confined disease) versus "nonfavorable" pathology (defined as Gleason score on prostatectomy greater than or equal to 4+3 or non-organ-defined disease). The second validation study separated favorable from nonfavorable pathology (AUC 0.68, $p<0.001$, odds ratio 20.9).

Clinical Utility

An industry-sponsored simulation study published in 2015 modeled the effects of using the ProMark™ test on 60-year-old patients with early prostate cancer (Gleason 3+3 and 3+4).[39] This study projected that the use of the test in this population could improve patient outcomes and reduce costs, but this has not been replicated in actual patients.

No published prospective studies on the clinical utility of the ProMark™ test were identified, therefore the current data are insufficient to establish the analytic and clinical validity and clinical utility of the ProMark™ test.

PANGIA PROSTATE

No published studies evaluating the PanGIA Prostate test were identified.

PROLARIS

The Prolaris® Prostate Cancer Prognostic Test calculates a risk score for prostate cancer-specific mortality and the 10-year risk of metastatic disease in men with prostate cancer. The Prolaris® algorithm combines clinical and pathologic factors with the RNA expression level of 31 cell cycle progression genes and 15 housekeeper genes.

Clinical Validity

Cuzick (2012) examined the Prolaris® prognostic value for prostate cancer death in a conservatively managed needle biopsy cohort.[40] Cell cycle expression data were read blind to

all other data. Patients were identified from 6 cancer registries in Great Britain and were included if they had clinically localized prostate cancer diagnosed by needle biopsy between 1990 and 1996; were younger than 76 years at diagnosis; had a baseline PSA measurement; and were conservatively managed. Potentially eligible patients who underwent RP, died, showed evidence of metastatic disease within 6 months of diagnosis, or received hormone therapy before diagnostic biopsy were excluded. The original biopsy specimens were retrieved and centrally reviewed by a panel of expert urologic pathologists to confirm the diagnosis and, where necessary, to reassign Gleason scores.[41] Of 776 patients diagnosed by needle biopsy and for which a sample was available to review histology, needle biopsies were retrieved for 527 (68%), 442 (84%) of which had adequate material to assay. From the 442 samples, 349 (79%) produced a CCP score and had a complete baseline and follow-up information, representing 45% of 776 patients initially identified. The median follow-up time was 11.8 years. Ninety deaths from prostate cancer occurred within 2799 person-years.

The primary, unadjusted analysis found a 1-unit increase in CCP score associated with a 2-fold increase (HR=2.02) in the risk of dying from prostate cancer. In a multivariate model including CCP, Gleason score, and PSA level, the adjusted HR for a 1-unit increase in CCP score was 1.65. However, changes in HRs may not reflect meaningful changes in absolute risk. Kaplan-Meier analyses of the 10-year risk of prostate cancer death are stratified by CCP score groupings. It appears that there might be a large change in risk for scores below 2 compared with above 2, but no CIs are reported so it is impossible to draw conclusions. Measures that would suggest improved discriminatory ability (e.g., area under the curve [AUC] or reclassification) compared with an existing nomogram were not reported in Cuzick (2012). The authors did not provide evidence that the test could correctly reclassify men initially at high-risk to lower risk to avoid overtreatment, or conversely, correctly reclassify those initially at low-risk to high-risk to avoid undertreatment.

Cuzick (2015) examined 3 U.K. cancer registries from 1990 to 2003 to identify men with prostate cancer who were conservatively managed following needle biopsy, with follow-up through December 2012.[42] The authors stated that the samples did not overlap with Cuzick (2012). Men were excluded if they had undergone RP or RT within 6 months of diagnosis. A combination of the CCP and CAPRA scores (called the combined clinical cell cycle risk [CCR] score) was used to predict prostate cancer death. There were 989 men who fit eligibility criteria; CCP scores were calculable for 761 (77%), and combined CCP and clinical variables were available for 585 (59%). Median age at diagnosis was 70.8 years, and the median follow-up was 9.5 years. The prostate cancer mortality rate was 17% (n=100), with 29% (n=168) dying from competing causes. Higher CCP scores were associated with increased 10-year risk of prostate cancer mortality: 7% (CCP score <0), 15% (CCP score 0-1), 36% (CCP score 1-2), and 59% (CCP score >2). For the CCR score, the HR for 10-year prostate cancer mortality increased to 2.17 (95% CI, 1.83 to 2.57). The C statistic for the CAPRA score was 0.74; adding the CCP score increased the C statistic to 0.78 (no CIs for the C statistic were reported). Estimates with CIs for 10-year death rates for the CCR score are provided; however, the predictions appear to cross 100% for CCR of about 6. Treatment changes after 6 months were documented in only part of 1 of the 3 cohorts; at 24 months, 45% of the men in this cohort had undergone RT or prostatectomy.

Based on the validation studies published by Cuzick[40, 42], there is an association between CCP and the risk of death on the relative scale but does not necessarily indicate that there is a difference in absolute risk that would be meaningful for clinical decision making. The data

provided raises several concerns. Even the lowest risk group shown in Cuzick (2012) has a 10-year death rate of 20%, which may be explained by the population characteristics (ie, not PSA screen-selected, a third with Gleason >7 score and half with PSA level >25 ng/mL); however, a death rate of 20% is unlikely to be low enough to forgo immediate treatment.[40]

Lin (2018) also reported reclassification of men using the CCR score threshold (0.8) in a group of 19,215 consecutive patients whose biopsies were sent for Prolaris® testing between 2013 and 2016[43]. 14,685 of the 19,215 men had a low or favorable intermediate risk by NCCN risk classification. However, the authors said that only 8177 of the 19,215 men met NCCN criteria for active surveillance based on low/favorable intermediate risk clinicopathologic features. It is not clear why fewer men were categorized as meeting NCCN low/favorable intermediate criteria for the purposes of demonstrating reclassification and, therefore, it is not clear how many of the 14685 men at low- or intermediate-risk by NCCN criteria would have been reclassified using the CCR threshold.

Clinical Utility

Three decision-impact studies have assessed the potential impact of Prolaris® on physicians' treatment decisions in patients.[44-46] The authors of these studies suggested that their findings supported the "clinical utility" of the test, based on whether the results would lead to a change in treatment. Pathology results were not reported for these studies. Given the lack of established clinical validity and no reported outcomes, it is uncertain whether any treatment changes were clinically appropriate.

Section Summary

For individuals who have clinically localized untreated prostate cancer who receive Prolaris®, the evidence includes retrospective cohort studies of clinical validity using archived samples in patients of mixed risk categories. Relevant outcomes include overall survival (OS), disease-specific survival, quality of life (QOL), and treatment-related morbidity. For the low-risk group, the Prostate Testing for Cancer and Treatment trial showed 99% 10-year disease-specific survival in mostly low-risk patients receiving active surveillance. The low mortality rate estimated with tight precision makes it unlikely that a test intended to identify a subgroup of low-risk men with a net benefit from immediate treatment instead of active surveillance would find such a group. For the intermediate-risk group, the evidence of improved clinical validity or prognostic accuracy for prostate cancer death using Prolaris® Cell Cycle Progression score in patients managed conservatively after a needle biopsy has shown some improvement in areas under the receiver operating characteristic curve over clinicopathologic risk stratification tools. There is limited indirect evidence for potential clinical utility. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have localized prostate cancer treated with RP who receive Prolaris®, the evidence includes retrospective cohort studies of clinical validity using archived samples. Relevant outcomes include OS, disease-specific survival, QOL, and treatment-related morbidity. No direct evidence is available to support the clinical utility of Prolaris® for improving net outcomes of patients with localized prostate cancer following RP. The chain of evidence is also incomplete. Decision-curve analysis did not provide convincing evidence of meaningful improvement in net benefit by incorporating the cell cycle progression (CCP) score. Evidence of improved clinical validity or prognostic accuracy for prostate cancer death using the Prolaris® Cell Cycle Progression score in patients after prostatectomy has shown some

improvement in areas under the receiver operating characteristic curve over clinicopathologic risk stratification tools. Although Prolaris® CCP score may have an association with biochemical recurrence (BCR), disease-specific survival outcomes were reported in only 1 analysis. A larger number of disease-specific survival events and precision estimates for discrimination measures are needed. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

SELECTMDx FOR PROSTATE CANCER

SelectMDx for Prostate Cancer is a urine-based test that calculates a risk score for high-grade prostate cancer based on *HOXC6* and *DLX1* mRNA expression levels and traditional risk factors.

Hendriks et al (2021) evaluated the SelectMDx test to detect high-grade prostate cancer in biopsy-naive men.[47] In total, 599 men in the Netherlands with PSA level of 3 ng/mL or greater scheduled for their initial biopsy were included in the study. All subjects underwent a multi-parametric magnetic resonance imaging (MRI) test and biopsy after urine sample and DRE were complete. The primary outcome was the detection rates of low- and high-grade prostate cancer and the number of biopsies avoided in four distinct diagnostic strategies:

1) SelectMDx test only
2) MRI only
3) SelectMDx test followed by MRI when SelectMDx test was positive (conditional strategy)
4) SelectMDx and MRI in all (joint strategy)

Decision curve analysis was performed to assess clinical utility. Overall, prevalence of high-grade prostate cancer was 31% (183/599). Thirty-eight percent of patients had negative SelectMDx tests in whom biopsy could be avoided. Decision curve analysis showed the highest net benefit for the MRI only strategy, followed by the conditional strategy at risk thresholds over 10%. Investigators also found that SelectMDx test led to a 35% reduction of overdetection of low-grade prostate cancer and could save 38% of MRIs, at the cost of missing 10% of high-grade prostate cancers compared to biopsy for all patients. However, the use of MRI alone in all patients to select for prostate biopsy had the highest net benefit as a prebiopsy stratification tool. No trials identified have compared health outcomes for patients managed with and without the SelectMDx for Prostate Cancer.

VA EVIDENCE SYNTHESIS PROGRAM REVIEW

The Veterans Health Administration published a systematic review that evaluated studies of three genomic classifier tests for patients with prostate cancer: Decipher, Oncotype, and Prolaris.[48] The review focused on three outcomes: risk classification, treatment recommendations, and key clinical outcomes at the time of prostate cancer diagnosis and after definitive initial treatment. While there is some evidence from observational studies that providers change treatment recommendations based on the risk classification result, this was not confirmed by the single RCT the authors noted. The review states that the tests may offer additional prognostic information and are potentially useful when treatment decisions are uncertain. However, the estimation of benefit from genomic classifier testing for prostate cancer risk stratification is limited by a lack of direct evidence of outcomes for patient

populations that have been treated with current care modalities. Further, the report notes the certainty of evidence for all three tests was either low or very low.

PRACTICE GUIDELINE SUMMARY

AMERICAN SOCIETY OF CLINICAL ONCOLOGY

In 2020, the American Society of Clinical Oncology (ASCO) published a guideline on molecular biomarkers in localized prostate cancer.[49] The guidelines state, "Currently, there are no strong data or expert guidelines to support active surveillance in otherwise healthy men with Grade Group 3 or higher cancer; therefore, we would consider the use of genomic biomarkers only in situations in which the assay result, when considered as a whole with routine clinical factors, is likely to affect a physician's recommendation or a patient's choice for surveillance versus treatment, but they should not be used routinely."

Specific recommendations included the following:

Molecular biomarkers to identify patients with prostate cancer who are most likely to benefit from active surveillance:

- Recommendation 1.1. Commercially available molecular biomarkers (i.e. Oncotype Dx Prostate, Prolaris, Decipher, and ProMark) may be offered in situations in which the assay result, when considered as a whole with routine clinical factors, is likely to affect management. Routine ordering of molecular biomarkers is not recommended (Type: Evidence based; Evidence quality: Intermediate; Strength of recommendation: Moderate).

- Recommendation 1.2. Any additional molecular biomarkers evaluated do not have sufficient data to be clinically actionable or are not commercially available and thus should not be offered (Type: Evidence based; Evidence quality: Insufficient; Strength of recommendation: Moderate).

Molecular biomarkers to diagnose clinically significant prostate cancer:

- Recommendation 2.1. Commercially available molecular biomarkers (i.e. Oncotype Dx Prostate, Prolaris, Decipher, and ProMark) may be offered in situations in which the assay result, when considered as a whole with routine clinical factors, is likely to affect management. Routine ordering of molecular biomarkers is not recommended (Type: Evidence based; Evidence quality: Intermediate; Recommendation: Moderate).

- Recommendation 2.2. Any additional molecular biomarkers evaluated do not have sufficient data to be clinically actionable or are not commercially available and thus should not be offered (Type: Evidence based; Evidence quality: Insufficient; Strength of recommendation: Moderate).

Molecular biomarkers to guide the decision of post prostatectomy adjuvant versus salvage radiation:

- Recommendation 3.1. The Expert Panel recommends consideration of a commercially available molecular biomarker (eg, Decipher Genomic Classifier) in situations in which the assay result, when considered as a whole with routine clinical factors, is likely to affect management. In the absence of prospective clinical trial data, routine use of

genomic biomarkers in the postprostatectomy setting to determine adjuvant versus salvage radiation or to initiate systemic therapies should not be offered (Type: Evidence based; Evidence quality: Intermediate; Strength of recommendation: Moderate).

- Recommendation 3.2. Any additional molecular biomarkers evaluated do not have sufficient data to be clinically actionable or are not commercially available and thus should not be offered (Type: Evidence based; Evidence quality: Insufficient; Strength of recommendation: Moderate).

AMERICAN UROLOGICAL ASSOCIATION AND SOCIETY OF UROLOGIC ONCOLOGY GUIDELINES

The America Urological Association and the Society of Urologic Oncology published a joint guideline on early detection of prostate cancer (2023)[50]. The guidelines include the following statements regarding urine and serum markers:

- Clinicians may use adjunctive urine or serum markers when further risk stratification would influence the decision regarding whether to proceed with biopsy. (Conditional Recommendation; Evidence Level: Grade C)

- After a negative biopsy, clinicians may use blood, urine, or tissue-based biomarkers selectively for further risk stratification if results are likely to influence the decision regarding repeat biopsy or otherwise substantively change the patient's management. *(*Conditional Recommendation; Evidence Level: grade C*)*

AMERICAN UROLOGICAL ASSOCIATION AND AMERICAN SOCIETY FOR RADIATION ONCOLOGY

The American Urological Association and American Society for Radiation Oncology published guidelines on clinically localized prostate cancer (2022).[51] The guidelines include the following statements on risk stratification:

1. Clinicians should use clinical T stage, serum PSA, grade group (Gleason score), and tumor volume on biopsy to risk stratify patients with newly diagnosed prostate cancer. (Strong recommendation; Evidence level: Grade B)

2. Clinicians may selectively use tissue-based genomic biomarkers when added risk stratification may alter clinical decision-making. (Expert opinion)

3. Clinicians should not routinely use tissue-based genomic biomarkers for risk stratification or clinical decision-making. (Moderate recommendation; Evidence level: Grade B)

NATIONAL COMPREHENSIVE CANCER NETWORK

National Comprehensive Cancer Network (NCCN) guidelines for early detection of prostate cancer (v.2.2024) recommend that any man with a PSA level greater than 3 ng/mL undergo further evaluation that includes consideration of biomarkers that improve the specificity of screening.[52] The guidelines also state:

> "Consider biomarkers and/or PSA density when deciding whether to avoid a biopsy in an individual with a negative multi-parametric MRI result. Biomarkers that improve the

specificity of detection are not, as yet, mandated as first-line screening tests in conjunction with serum PSA. However, there may be some patients who meet PSA standards for consideration of prostate biopsy, but for whom the patient and/or the physician wish to further define risk. Percent-free PSA may improve cancer detection. The probabiliby of high-grade cancer (Gleason score ≥ 3+4, Grade Group 2 or higher) may be further defined utilizing the Prostate Health Index (PHI), SelectMDx, 4Kscore, ExoDx Prostate Test, MyProstateScore (MPS), and IsoPSA. Extent of validation of these tests across diverse populations is variable. It is not known how such tests could be applied in optimal combination with MRI."

The NCCN guidelines for prostate cancer (v.1.2025), Principles of Risk Stratification and Biomarkers state, "Currently the primary method for personalization of treatment from localized to advanced prostate cancer is based on prognostic risk stratification, rather than the use predictive biomarkers."[53] Further, "It is acknowledged that there are methods of risk stratification with superior prognostic performance to NCCN risk groups. However, they have not been routinely reported in clinical trials. This limits the ability to provide evidence-based guideline treatment recommendations using these methods. Thus, the NCCN Guidelines continues to use NCCN categories and subgroups of risk as a framework." For clarity these tools are separated by type and category:

Type:

- Standard Tools: These include clinical and/or pathologic variables routinely collected to assign a patient to an NCCN category and/or subgroup. Examples include TNM stage, Grade Group, PSA, and metastatic volume of disease.
- Clinical and Pathologic Tools: These include clinical and/or pathologic tools that are generally derived from standard tools. Examples include multivariable models or nomograms, histologic variants, and PSA kinetics.
- Advanced Tools: These involve an additional test above what is collected to assign an NCCN category or subgroup. These may include, but are not limited to, germline or somatic tests, gene expression tests, digital histopathology-based tests, imaging, and circulating markers.

Category:

- Prognostic: Discriminates the risk of developing an oncologic endpoint (e.g., distant metastasis). The relative benefit of a treatment (i.e., the treatment effect or hazard ratio) is generally similar across a prognostic spectrum, although the absolute benefit of an intervention may vary by risk (i.e., number needed to treat [NNT]). Ideally, prognostic biomarkers independently discriminate and are associated with a clinically meaningful endpoint above and beyond standard tools relevant to that disease setting that ultimately helps guide a therapeutic decision.
- Predictive: Discriminates a difference in the relative benefit of a specific treatment for an oncologic endpoint. Ideally, predictive biomarkers have been demonstrated to measure a biomarker-treatment interaction that ultimately helps guide a therapeutic decision in the context of a randomized trial, specifically randomizing the treatment of interest.

SUMMARY

The research on how protein biomarkers related to prostate cancer can be used to improve health outcomes for patients is variable and incomplete. Some tests may be useful to predict risk in the diagnosis or prognosis of prostate cancer, however more research is needed to show how much these tests can add to the currently available tests, and what effects they have on treatment decisions and outcomes. Therefore, use of protein biomarker testing for risk assessment, diagnosis, prognosis, and management of prostate cancer is considered investigational.

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CODES

Codes	Number	Description
CPT	0021U	Oncology (prostate), detection of 8 autoantibodies (ARF 6, NKX3-1, 5'-UTR-BMI1, CEP 164, 3'-UTR-Ropporin, Desmocollin, AURKAIP-1, CSNK2A2), multiplexed immunoassay and flow cytometry serum, algorithm reported as risk score
	0228U	Oncology (prostate), multianalyte molecular profile by photometric detection of macromolecules adsorbed on nanosponge array slides with machine learning, utilizing first morning voided urine, algorithm reported as likelihood of prostate cancer
	0359U	Oncology (prostate cancer), analysis of all prostate-specific antigen (PSA) structural isoforms by phase separation and immunoassay, plasma, algorithm reports risk of cancer
	0376U	Oncology (prostate cancer), image analysis of at least 128 histologic features and clinical factors, prognostic algorithm determining the risk of distant metastases, and prostate cancerspecific mortality, includes predictive algorithm to androgen deprivationtherapy response, if appropriate
	0495U	Oncology (prostate), analysis of circulating plasma proteins (tPSA, fPSA, KLK2, PSP94, and GDF15), germline polygenic risk score (60 variants), clinical information (age, family history of prostate cancer, prior negative prostate biopsy), algorithm reported as risk of likelihood of detecting clinically significant prostate cancer
	81313	*PCA3*/KLK3 (prostate cancer antigen 3 [non-protein coding]/kallikrein-related peptidase 3 [prostate specific antigen]) ratio (eg, prostate cancer)
	81479	Unlisted molecular pathology procedure
	81539	Oncology (high-grade prostate cancer), biochemical assay of four proteins (Total PSA, Free PSA, Intact PSA, and human kallikrein-2 [hK2]), utilizing plasma or serum, prognostic algorithm reported as a probability score
	81599	Unlisted multianalyte assay with algorithmic analysis
	84999	Unlisted chemistry code
HCPCS	None	

Date of Origin: *October 2015*