KAISER PERMANENTE®

**Kaiser Foundation Health Plan of Washington**

# *Clinical Review Criteria*

## 4Kscore Test: Predicting the Risk of Aggressive Prostate Cancer

- 4KRK
- Four Kallikrein Markers
- Kallikrien Panel



## Criteria

### For Medicare Members

| Source | Policy |
|---|---|
| CMS Coverage Manuals | None |
| National Coverage Determinations (NCD) | None |
| Local Coverage Determinations (LCD) | None |
| Local Coverage Article | None |
| KPWA Medical Policy | For CPT code 81539 - Due to the absence of a NCD, LCD, or other coverage guidance, KPWA has chosen to use their own Clinical Review Criteria, "4Kscore Test: Predicting the Risk of Aggressive Prostate Cancer," for medical necessity determinations. Use the Non-Medicare criteria below. |

### For Non-Medicare Members

There is insufficient evidence in the published medical literature to show that this service/therapy is as safe as standard services/therapies and/or provides better long-term outcomes than current standard services/therapies.

The following information was used in the development of this document and is provided as background only. It is provided for historical purposes and does not necessarily reflect the most current published literature. When significant new articles are published that impact treatment option, KPWA will review as needed. This information is not to be used as coverage criteria. Please only refer to the criteria listed above for coverage determinations.

## Background

Prostate Specific Antigen (PSA) is the most widespread test for prostate cancer (PCa) screening. However, it is associated with a high risk of overdetection and overtreatment. Since its introduction into practice in the late 1980s, PSA testing has led to a significant increase in the incidence of prostate cancer and migration to an earlier stage at diagnosis. Most men with an elevated PSA either do not have prostate cancer or have a low-risk disease that is unlikely to affect the quality or length of life if left untreated. Between 17% and 50% of men with prostate cancer detected by PSA test have indolent tumors that would not have led to clinical disease. In addition PSA levels may be elevated by conditions other than cancer such as benign prostatic hyperplasia, and prostatitis. The specificity and sensitivity of the PSA test used alone in detecting prostate cancer range from 20-40% and 70-90% respectively, with an AUC (area under the receiver operating characteristic [ROC]) curve of 0.55-0.71 (depending on the cutoff value used), and a positive predictive value (PPV) of only 25-40%. The low specificity of the PSA test, results in performance of a large number of unnecessary biopsy procedures with the associated anxiety and complications. It is estimated that more than one million men undergo prostate biopsy every year in the USA, the majority of which are potentially avoidable (Vickers 2010, Bratt 2012, Voigt 2014, Parekh 2015).



Back to Top

Continuous efforts are being made to improve the accuracy of the PSA test and/or develop new biomarkers for prostate cancer screening. PSA density and PSA velocity have been used, but were found to only slightly improve the predictive value of PSA, to a level that is insufficient to distinguish between aggressive and indolent forms of prostate cancer. PCA3 and TMPRSS2-ERG fusion biomarkers measured in the urine immediately after a vigorous prostate massage, were also evaluated, but each has its limitations (Punnen 2015, Ferro 2016).

Currently the prediction tools used to preoperatively distinguish between an aggressive and a pathologically insignificant disease incorporate PSA level, clinical stage, as well as biopsy variables such as transrectal ultrasound prostate volume, Gleason grade, number of positive biopsy cores, percentage of cancer in any core sample, total cancer length, and noncancer tissue in biopsy cores. The AUC for the accuracy of these prediction tools ranges from 0.70-0.80 (Carlsson 2013).

The 4Kscore® (4KRK) test (OPKO Lab, Nashville, TN) is a new blood test that has been introduced and evaluated for its ability to accurately predict the risk of aggressive prostate cancer. The test incorporates a panel of four kallikrein protein biomarkers (total PSA [tPSA], free PSA [fPSA], intact PSA [iPSA], and human kallikrein-related peptide 2 [hK2]), together with clinical information (age, and optionally the results of a DRE), in an algorithm that, according to some investigators, provides a percent risk for a high grade cancer (Gleason score ≥7). Tissue kallikrein or kallikrein-related enzymes are a family of 15 secreted serine proteases, the regulatory functions of which are linked to the development of malignancy, neurodegeneration, inflammation and other disorders. Messenger RNA expression of all kallikreins can be detected in the prostate tissue, but KLK2 (also known as human kallikrein2 [hK2]), and KLK3 (also known as PSA) are the most dominant. Some researchers found that in prostate cancer there is a dysregulation and overexpression of both PSA and hK2 and that their levels increase as the prostate cancer becomes more undifferentiated. They also indicate that these kallikreins directly and indirectly contribute to prostate cancer progression and metastasis (Konety 2015, Punnen 2015, McDonald 2016).

Several European studies evaluated the ability of the 4Kscore to distinguish between a pathologically insignificant and an aggressive disease. Based on their analyses, several investigators suggest that 4Kscore test would play an important clinical role as a reflex test before performing an initial prostate biopsy in men with elevated PSA, abnormal DRE results, or after a negative biopsy and persistently higher PSA levels (Punnen 2015). According to the manufacturer, the 4Kscore Test does not provide a diagnosis of prostate cancer; it is designed to help clarify the decision on whether or not to perform a biopsy based on the probability of a patient having aggressive prostate cancer. The test should not be used in isolation to make the decision on the need for biopsy. Other factors such as health status, PSA history medical history, family history of prostate cancer, etc., should all be considered with the 4Kscore risk level into a shared decision-making with the patient.

## Medical Technology Assessment Committee (MTAC)

***4Kscore Test for Prostate Cancer***

**03/21/2016: MTAC REVIEW**

**Evidence Conclusion:** *Clinical validity (Predictive accuracy) of the 4Kscore test* The four kallikrein markers were initially validated in Europe using retrospective data from multiple European cohorts that participated in European Randomized Study of Prostate Cancer Screening (ERSPC). These were followed by a study in the UK using retrospective data from ProtecT study cohort, and a prospective study conducted in the USA. All 4Kscore validation studies compared its predictive accuracy versus the base model using total PSA and reported the results in the area under the receiver operating characteristic curve (AUC). AUC only focuses on the predictive accuracy of a model. It does not account for potential harms, benefits or cost, and may not capture the tradeoffs that the physician and patient face in making a decision about interventions that can carry both benefits and harms (Baker, 2012). Voigt and colleagues' meta-analysis (Evidence Table 1) pooled data from seven separate trials participating in the ERSPC. The results of the meta-analysis as well as the results of the individual studies it included, suggest that an algorithm using a panel of tPSA, fPSA, iPSA, and hK2 measured in the serum, together with age and optional DRE, is more accurate than measuring total PSA (tPSA) alone in predicting high grade cancer among men with a PSA levels ≥ 3 ng/mL. The pooled mean difference in AUC between the Kallikrein clinical model vs. base clinical model was 0.10 (95% CI, 0.08- 0.12), $p<0.00001$, for predicting any cancer and 0.08 (95% CI, 0.05-0.11), $p<0.00001$ for predicting high-grade cancer. Bryant and colleagues (2015, Evidence Table 2) validated a statistical model based the four kallikrein markers using retrospective data from the Prostate Testing for Caner and Treatment (ProtecT study) conducted in the UK. In that study, men with PSA ≥3 ng/mL underwent an extended 10-core biopsy (sextant biopsy in ERSPC). The kallikrein markers were retrospectively measured in cryopreserved blood, mainly plasma rather than serum. Because of these differences from the ERSPC, the investigators generated new prediction models modified from those developed from the ERSPC cohorts. Similar to the other European studies, the results of the UK study showed that the statistical model

 Back to Top

including the panel of four kallikrein markers significantly improved the prediction of high grade cancer vs. the use of total PSA plus age. The incremental increase in the AUC with using age + a panel of 4K markers versus age + tPSA was 0.085 for any grade prostate cancer and 0.082 for high-grade cancer. It is to be noted however, that these studies used retrospective data form earlier cohorts from European studies conducted among Caucasian men 50 years of age or older. Plasma or serum samples have been stored for several years and may have been previously thawed and refrozen, which would degrade the kallikrein markers. The trials participating in the ERSPC used sextant biopsy and the ProtecT study used 10-core biopsy. Parekh et al, 2015 (Evidence Table 3) prospectively validated the 4Kscore test in the USA. The study enrolled 1,300 men referred to biopsy (regardless of their PSA level or clinical findings) in 26 urology centers in the USA. 300 men were used for calibrating the algorithm and 1,012 for its validation. The primary outcome was Gleason score ≥ 7 prostate cancer (PCa) on prostate biopsy. Accuracy of the 4Kscore test was assessed by the AUC, calibration plots, and decision curve analysis. The great majority of the participants (86%) were white men, which may limit generalization of the results. The authors compared the predictive accuracy of the 4Kscore vs. a modified Prostate Cancer Prevention Trial Risk Calculator (PCPTRC) 2.0. The results showed that the 4Kscore had a significantly higher discrimination in detecting Gleason ≥7 cancer compared to modified PCPTRC 2.0 (AUC 0.82 versus 0.74, p<0.0001).

The results of validation studies on the predictive accuracy of the 4Kscore may be summarized in the following table: *The AUC for discriminating /predicting Gleason ≥7 cancer using the full panel 4Kscore**

| | **N participants** | **AUC (95% CI)** |
|---|---|---|
| USA validation study (Parekh, 2015)* | 1,012 | 0.82 (95% CI, 0.79 to 0.85) |
| UK study (Bryant, 2015)** | 6,129 | 0.82 (95% CI, 0.80 to 0.84) |
| European trials participating in ERSPC study | | |
| Unscreened cohorts | 262 | 0.87 |
| France (Benchikh, 2010) | 740 | 0.83-0.84 |
| Goteborg (Vickers, 2008) | 2,914 | 0.76-0.78 |
| Rotterdam (Vickers, 2010) | | |
| Screened cohorts | 1.241 | 0.83 |
| Goteborg (Vickers, 2008) | 1,501 | 0.80 |
| Rotterdam (Vickers, 2010) | | |

*Compared to AUC 0.74 with modified Prostate Cancer Prevention Trial Risk Calculator (PCPTRC) 2.0 (P<0.0001)
** Compared to AUC of 0.63 (95% CI, 0.62-0.65), for total PSA +age (p <0.001).

- AUC for total PSA models ranged between the European studies from 0.51 to 0.77.
- Mean difference in AUC between 4K model and the base model (consisting of age total PSA, and DRE) in predicting high grade cancer varied between 0.10 (95% CI, 0.06-0.16) to 0.13 (95% CI, 0.11-0.15) depending on whether DRE results were or were not included with the 4K panel and age.

*Clinical utility of the 4Kscore test* Clinical utility of a test implies that high-level evidence shows that the use of the marker improves patient outcome sufficiently to justify its incorporation into routine clinical care (NCCN Task Force [Febbo 2011]).There are no published RCTs or prospective controlled studies, to date, that examined the clinical utility of the 4Ksore test or its therapeutic impact, i.e. whether its results would have an effect on the treatment decision-making and improve patient outcomes. The published studies examined and validated the predictive ability of the 4Kscore test, but did not directly examine its impact on the clinical outcomes. In order to investigate the potential clinical effect of the four kallikrein markers in the blood, the investigators used decision analyses to simulate outcomes if biopsy decisions have been based on various cut-points from the models. Decision analyses methods are based on simulations using estimates of the probability and sequelae of events in a hypothetical cohort of patients (Vickers, 2006). Bryant and colleagues' 2015 (Evidence Table 2), decision curve analysis based on various cutpoints showed that a model using a threshold representing a 6% risk of Gleason score ≥7 in men with PSA ≥3 ng/ml, would reduce the biopsy rate by 42.8%, but at the expense of missing 14 of 133 (10.5%) high grade cancers. The analysis of the US prospective study (Parekh et al, 2015, Evidence Table 3) suggests that the use 4Kscore test among men with PSA ≥3 ng/ml, may potentially reduce the number of prostate biopsies, but may also fail to detect a small number of significant cancers depending on the cutoff value used. Using 6% risk as a cutoff would reduce 30% of the biopsies, and delay the diagnosis of 1.3% of high grade cancers. A ≥9% cutoff would reduce 43% biopsies and delay diagnosis of 2.4% Gleason ≥7 cancers. Konety and colleagues, 2015 (Evidence Table 4), retrospectively examined the impact of the 4Kscore Test on the urologist-patient decisions about performing a biopsy in men with abnormal PSA and/or DRE results. The study retrospectively collected data from participating urologists who ordered the 4Kscore Test as part of their assessment of men referred their practice for abnormal PSA and or DRE. The results of the analysis suggest that performing the 4Kscore Test resulted in 64.6% reduction in prostate biopsies among the 611 patients seen by the participating urologists. Due to its design and limitations, the study does not provide sufficient evidence to

 Back to Top

determine the clinical utility of the test. Conclusion: There is fair evidence from a number of validation studies that 4Kscore test may improve the predictive accuracy of total PSA when used among mainly white men with PSA level ≥ 3ng/mL. As indicated earlier the predictive accuracy of a marker or test does not account for potential harms, and benefits, and may not capture the tradeoffs that the physician and patient face in making a decision about interventions that can carry both benefits and harms. There is insufficient evidence on the clinical utility of the 4Kscore test. There is insufficient evidence to determine the therapeutic impact of the 4Kscore test or the effect of the treatment decision based on the results of the test on the patient outcomes.

**Articles:** The search for studies on the accuracy of the 4Kallikrein panel in predicting high grade prostate cancer, revealed one study that prospectively evaluated the test among men in the USA, and a number of European studies that used retrospective data from several cohorts of screened and unscreened men participating in European Randomized Study of Prostate Cancer (ERSPC) and one cohort from the British ProtecT study. A meta-analysis that pooled the results of seven studies using the ERSPC cohorts was also identified. The search did not reveal any randomized controlled trial that examined the clinical utility of the 4Kscore test, only an observational study that analyzed retrospective data for men receiving the test. The following studies were selected for critical appraisal: Voigt JD, Zappala SM, Vaughan ED, et al. The Kallikrein Panel for prostate cancer screening: its economic impact. Prostate. 2014 Feb; 74(3):250-259 See Evidence Table 1. Bryant RJ, Sjoberg DD, Vickers AJ, et al. Predicting high-grade cancer at ten-core prostate. See Evidence Table 2. Parekh DJ, Punnen S, Sjoberg 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 Sep; 68(3):464-470. See Evidence Table 3.. biopsy using four kallikrein markers measured in blood in the ProtecT study. J Natl Cancer Inst. 2015 Apr 11; 107. Konety B, Zappala SM, Parekh DJ, et al. The 4Kscore test reduces prostate biopsy rates in community and academic urology practices. Rev Uorl. 2015; 17 (4):231-240. See Evidence Table 4.

The use of 4Kscore Test for Prostate Cancer does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

| Date Created | Date Reviewed | Date Last Revised |
|---|---|---|
| 03/21/2016 | 04/05/2016[MPC], 02/07/2017[MPC], 11/07/2017[MPC] , 09/04/2018[MPC] | 04/05/2016 |

[MPC] Medical Policy Committee

| Revision History | Description |
|---|---|
| 04/05/2016 | Created criteria; Added MTAC review |
| 02/07/2017 | Medicare is silent; MPC approved to adopt GHC criteria for Medicare members |
| 10/10/2017 | Added Medicare instructions for 0010M and 81539 |
| 8/8/2018 | Removed 0010M |

## Codes

**CPT code – 81539**



Back to Top