JM Palmetto - 4Kscore Assay

CPT: 81539 (Biochemical assay of four proteins – Total PSA, Free PSA, Intact PSA, & Human Kallikrein HK2)

CMS Policy for Alabama, Georgia, North Carolina, South Carolina, Tennessee, Virginia, and West Virginia

Local policies are determined by the performing test location. This is determined by the state in which your performing laboratory resides and where your testing is commonly performed.

Medically Supportive ICD Codes are listed on subsequent page(s) of this document.

Coverage Indications, Limitations, and/or Medical Necessity

This is a non-coverage policy for the 4Kscore assay (developed by OPKO; marketed by BioReference Laboratory, NJ). This test is a laboratory developed test (LDT) and has not undergone FDA review or scrutiny. Review of the available evidence is summarized below.

The 4Kscore test consists of a panel of four kallikreins in blood that is supposed to reduce unnecessary biopsy in men being considered for biopsy of the prostate for potential cancer. The clinical features of this group are poorly defined. The kallikreins consist of total PSA, free PSA, intact PSA and kallikrein-related peptidase 2 (hK2). The authors of the training and validation study[1] claim that the panel of kallikrein markers can predict high grade prostate cancer on a prostate biopsy in previously unscreened men with elevated PSA. They also claim to have replicated their previous findings where they claim that application of a statistical model incorporating all four kallikreins leads to superior clinical results compared with the current strategy of biopsying all men with elevated PSA. These data suggest that the number of men undergoing biopsy could be reduced to half using 20% or greater risk of any cancer as a tentative threshold for biopsy, with approximately 20% of cancers remaining undetected among previously unscreened men. However, most of these cancers would be low-grade and low-stage cancers typically associated with over diagnosis, while few high-grade cancers would be missed. They claim *"a large number of unnecessary biopsies can be avoided at the expense of only a small number of men with advanced cancer being advised against biopsy, few of whom would have high-stage or high-grade disease. Accordingly, application of our model as part of PSA screening would reduce the harms associated with unnecessary biopsy".*

Despite the claims offered by these authors, their study is significantly flawed. Their model includes patients outside of the intended use population (PSA > 10 ng/mL) and patients who previously were biopsied with no cancer discovered. Furthermore, in their iteration of the formula it is unclear how much hK2 contributes above using all the other components which are commercially available. Total PSA contribution is very significant. The AUC of the full model is 0.821, and without the incorporation of the hK2 the AUC is 0.806 with overlapping confidence intervals. Throughout the studies there is 1) inconsistent use of PSA as a threshold for biopsy; 2) significant changes to the methodology (use of $F(ab')_2$ fragments of the monoclonal capture antibodies); and 3) modification of the algorithm. Furthermore, earlier data was generated on (usually) a 6 core sextant biopsy and likely does not reflect the tissue volume assessed in American men.

In a Swedish case-control study nested within a population-based cohort [2], the four kallikreins were combined into a statistical risk model based on the Vickers validation that gives risk of any grade (or Gleason score=) cancer at prostate biopsy. More than 12,500 men were followed for >15 years. PSA testing, performed on cryopreserved blood collected at age 50 or 60, was used to predict metastasis at 15- to 20-yr follow-up. In the subset of men with modestly elevated PSA, a pre-specified model based on a panel of four KLK markers increased the predictive discrimination of developing clinically diagnosable prostate cancer. Among men with modestly elevated PSA at age 50 or 60, the authors claim the four KLK (4Kscore assay) panel yielded C-indexes from 0.82 to 0.88 for the prediction of documented distant metastasis. The authors conclude that screening at ages 50-60 years should focus on men with PSA in the top quartile, and use the kallikrein panel to aid biopsy decision making.

Despite the claims offered by these authors, there are many concerns. The discussion alludes to the fact that if patients were selected by PSA of 4 or above, or selecting age adjusted PSA cut-offs for biopsy, the number of biopsies excluded would be similar but more advanced cancer would be missed. This data is statistically modeled and hypothetical, and generated in a group of patients biopsied under techniques not practiced today. Furthermore, the authors chose a 5 year end point for supposedly missed clinically diagnosable prostate cancer. However, the curves rise significantly after 5 years to potentially unacceptable levels (almost 4% of the population at 10 years).

Assay validation should be specific to the intended use population and intended use. Although the Vickers study included patients with elevated PSA in their training and validation study, the assay validation was not specific to identifying men at risk for developing clinically diagnosable prostate cancer at 5 years (an unacceptably short endpoint).

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The most recent data presented in the Parekh study[3] has a number of flaws.

This study includes men with PSA levels >10 ng/mL who may have increased risk of cancer and may require biopsy.

This subgroup (PSA levels >10 ng/mL) is not separately modelled to determine if modeling adds benefit.

The importance of total PSA and it is fractions are obvious in the latest iteration of the 4K model. The AUC of the full model is 0.821, and without the incorporation of the hK2 the AUC is 0.806 with overlapping confidence intervals. This suggest that hK2 in the model/algorithm adds little. Its significance is unknown.

The AUC of this model with total PSA should have been reported, as well as reports of the stepwise addition of the other measurements to determine how the markers perform relative to total PSA. Confidence intervals should have been reported to determine overlap, as well as comparison with an updated prostate cancer risk calculator such as Rotterdam Prostate Cancer Risk Calculator.

The clinical characteristics of the patients are very poorly defined - men in need of biopsy - yet the model includes men with prior negative biopsies.

In a retrospective study by Bryant, et al.[4] involving cryopreserved blood from >6000 men in a large randomized prospective clinical trial involving contemporary extended 10-coare biopsies, the four kallikrein panel was used to demonstrate prediction improvement of biopsy outcomes compared with total PSA and age. Because the previous statistical models were based on the kallikrein levels measured in serum for previously unscreened men undergoing sextant prostate biopsy, and because levels of some of the kallikrein markers differ in plasma vs serum, new prediction models were generated in this study and reported new AUCs. The authors also used decision curve analysis to investigate whether the models could reduce the number of men undergoing biopsy without delaying the diagnosis of high-grade disease in many men. They claim that using a 6% risk of high-grade cancer as an illustrative cutoff, for 1000 biopsied men with PSA levels of 3.0ng/mL or higher, the model would reduce the need for biopsy in 428 men, detect 119 high-grade cancers, and delay diagnosis of 14 of 133 high-grade cancers. They claim the 4 kallikrein assay can predict the result of the prostate biopsy, and differentially detect high-grade disease. However, the new AUC confidence levels of the model with or without hK2 overlap, and men with PSA = 10 ng/mL were included. Furthermore, the model used total PSA and free PSA (did not use intact PSA) with a free to total PSA ratio. These components can easily be calculated, and require no need for expensive testing.

The Bryant study highlights a turning point with the development of a new model/algorithm in response to changes in biopsy and grading practices, and was subsequently locked down and applied to the Swedish community study, the Stattin long-term follow-up study and the Parekh validation study. Furthermore, the Bryant authors have not proven the validation of the assay, and admit their findings need to be confirmed in prospective research using clinical cohorts.

Finally, Konety, et al.[5] is marketed as a prospective decision impact study. In this study, 611 patients seen by 35 academic and community urologists in the US ordered the 4Kscore tests as part of their assessment of men referred for abnormal PSA and/or DRE. The authors report that the *"results for the patients were stratified into low risk (< 7.5%), intermediate risk (7.5%-19.9%), and high risk (20%) for aggressive prostate cancer. The 4Kscore Test results influenced biopsy decisions in 88.7% of the men. Performing the 4Kscore Test resulted in a 64.6% reduction in prostate biopsies in patients; the actual percentage of cases not proceeding to biopsy were 94.0%, 52.9%, and 19.0% for men who had low-, intermediate-, and high-risk 4Kscore Test results, respectively. A higher 4Kscore Test was associated with greater likelihood of having a prostate biopsy (p < 0.001). Among the 171 patients who had a biopsy, the 4Kscore risk category is strongly associated with biopsy pathology. The 4Kscore Test, as a follow-up test for an abnormal PSA and/or DRE results, significantly influenced the physician and patient shared decision in clinical practice, which led to a reduction in prostate biopsies while increasing the probability of detecting aggressive cancer."*

The Konety, et al. study, although marketed as a prospective study, is not a prospective study. A prospective clinical utility study requires prospective enrollment of patients, treatment according to a defined pathway using the test result as an integral part of the care plan, and must demonstrate statistically and clinically significant improvement in healthcare outcomes versus the currently accepted standard of care by contemporary controls. However, in the methods section of this article, the authors specify that the study was "retrospective", and *"no restrictions were placed on the urologists in deciding which patients received the 4Kscore test or in making decisions with the patient about whether to proceed with prostate biopsy"*. At best, this study represents a retrospective observational study or survey.

Finally, there is this assumption that missing an NCCN low risk patient will cause no harm. The only data for this is in men following biopsy documentation and subsequent active surveillance (AS). There is no evidence that observing a man with undiagnosed low risk prostate cancer and projected longevity would not suffer harm. There are no recommendations on suggested follow up if the 4Kscore suggests no indication for biopsy. There is an unproven statement that serial PSA will identify patients who may evolve and capture the missed high risk patients. Independent evidence suggests the main indication for cessation of AS is not PSA progression, but a worsening repeat biopsy.

In summary, the intended use population has been inadequately validated; the 4Kscore model has continuously changed; the model has been recurrently tested on potentially inappropriate patients (PSA > 10) and patients with inadequate biopsy sampling; it is unclear how much the hK2 and possibly intact PSA contribute to the model; the value of the 4Kscore model/algorithm is fraught with statistical hypothesis and not prospective outcomes or concordance in a defined patient population likely to be considered for biopsy (eg: PSA 3-10 ng/mL); assumptions are made that no harm will come to following young men with unknown low grade prostate cancer (not on AS); there is significant difficulty equating the model used in the Swedish study to the presently proposed formula; and the incidence of clinically diagnosable prostate cancer in patients with low risk by the model/algorithm at 10 years is very concerning.

Consequently, due to significant issues with assay validation and absence of clinical utility, 4Kscore testing is not reasonable and necessary and is not covered by Medicare.

Medicare Local Coverage Determination Policy

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There is a frequency associated with this test. Please refer to the Limitations or Utilization Guidelines section on previous page(s).

The ICD10 codes listed below are the top diagnosis codes currently utilized by ordering physicians for the limited coverage test highlighted above that are also listed as medically supportive under Medicare's limited coverage policy. **If you are ordering this test for diagnostic reasons that are not covered under Medicare policy, an Advance Beneficiary Notice form is required.**
Note—Bolded diagnoses below have the highest utilization

Code	Description
N/A	N/A

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To view the complete policy and the full list of medically supportive codes, please refer to the CMS website reference www.cms.gov ►

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