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

Effective: April 1, 2023

Next Review: October 2023
Last Review: March 2023

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 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 indicate 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.

**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). 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. 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.

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. 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 ≤ 5%).
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). 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] 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. 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. 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.

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). 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. 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. 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.

**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.[23] 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 R² 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.[24] 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).[25] 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.

**ONCOTYPE DX® AR-V7 NUCLEUS DETECT**

**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.[26] 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.[27]

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.[26] 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.[27] However, patients that were positive for AR-V7 still received a clinical benefit from taxane chemotherapy.[28]

**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.[29] 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.

**PANGIA PROSTATE**

No published studies evaluating the PanGIA Prostate test were identified.

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**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.[30] 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 (e.g., 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).

NATIONAL COMPREHENSIVE CANCER NETWORK

National Comprehensive Cancer Network (NCCN) guidelines for early detection of prostate cancer (v.1.2022) recommend that any man with a PSA level greater than 3 ng/mL undergo workup for benign disease, repeat PSA, and digital rectal examination.\cite{31} The guidelines also state:

"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 probability 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 yet."

The prostate cancer diagnosis and management guidelines (v.1.2023) provide a table of tools and tests for prostate cancer risk stratification that does not include protein biomarker tests.\cite{32} The panel states that "the use of AR-V7 tests in circulating tumor cells can be considered to help guide selection of therapy in the post-abiraterone/enzalutamide metastatic CRPC [castration-resistant prostate cancer] setting."

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.


25. Roth JA, Ramsey SD, Carlson JJ. Cost-Effectiveness of a Biopsy-Based 8-Protein Prostate Cancer Prognostic Assay to Optimize Treatment Decision Making in Gleason 3 + 3 and 3 + 4 Early Stage Prostate Cancer. The oncologist. 2015;20(12):1355-64. PMID: 26482553


Castration-Resistant Prostate Cancer. *JCO precision oncology*. 2020;4. PMID: 33154984


### CODES

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<td>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</td>
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<tr>
<td>81599</td>
<td>Unlisted multianalyte assay with algorithmic analysis</td>
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<tr>
<td>84999</td>
<td>Unlisted chemistry code</td>
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<tr>
<td>HCPCS</td>
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*Date of Origin: October 2015*