Medical Policy Reference Manual
Medical Policy

11.01.068 The 4Kscore® Test for Cancer Risk Assessment of Prostate Cancer

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Description

Prostate cancer is the most commonly diagnosed non-skin cancer and the third-leading cause of cancer death among men in the United States. Well-established risk factors for prostate cancer include increasing age, African ancestry, family history (5-10% of prostate cancers) and certain inherited genetic conditions (e.g., Lynch syndrome, BRCA1 and BRCA2 mutations). Prostate cancer screening has a potential to be over-diagnosed and over-treated due to its slow growth. The rate of tumor growth varies from very slow to moderately rapid. Some patients may have prolonged survival even after the cancer has metastasized to distant sites (e.g., bone). The overwhelming majority (92%) of prostate cancers are discovered at the local (cancer is confined entirely to the organ of origin) or regional (cancer extends into surrounding organs or tissues) stage with an overall 5-year survival of 99% (across all stages), and 29% for distant-stage disease (distant organs, tissues and lymph nodes are involved) (American Cancer Society, 2017). Ten-year survival rates vary depending on Gleason score (grading scheme for prostate cancer) and have been estimated to be 98.4% for Gleason 2 through 6, 92.1% for Gleason 7 (3 + 4), 76.5% for Gleason 7 (4 + 3), and 69.9% for Gleason scores between 8 and 10 (Wright et al., 2009).

Treatment for localized disease involve surgery, radiotherapy and in some cases, active surveillance therapy. Hormone therapy and chemotherapy are treatment options in cases involving inoperable or metastatic disease. Prostate cancer screening usually involves a digital rectal exam (DRE) and assessment of prostate-specific antigen (PSA) levels. Abnormal findings (i.e. serum PSA = 4 ng/ml and / or abnormal DRE) may result in a referral for biopsy and histological diagnosis (gold standard). Core biopsies may miss cancerous tissues and yield false-negative results. The risks (e.g., fever, bleeding and urinary difficulties), discomforts and burdens associated with biopsies along with the low yield for diagnosis presents a demand for noninvasive tests that differentiate potentially aggressive tumors (that should be referred for biopsy) from clinically insignificant localized tumors or other prostate related conditions.

Various tests have been developed to assist physicians and their patients with the shared decision to proceed with a prostate biopsy. The 4Kscore® test (OPKO) is a blood test that provides a personalized measure of percent risk for high-grade (Gleason ≥ 7) prostate cancer in the event a prostate biopsy is performed. The 4Kscore® is used prior to biopsy or after a negative biopsy, to predict the likelihood of aggressive cancer spreading to other parts of the body (distant metastasis) in the next 20 years. According to the manufacturer's website, the 4Kscore® is especially useful in assisting physicians and their patients decide whether to proceed with a prostate biopsy when other test results are equivocal. The score combines the measurement of 4 prostate-specific kallikreins (total PSA [tPSA], free PSA [fPSA], intact PSA [iPSA], human kallikrein [hK2]), with an algorithm including patient age, digital rectal exam (DRE: nodules or no nodules), and a prior negative prostate biopsy. The test is not intended for patients with a prior diagnosis of prostate cancer, age less than 40 years and greater than 80 years, DRE in the previous 4 days, who have received 5-alpha reductase inhibitor (5-ARI) therapy in the previous 6 months or who have received treatment (procedure or therapy) for symptomatic benign prostatic hypertrophy in the previous 6 months.

Policy

The 4Kscore® test, to predict the risk of Gleason 7 or greater prostate cancer and / or to predict the likelihood of distant metastasis within 20 years is considered **experimental / investigational** as it does not meet TEC criteria #2-5.

Policy Guidelines

1. The technology must have final approval from the appropriate U.S. government regulatory bodies:

The 4Kscore® test is an in-house laboratory test performed by OPKO and is regulated under the auspices of the Clinical Laboratory Improvement Amendments (CLIA). Premarket approval from the FDA is not required.

2. The scientific evidence must permit conclusions concerning the effect on health outcomes:

Evidence for the 4Kscore® test to predict the risk of aggressive prostate cancer is evaluated according to recommendations by the Centers for Disease Control and Prevention criteria:

Analytical validity (whether the test is accurate and reliable)
Clinical validity (whether the test provides clinically meaningful information)
Clinical utility (whether the test improves disease management and / or patient outcomes)

Analytical validity:
The 4Kscore® combines 4 blood biomarkers (total PSA [tPSA], free PSA [fPSA], intact PSA [iPSA], human kallikrein [hK2]). Total and free PSA are measured using FDA approved kits from Roche Diagnostics. Intact PSA and hK2 are proprietary tests validated by OPKO. The evidence describing any components of analytic validity for a test of kallikrein biomarkers is limited to one study (Vaisanen et al., 2006), in which findings from a new method to reduce false high results were reported. The new method eliminates assay interference in measurement of intact fPSA and free hK2. Female (n=1,092) heparin plasma samples (negligible PSA and hK2) were used as controls and male samples (n=957) were analyzed to identify samples showing interference, which in turn were used to optimize protocols for the immunoassays. Original assays (monoclonal antibodies) were compared to optimized assays. The new method was tested on another set of 444 samples and found that the optimized assay eliminated 70%-85% of the falsely elevated results.

Clinical validity:
The performance characteristics of a risk score (KLK) derived from 4 kallikrein biomarkers were estimated in several retrospective studies and a prospective study. Biopsy was generally used as the reference standard. Long-term follow-up from a national registry of prostate cancer was performed in some studies in Sweden. Screening PSA limits of 2 or 3 ng/mL (lower) were used in most studies. Men regardless of DRE, PSA or biopsy status were included. Mathematical methods used to calculate the KLK risk score varied across studies in terms of the source of kallikrein values (plasma or serum measurements), the additional risk factors included in the model (age, DRE, biopsies and other risk factors), and how kallikrein marker values were entered into the model (linearly, with splines or cubic splines).

The marketed version of the 4Kscore® test appears to have been used in 3 studies (Borque-Fernando et al., 2016; Konety et al., 2015; Parekh et al., 2015). Two of the three studies (Konety et al. 2015 & Parekh et al. 2015) were conducted in the United States. Cutoffs for categorizing risk into low, medium or high levels were only given in Konety et al. (2015).

The performance of the 4Kscore® test was validated by Parekh et al. (2015) in a blinded, prospective study at 26 urology centers in the United States involving 1,012 men scheduled for prostate biopsy regardless of age, PSA level, DRE or prior prostate biopsy. The primary objective of this study was to perform the first prospective evaluation of the 4Kscore® at predicting Gleason ≥ 7 prostate cancer in the U.S. The 4Kscore® outperformed (superior discrimination at detecting Gleason ≥ 7 prostate cancer) a modified Prostate Cancer Prevention Trial Risk Calculator 2.0 (PCPTRC 2.0) with an AUC ROC of 0.82 versus 0.74 ($p < 0.0001$).

In summary, the lack of standardization of cutoffs for recommending biopsy, variability in baseline PSA levels and positive DRE results are likely outside of the intended use population. Additionally, the lack of comparison to models using information from standard clinical examination creates an uncertainty around clinical performance characteristics such as sensitivity, specificity, and predictive value. African American men were not well represented in the study populations given their high burden of morbidity and mortality. Therefore, the evidence needed to draw conclusions on clinical validity is insufficient. Long-term follow-up data on the incidence of prostate cancer in men (U.S.) who did not have a biopsy following testing with the marketed version of 4Kscore® is needed. A case-control study by Stattin et al. (2015) with a cohort study of more than 17,000 Swedish men estimated that, for men ages 60 with PSA levels of 3 or higher and a KLK risk score less than 10%, the risk of metastasis at 20 years was 1.95% (95% CI, 0.64% to 4.66%).

Clinical Utility:
Parekh et al. (2015) estimated that 307 biopsies could have been avoided and 24 cancer diagnosis delayed with a 9% 4Kscore® cutoff from biopsy. Additionally, 591 biopsies would have been avoided with 48 delayed diagnosis using a 15% cutoff. These findings should be interpreted with some caution due to deficiencies in estimating the clinical validity for reasons described in the clinical validity section.

Konety et al. (2015) performed a survey of 35 academic and community U.S. urologists involving 611 patients with abnormal PSA levels or DRE (6%) identified from the 4Kscore® database at OPKO Lab. Urologists were retrospectively asked about their plans for biopsy before and after they received 4Kscore® test results and whether the test influenced their decision. Test results were stratified into 3 risk categories, low risk (< 7.5%), intermediate risk (7.5%-19.9%), and high risk (≥ 20%) for aggressive prostate cancer. The 4Kscore® results influenced decisions in 89% of men (as reported by the urologists) which led to a 64.6% reduction in prostate biopsies. The 4Kscore® risk categories correlated highly ($p<0.001$) with biopsy outcomes in 171 men with biopsy results, however, no other risk calculators were used for comparison. Prospective studies showing the impact of the 4Kscore® test on care management decisions are lacking and needed.

3. The technology must improve the net health outcome:

There is insufficient data on the long-term clinical outcomes of men who were not biopsied based on 4Kscore® test results. Therefore, it is not known if the technology improves the net health outcome.

4. The technology must be as effective as any established alternatives:

The scientific evidence comparing the performance of the 4Kscore® to models using information from standard clinical examination (e.g., PCPTRC 2.0) is insufficient. Therefore, an assessment of whether the 4Kscore® is as effective as the established alternatives cannot be made.

5. The improvement must be attainable outside the investigational settings:

Whether the technology can improve patient outcomes has not been established in the investigational settings, therefore, it is infeasible to evaluate the performance of the test outside of the investigational settings.

Update 2019:

A search of the peer reviewed literature was conducted from October 2017 through August 2019. Findings in the recent literature do not change the conclusions on the use of the 4Kscore® test for cancer risk assessment of prostate cancer. Therefore, the policy statement is unchanged.

Update 2021:

A search of the peer reviewed literature was conducted from September 2019 through August 2021. Findings in the recent literature do not change the conclusion on the use of the 4Kscore® test for cancer risk assessment of prostate cancer. Therefore, the policy statement is unchanged.

Cross References to Related Policies and Procedures

PCA3 Genetic Assay for Prostate Cancer 11.01.047
Epigenetic Assay for Detection and / or Management of Prostate Cancer 11.01.058
Gene Expression Assays for Managing Prostate Cancer 11.01.064

References

The following were among the resources reviewed and considered in developing this policy. By reviewing and considering the resources, CareFirst does not in any way endorse the contents thereof nor assume any liability or responsibility in connection therewith. The opinions and conclusions of the authors of these resources are their own and may or may not agree with those of CareFirst.

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