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Medical Policy

Subject	Protein Biomarkers for the Screening, Detection and Management of Prostate Cancer		
Document#:	LAB.00033	**Publish Date:**	07/10/2019~~08/29/2018~~
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Description/Scope

This document addresses the use of protein biomarkers ~~, specifically the 4Kscore® test,~~ for the screening, detection and management of prostate cancer. ~~The 4Kscore is a combination test that involves measures of fPSA (free prostate specific antigen), tPSA (total PSA), iPSA (intact PSA) and human kallikrein 2 (hK2) proteins.~~

Note: Please see the following related document(s) for additional information:

- GENE.00009 Gene-based Tests for Screening Detection and Management of Prostate Cancer
- LAB.00015 Detection of Circulating Tumor Cells in the Blood as a Prognostic Factor for Cancer

Position Statement

Investigational and Not Medically Necessary:

The use of protein biomarker tests, including but not limited to 4Kscore and androgen receptor splice variant-7 (AR-V7), ~~(that is, 4Kscore)~~ for the screening, detection, and management of prostate cancer is~~are~~ considered **investigational and not medically necessary.**

Rationale

4Kscore

The 4Kscore test (OPKO Diagnostics, LLC) is a combination test that involves measures of fPSA (free prostate specific antigen), tPSA (total PSA), iPSA (intact PSA), and human kallikrein 2 (hK2) proteins. It combines data from ~~combines data from~~ blood levels of the four kallikrein proteins ~~: tPSA, fPSA, iPSA, and human kallikrein 2~~ along with clinical information (age, digital rectal examination [~~(~~DRE]~~)~~ findings, and a history of prior negative

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biopsy result). A proprietary statistical algorithm is then used to calculate a percentage risk (< 1% to > 95%) of having a Gleason score ≥ 7 if a prostate biopsy were to be performed.

There are currently only a limited number of industry-supported, published peer-reviewed clinical trials evaluating the use of the 4Kscore test. The first was a study conducted by Vickers and colleagues (2008) that hypothesized if a multivariable model of four kallikrein proteins (tPSA, fPSA iPSA and hK2) could prognosticate the outcome of prostate biopsy in 740 unscreened males with elevated total PSA during the first round of the European Randomized Study of Screening for Prostate Cancer (ERSPC). The ERSPC was a very large randomized trial which commenced in the 1990s to evaluate the effectiveness of prostate specific antigen (PSA) screening and its correlation with mortality. Their findings revealed that these four kallikrein proteins in a blood sample could forecast prostate biopsy results. Their sensitivity analysis prediction models were based on fresh tPSA and fPSA blood samples and thawed iPSA and hK2 blood (cryopreserved) samples. The results of the study demonstrated that adding fPSA and iPSa to the model improved the area under the curve (AUC) from 0.68 to 0.83 ($p<0.0005$) and from 0.72 to 0.84 ($p<0.0005$) for the laboratory and clinical models respectively, which reduces the probability of prostate biopsy. They proposed that the results would allow providers and their patients to discuss the pros and cons of biopsy versus continued screening. In a second study by Vickers and colleagues (2010) the authors attempted to replicate their previous results in a large, independent, representative, population-based study involving 2914 individuals with elevated PSA > 3 ng/mL. The authors concluded that the use of a four kallikrein panel improved the AUC from 0.64 to 0.76 and 0.70 and 0.78 respectively ($p<0.001$ for both AUCs) for models with and without DRE which conclusively can foretell prostate cancer biopsy results in males with elevated PSA. It was further concluded that the overall percentage of prostate biopsies conducted would be reduced with the use of the kallikrein panel.

Carlsson and colleagues (2013) sought to prove that the four kallikrein panel statistical model could differentiate between diagnostically insignificant and aggressive disease on tissue specimens post-radical prostatectomy to determine the percentage of avoidable surgeries. This study was an arm of the Rotterdam ERSPC with 392 subjects. Their findings suggested that the four kallikrein biomarkers in blood samples provided accurate results that could possibly decrease the percentage of avoidable treatment. The authors found that the addition of the kallikrein biomarker panel improved the base clinical model (incorporating age, stage, PSA, prior negative biopsy) with an AUC of 0.81 to an AUC of 0.84 ($p<0.0005$). They postulated that the application of this model in a clinical setting potentially reduces the rate of surgery by 135/1000 individuals overall and by 110/334 with inconsequential disease. They noted that proof existed for the clinical utility of the model for future use.

In a multi-center prospective study by Parekh and colleagues (2014), 1012 subjects were scheduled for prostate biopsy where the Gleason score was ≥ 7 PCa. The AUC and decision curve analysis (DCA) prognosticated with probability comparisons to reduce the percentage of prostate biopsies and their subsequent impact on postponing diagnosis. The Gleason ≥ 7 PCa score was found in 231/1012 (23%) subjects and confirmed a larger discrimination (AUC 0.82) and net benefit in comparison to a modified Prostate Cancer Prevention Trial (PCPT) Risk Calculator 2.0 standard of care model. It was estimated that a probable decrease of 30-58% in the number biopsies with a delayed diagnosis was in 1.3-4.7% of Gleason ≥ 7 PCa scores. The authors concluded that the 4Kscore test showed outstanding clinical utility in uncovering PCa and may be a useful instrument to identify at-risk males.

Bryant and colleagues (2015) conducted a retrospective study utilizing a two-sided statistical model with cryopreserved four kallikrein biomarker serum hypothesizing the test can predict biopsy outcome in 6129 subjects (4765 for any Gleason grade at 10 core biopsy and 1364 to serve as impartial serum biomarkers). The authors selected males with elevated PSA (≥ 3.0 ng/mL) and who also participated in the Prostate Testing for Cancer and Treatment (Protec T) trial. The results of the four kallikrein model showed improved cancer detection versus with PSA and age variables. The AUC for kallikrein biomarkers was "0.719 (95% confidence interval [CI], 0.704 to 0.734) vs. 0.634 (95% CI, 0.617 to 0.651; p<0.001) for PSA and age for any-grade cancer and 0.820 (95% CI, 0.802 to 0.838) vs. 0.738 (95% CI, 0.716 to 0.761) for high-grade cancer." For 1000 subjects who underwent biopsies with PSA levels > 3.0 ng/mL, the model would lessen the rate of biopsy in 428 men, identify 119 high-grade cancers and defer diagnosis of 14/133 high-grade cancers using a 6% endpoint. The authors concluded that a kallikrein biomarker statistical model can prevent biopsies while postponing high-grade cancer diagnoses in few men.

A multi-institutional clinical utility study was performed by Konety and colleagues (2015) to evaluate the effect of the 4Kscore test in lieu of prostate biopsy for males referred to urologists for atypical PSA and/or DRE results. The study involved 611 subjects in 35 United States academic and community settings. A 4Kscore test was ordered as part of the urology referral with concomitant findings stratified into low risk (< 7.5%), intermediate risk (7.5%-19.9%), and high risk (≥ 20%). The 4Kscore results affected the prostate biopsy decision in 88.7% of subjects with a 64.6% decrease in biopsies in the low and intermediate risk males. Those males with a greater 4Kscore were more likely to have a biopsy (p<0.0001). Of the 171 subjects biopsied the risk stratification was strongly correlated with pathology.

In a 2017 meta-analysis by Russo and colleagues, the authors reported on the diagnostic accuracy of prostate health index (PHI) and 4K panel for detection of prostate cancer and high-grade prostate cancer (high grade

defined as Gleason score ≥ 7). A total of 28 studies that included 16,762 individuals were analyzed. For PHI for prostate cancer detection, the sensitivity was 0.89 and accuracy was 0.76. The 4K panel for prostate cancer showed a sensitivity of 0.74 and accuracy was 0.72. Regarding PHI, the negative predictive values ranged from 0.15 to 0.63, and positive predictive values ranged from 0.76 to 0.98. For the 4K panel, the negative predictive values ranged from 0.28 to 0.64, and positive predictive values ranged from 0.59 to 0.92. For detection of high-grade prostate cancer, the PHI showed a sensitivity of 0.93 and specificity of 0.34 with the 4K panel showing a sensitivity of 0.87 and specificity of 0.61. The accuracy for PHI was 0.82 and 0.81 for 4K panel. Regarding PHI, the negative predictive values ranged from 0.05 to 0.31, and positive predictive values ranged from 0.88 to 0.99. For the 4K panel, the negative predictive values ranged from 0.08 to 0.43, and positive predictive values ranged from 0.95 to 0.99. While both the PHI and 4K panel showed fair diagnostic accuracy for overall prostate cancer detection with fair sensitivity and specificity, there is no demonstration that the use of such tests improves overall health outcomes or reduces other more invasive screening methods.

In a 2018 non-randomized, observational, prospective, blinded study by Borque-Fernando and colleagues, the authors analyzed the ability of the 4Kscore to predict tumor reclassification prospectively by upgrading at a confirmatory biopsy at 6 months from the initial biopsy. Inclusion criteria were participants with PSA ≤ 10 ng/mL, cT1c-T2a, Grade group 1, ≤ 2 cores, and ≤ 5 mm/50% length core involved. A total of 137 participants were analyzed (having received a confirmatory biopsy 6 months after an initial biopsy). After local and central pathological review, 18 participants were reclassified in grade at the confirmatory biopsy. Using 7.5% as cutoff for the 4Kscore, the authors found the sensitivity for finding Grade group ≥ 2 at confirmatory biopsy was 89% (95% CI; 65–99%) and specificity was 29%. The positive predictive value was 16% (CI 9–25%) and negative predictive value 95% (CI 82–99%). There were no reclassifications to Grade group 3 for the participants with 4Kscore below 7.5% and 2 participants who missed Grade group 2 were reclassified. The authors note the main limitations of this study are the relatively small number of participants and the low number of only 18 reclassification events. While the study was prospective and blinded, the authors also note that "our model has to be validated in another series of patients and also be studied in conjunction with other tools."

The National Comprehensive Cancer Network® (NCCN) Clinical Practice Guidelines in Oncology for Prostate Cancer Early Detection (2019) state that consideration may be given to biomarkers such as 4Kscore before biopsy in men with serum PSA levels of > 3 ng/ml who desire more specificity. These tests are also options for men being considered for repeat biopsy after an initial benign result (2A recommendation).

In a~~n updated~~ U.S. Preventive Services Task Force (USPSTF) recommendation, the PSA-based screening for prostate cancer was given a C recommendation noting that:

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> For men aged 55 to 69 years, the decision to undergo periodic prostate-specific antigen (PSA)–based screening for prostate cancer should be an individual one. Before deciding whether to be screened, men should have an opportunity to discuss the potential benefits and harms of screening with their clinician and to incorporate their values and preferences in the decision. (USPSTF, 2018).

While screening offers a small potential benefit of reducing the chance of death from prostate cancer in some men, many men will experience potential harms of screening, including false-positive results that require additional testing and possible prostate biopsy; overdiagnosis and overtreatment; and treatment complications.

~~While the results of these industry-sponsored studies are promising, they have not demonstrated that use of the 4Kscore has shown to improve subsequent health-related outcomes such as mortality, morbidity, or quality of life. Further, it has not been demonstrated that the use of the 4K score reduces prostate biopsies in clinical practice; the clinical impact of using the 4Kscore Test for biopsy decisions is also uncertain.~~

Androgen Receptor Splice Variant-7 (AR-V7)

The AR-V7 is a promising biomarker in the emergence and progression of metastatic castration-resistant prostate cancer. This Oncotype DX AR-V7 test is a blood test which identifies AR-V7 proteins in the nucleus of circulating tumor cells. Detection of the splice isoform AR-V7 in circulating tumor cells has been associated with resistance to commonly prescribed AR-targeted drugs.

In a 2019 study by Sharp and colleagues, the authors evaluated the reproducibility of AR-V7 testing, and associations with clinical characteristics, circulating tumor cell counts, tumor biopsy AR-V7 protein expression and overall survival. Using blood samples from 181 participants with metastatic castration-resistant prostate cancer and 136 participants with circulating tumor cell counts along with 58 participants with matched biopsies, AR-V7 status was determined. Overall, 95/277 samples were found to be positive for circulating tumor cells, 86/277 samples were positive for circulating tumor cells and negative for AR-V7, and 96/277 samples were positive for both circulating tumor cells and AR-V7. After taking baseline characteristics into consideration, the authors noted that overall survival was shorter in participants with positive circulating tumor cells and positive AR-V7 than in participants with negative circulating tumor cells. There was no evidence that participants with positive circulating tumor cells and positive AR-V7 had worse overall survival than participants with positive circulating tumor cells and negative AR-V7. The most significant limitation of this study was the heterogeneity of treatments received which did not allow the authors to evaluate AR-V7 expression as a predictive biomarker

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of response to treatment. While testing that determines circulating tumor cell AR-V7 status has the potential to impact treatment decisions, the authors note "Robust clinical qualification of these assays is required before their routine use."

In a 2019 multicenter, prospective blinded validation study by Armstrong and colleagues, the authors sought to validate two circulating tumor cell AR-V7 assays in predicting progression-free survival and overall survival with abiraterone or enzalutamide in participants with metastatic castration-resistant prostate cancer. The authors evaluated the ability of pretreatment AR-V7 status in circulating tumor cells to predict treatment outcomes with abiraterone or enzalutamide by using the Johns Hopkins University modified-AdnaTest circulating tumor cell AR-V7 mRNA assay and the Epic Sciences circulating tumor cell nuclear-specific AR-V7 protein assays. The primary objective was to validate that participants with negative AR-V7 have prolonged progression-free survival with abiraterone or enzalutamide compared with participants with positive AR-V7 at the trial level. Using a cohort of 118 participants with high-risk metastatic castration-resistant prostate cancer, 55 were treated with abiraterone, 58 were treated with enzalutamide, and 5 received both therapies concurrently. Among surviving participants, the median follow-up time was 19.6 months. For the overall cohort, median progression-free survival was 5.8 months (95% CI, 4.1 to 7.6 months) and median overall survival (OS) was 20.3 months (95% CI, 17.0 to 27.2 months). At baseline, using the Johns Hopkins University assay, 28 participants were found to be AR-V7 positive, 88 participants were AR-V7 negative and 2 participants were unevaluable. Using the Epic protein-based assay, 11 participants were AR-V7 positive, 96 were AR-V7 negative, and 11 participants were unevaluable. With the Johns Hopkins University assay, the median progression-free survival for those who were AR-V7 positive was 3.1 months versus 6.9 months for the participants who were AR-V7 negative. Median overall survival for participants who were AR-V7 positive was 10.8 months and 27.2 months for those who were AR-V7 negative. Using the Epic AR-V7 protein assay, the median progression-free survival for AR-V7 positive participants was 3.1 months and 6.1 months for the participants who were AR-V7 negative. The median overall survival for those who were AR-V7 positive was 8.4 months compared to 25.5 months for the participants who were AR-V7 negative. While this was a relatively large cohort, there were only 11 and 28 participants who tested positive for AR-V7 by the two different assays. The authors noted that larger controlled studies are needed to confirm the predictive value of AR-V7.

In a 2018 study by Scher and colleagues, the authors sought to determine whether AR-V7 protein in circulating tumor cells can determine overall survival in participants with metastatic castration-resistant prostate cancer who have been treated with taxanes versus androgen receptor signal (ARS) inhibitors. A total of 142 blood samples (70 before initiation of therapy with an ARS inhibitor and 72 before initiation of therapy with a taxane) were used for the analysis in the second-line or greater therapy setting. The observed median survival time for

participants who received ARS inhibitors was 16 months compared to 12.9 months for those who received taxanes. There was no significant difference in survival rates between the two groups. For the participants who were treated with ARS inhibitors, there was a more favorable survival outcome for those who were AR-V7 negative compared to those who were AR-V7 positive. For the participants who were AR-V7 negative and treated with ARS inhibitors, the median survival was 19.8 months and 12.8 months if they were treated with a taxane. The major limitation to this study was that participants were not prospectively randomized to treatment based on biomarker results. It is unknown how the biomarker status affects treatment decisions.

The NCCN Clinical Practice Guidelines in Oncology for Prostate Cancer (2019) state that the use of AR-V7 testing can be considered to assist with selection of the appropriate therapy for castration-resistant prostate cancer after progression on AR-targeted drugs.

While the results of these industry sponsored studies are promising, they have not demonstrated that the use of protein biomarker testing has shown to improve health related outcomes and how the use of biomarker results affects treatment decisions.

Background/Overview

Prostate cancer is the most commonly diagnosed cancer, other than skin cancers, in North American men. According to the American Cancer Society (20198), estimated new cases and disease-related deaths from prostate cancer in the United States in 20189 is 174,650164,690 and 31,62029,430 respectively. Prostate cancer is the second leading cause of cancer death in American men, exceeded only by lung cancer. Men in the United States have about 1 chance in 9 of eventually being diagnosed with this malignancy and about 1 man in 41 will eventually die of the disease.

At this time, the gold standard for diagnosis of prostate cancer is a prostate biopsy. However, this technique is invasive and poses some risks to the individual.

In an attempt to create a reliable, accurate and clinically useful non-invasive alternative to prostate biopsy, researchers have developed laboratory teststhe 4Kscore test..

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These protein biomarker tests are not ~~4Kscore test is not~~ FDA approved, but rather are offered ~~is offered~~ as ~~a~~ LLaboratory Developed Tests (LDT). ~~through BioReference Laboratories and GenPath Diagnostics, both CLIA-Certified and CAP-Accredited laboratories and wholly owned subsidiaries of OPKO Health.~~

~~The National Comprehensive Cancer Network® (NCCN) NCCN Clinical Practice Guidelines in Oncology for Prostate Cancer Early Detection (V.2.2018) states that consideration may be given to biomarkers such as 4Kscore before biopsy in men with serum PSA levels of > 3ng/ml who desire more specificity. These tests are also options for men being considered for repeat biopsy after an initial benign result (2A recommendation).~~

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

When services are Investigational and Not Medically Necessary:
For the following procedure code, or when the code describes a procedure indicated in the Position Statement section as investigational and not medically necessary.

CPT

81479	Unlisted molecular pathology procedure [when specified as AR-V7 protein biomarker testing]
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 4Kscore test, OPKO Health, Inc.

ICD-10 Diagnosis

All diagnoses

References

Peer Reviewed Publications:

1. Armstrong AJ, Halabi S, Luo J, et al. Prospective multicenter validation of androgen receptor splice variant 7 and hormone therapy resistance in high-risk castration-resistant prostate cancer: the PROPHECY study. J Clin Oncol. 2019; 37(13):1120-1129.
2. Borque-Fernando Á, Rubio-Briones J, Esteban LM, et al. Role of the 4Kscore test as a predictor of reclassification in prostate cancer active surveillance. Prostate Cancer Prostatic Dis. 2019; 22(1):84-90.
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8. Scher HI, Graf RP, Schreiber NA, et al. Assessment of the validity of nuclear-localized androgen receptor splice variant 7 in circulating tumor cells as a predictive biomarker for castration-resistant prostate cancer. JAMA Oncol. 2018; 4(9):1179-1186.
9. Sharp A, Welti JC, Lambros MBK, et al. Clinical utility of circulating tumour cell androgen receptor splice variant-7 status in metastatic castration-resistant prostate cancer. Eur Urol. 2019 Apr 27.
~~6.~~10. Vickers A, Cronin A, Roobol M, et.al. Reducing unnecessary biopsy during prostate cancer screening using a four-kallikrein panel: an independent replication. J Clin Oncol. 2010; 28(15):2493-2498.
~~7.~~11. Vickers A, Hugosson J, Lilja H. A panel of kallikrein markers can reduce unnecessary biopsy for prostate cancer: data from the European Randomized Study of Prostate Cancer Screening in Göteborg, Sweden. BMC Med. 2008; 6:19.

Government Agency, Medical Society, and Other Authoritative Publications:

1. American Cancer Society. About prostate cancer. 201~~8~~. Available at: https://www.cancer.org/cancer/prostate-cancer/about.html. Accessed on March 12, 2019~~May 17, 2018~~.

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2. NCCN Clinical Practice Guidelines in Oncology (NCCN).© 20198. National Comprehensive Cancer Network. For additional information visit the NCCN website: http://www.nccn.org/index.asp. Accessed on March 12, 2019May 17, 2018.
   - Prostate Cancer Early Detection. V.12.20198. Revised January 31, 2019April 5, 2018.
   - Prostate Cancer. V.2.2019. Revised April 17, 2019.
3. U. S. Preventive Services Task Force. Grossman DC, Curry SJ, Owens DK, et al. Screening for prostate cancer: US Preventive Services Task Force recommendation statement. JAMA. 2018; 319(18):1901-1913.

Index

The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.

Document History

Status	Date	Action
Revised	06/06/2019	Medical Policy & Technology Assessment Committee (MPTAC) review. Clarified INV/NMN statement to include 4Kscore and AR-V7. Updated Description/Scope, Rationale, Background/Overview, References, and Index sections. Updated Coding section; added 81479 NOC code.
Reviewed	07/26/2018	Medical Policy & Technology Assessment Committee (MPTAC) review.
Reviewed	07/18/2018	Hematology/Oncology Subcommittee review. Updated Rationale, Background/Overview and References sections.
Reviewed	11/02/2017	MPTAC review.
Reviewed	11/01/2017	Hematology/Oncology Subcommittee review. Updated Rationale, Background/Overview, and References sections. The document header wording updated from “Current Effective Date” to “Publish Date.” Updated Coding section to remove 0010M deleted 12/31/2016.
New	11/03/2016	MPTAC review.
New	11/02/2016	Hematology/Oncology Subcommittee review. Initial document development.