

Protein Biomarkers for Screening, Detection, and/or Management of Prostate Cancer

Effective: January 1, 2019

Next Review: October 2019

Last Review: November 2018

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 have been proposed as a means to risk-stratify patients with prostate cancer to improve accuracy for determining who undergoes biopsy/rebiopsy and to guide treatment decisions.

MEDICAL POLICY CRITERIA

Protein biomarkers 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., Apifyn[®]);
- B. Kallikrein markers (e.g., 4Kscore[™] Test);
- C. Immunofluorescence markers (e.g., Promark[™])

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

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:

- Apifyn[®] (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.

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.

Vickers (2017) reported results from an individual patient data meta-analysis from 2,891 men from eight cohorts previously using the four-kallikrein panel.^[1] The authors evaluated the predictive value for high grade (Gleason 7+) cancer in a subgroup of men with either positive digital rectal exam or PSA 10 to 25 ng/mL. The fixed-effects discrimination of the kallikrein model was 0.84 vs 0.69 (difference 0.128, 95% confidence interval [CI] 0.098-0.159) 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.

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 4765 men in the ProtecT study.^[2] Cryopreserved blood from men with elevated PSA (≥ 3.0 ng/mL) was tested to predict any-grade or high-grade (Gleason score ≥ 7) prostate cancer. Area under the curve (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.^[3]

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.^[4] 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 \geq 7) (median 0.511 and 0.107ng/mL, respectively). They also have published precision values for iPSA (0.01 to 0.10 ng/mL CV \leq 15%, 0.11 to 1.0 ng/mL CV \leq 8%, 1.1 to 15 ng/mL CV \leq 5%) and hK2 (0.01 to 0.10 ng/mL CV \leq 10%, 0.11 to 1.0 ng/mL CV \leq 8%, 1.1 to 8 ng/mL CV \leq 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: \geq 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).^[5-9] 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 (\geq 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).^[10] 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.

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.^[11] 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 recent study examined the use of the 4Kscore in higher-risk patients with either a positive DRE or PSA 10-25 ng/ml.^[12] This was a meta-analysis of individual patient data from 2,891 subjects, collected from 8 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.

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).^[13] 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 (ρ), negative correlations were observed between PSA and AAPSA levels among all 95 men combined (ρ -0.321, $p=0.0021$, fitted slope -0.288, $p=0.0048$), and in metastatic patients (ρ -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.

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.^[14] 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 percent confidence interval, 0.78 to 0.95) and 81.6 percent sensitivity (95 percent confidence interval, 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 (area under the curve for the autoantibody signature, 0.93; 95 percent confidence interval, 0.88 to 0.97; area under the curve for PSA, 0.80; 95 percent confidence interval, 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.^[15] 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.^[16] 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% of 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).^[17] 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.

PRACTICE GUIDELINE SUMMARY

Current National Comprehensive Cancer Network (v2.2018) guidelines for early detection of prostate cancer recommend that any man with a PSA level greater than 3 ng/mL undergo workup for benign disease, repeat PSA, and digital rectal examination.^[18] The guidelines also recommend consideration of biomarkers that improve the specificity of screening including percent free PSA, phi, and 4Kscore in patients with a PSA level greater than 3 ng/mL who

have not yet had a biopsy, and consideration of percent free PSA, phi, 4Kscore, PCA3, and ConfirmMDx in men who had a negative biopsy but are thought to be at higher risk (category 2A evidence). NCCN noted that these tests may be especially useful in men with PSA levels between 3 ng/mL and 10 ng/mL. NCCN considers ExoDx Prostate (IntelliScore) the Mi-Prostate Score (MiPS), and Select MDx to be investigational at the time of the update.

In the prostate cancer diagnosis and management guidelines (v.4.2018), the NCCN panel suggest that men with low or favorable intermediate clinically localized disease may consider Decipher, Oncotype DX Prostate, Prolaris, or ProMark during initial risk stratification and Decipher may be considered during workup for radical prostatectomy, although the panel warns that the utility of these assays has not been fully assessed in randomized controlled trials.^[19]

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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21. BlueCross BlueShield Association Medical Policy Reference Manual "Gene Expression Profiling and Protein Biomarkers for Prostate Cancer Management." Policy No. 2.04.111

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
	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	

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