

Medical Policy

Subject	Protein Biomarkers for the Screening, Detection and Management of Prostate Cancer	Publish Date:	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

Position Statement

Investigational and Not Medically Necessary:

The use of protein biomarker tests (that is, 4Kscore) for the screening, detection, and management of prostate cancer are considered **investigational and not medically necessary**.

Rationale

The 4Kscore test (OPKO Diagnostics, LLC) combines data from blood levels of 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 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.

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Protein Biomarkers for the Screening, Detection and Management of Prostate Cancer

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.

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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 ($\geq 20\%$). 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 an updated U.S. Preventive Services Task Force (USPSTF) recommendation, the PSA-based screening for prostate cancer was given a C recommendation noting that:

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.

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Protein Biomarkers for the Screening, Detection and Management of Prostate Cancer

Background/Overview

Prostate cancer is the most commonly diagnosed cancer, other than skin cancers, in North American men. According to the American Cancer Society (2018), estimated new cases and disease-related deaths from prostate cancer in the United States in 2018 is 164,690 and 29,430 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 the 4Kscore test.

The 4Kscore test is not FDA approved, but is offered as a Laboratory Developed Test (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**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

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All diagnoses

References**Peer Reviewed Publications:**

1. Bryant RJ, Sjöberg DD, Vickers AJ, et.al. Predicting high-grade cancer at ten-core prostate biopsy using four kallikrein markers measured in blood in the ProtecT study. *J Natl Cancer Inst.* 2015; 11:107(7).
2. Carlsson S, Maschino A, Schröder F, et.al. Predictive value of four kallikrein markers for pathologically insignificant compared with aggressive prostate cancer in radical prostatectomy specimens: results from the European Randomized Study of Screening for Prostate Cancer section Rotterdam. *Eur Urol.* 2013; 64(5):693-699.
3. Konety B, Zappala SM, Parekh DJ, et.al. The 4Kscore® test reduces prostate biopsy rates in community and academic urology practices. *Rev Urol.* 2015; 17(4):231-240.
4. Parekh DJ, Punnen S, Sjöberg DD, et.al. A multi-institutional prospective trial in the USA confirms that the 4Kscore accurately identifies men with high-grade prostate cancer. *Eur Urol.* 2015; 68(3):464-470.
5. Russo GI, Regis F, Castelli T, et al. A systematic review and meta-analysis of the diagnostic accuracy of prostate health index and 4-kallikrein panel score in predicting overall and high-grade prostate cancer. *Clin Genitourin Cancer.* 2017; 15(4):429-439.
6. 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. 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. 2018. Available at: <https://www.cancer.org/cancer/prostate-cancer/about.html>. Accessed on May 17, 2018.
2. NCCN Clinical Practice Guidelines in Oncology (NCCN).® 2018. National Comprehensive Cancer Network. For additional information visit the NCCN website: <http://www.nccn.org/index.asp>. Accessed on May 17, 2018.
 - Prostate Cancer Early Detection. V.2.2018. Revised April 5, 2018.
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.

Index4Kscore test
OPKO Diagnostics

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.

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Document History

Status	Date	Action
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.

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