A Multi-Institutional Prospective Trial Confirms Noninvasive Blood Test Maintains Predictive Value in African American Men

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Purpose: The 4Kscore® test accurately detects aggressive prostate cancer and reduces unnecessary biopsies. However, its performance in African American men has been unknown. We assessed test performance in a cohort of men with a large African American representation.

Materials and Methods: Men referred for prostate biopsy at 8 Veterans Affairs medical centers were prospectively enrolled in the study. All men underwent phlebotomy for 4Kscore test assessment prior to prostate biopsy. The primary outcome was the detection of Grade Group 2 or higher cancer on biopsy. We assessed the discrimination, calibration and clinical usefulness of 4Kscore to predict Grade Group 2 or higher prostate cancer and compared it to a base model consisting of age, digital rectal examination and prostate specific antigen. Additionally, we compared test performance in African American and nonAfrican American men.

Results: Of the 366 enrolled men 205 (56%) were African American and 131 (36%) had Grade Group 2 or higher prostate cancer. The 4Kscore test showed better discrimination (AUC 0.81 vs 0.74, $p < 0.01$) and higher clinical usefulness on decision curve analysis than the base model. Test prediction closely approximated the observed risk of Grade Group 2 or higher prostate cancer. There was no difference in test performance in African American and nonAfrican American men (0.80 vs 0.84, $p = 0.32$), The test outperformed the base model in each group.

Conclusions: The 4Kscore test accurately predicts aggressive prostate cancer for biopsy decision making in African American and nonAfrican American men.

Key Words: prostatic neoplasms; biomarkers, tumor; kallikreins; African Americans; neoplasm grading

Abbreviations and Acronyms

AA = African American
DRE = digital rectal examination
GG = Grade Group
PSA = prostate specific antigen

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THE 4Kscore test is a noninvasive blood test that incorporates biomarker and clinical information into an algorithm that was specifically designed to predict the risk of aggressive prostate cancer on prostate biopsy. The test combines the levels of 4 kallikrein proteins that are found in the blood,

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including total, free and intact PSA, and human kallikrein-related peptidase 2, with important clinical information, specifically patient age, digital rectal examination findings and prior biopsy status. The result is the individualized probability of finding GG2 or higher prostate cancer if biopsy were to be performed.

A previous prospective trial validated 4Kscore in a multi-institutional study in more than 1,000 enrolled men from a total of 26 primarily community based practices across the United States.[1] The 4Kscore test showed excellent accuracy for detecting GG2 prostate cancer (AUC 0.82) while potentially allowing for a substantial reduction in the number of unnecessary biopsies that would have been performed. However, generalizability was limited by the small number of AA men (8.4%) who participated in the study, preventing any reliable conclusions about test performance in this population. More research was needed to know how well 4Kscore may be generalized to other populations of men undergoing care in different health systems, particularly the Veterans Administration, where the majority of men who receive care are AA.

The primary objective of this study was to evaluate the usefulness of the 4Kscore test in a completely independent cohort of men from the Veterans Administration, where most urological patients are AA. We also sought to compare 4Kscore performance in AA vs nonAA men. To accomplish this goal we performed a multi-institutional, prospective trial among men undergoing prostate biopsy at a total of 8 Veterans Affairs hospitals in the United States.

METHODS

Patient Population

In this study we prospectively enrolled men who were referred for prostate biopsy at a total of 8 Veterans Affairs hospitals across the United States from July 2015 to October 2016. Each patient provided a blood sample prior to transrectal ultrasound guided biopsy. A minimum of 10 cores was required for the biopsy. All phlebotomy samples were collected and processed according to the study protocol and shipped to the manufacturer for kallikrein biomarker measurements and 4Kscore calculation. All men underwent DRE at the time of biopsy, which was reported as normal or abnormal and used as a variable in the 4Kscore algorithm. Prior biopsy status (yes or no) and patient age at study enrollment were recorded and also used in the algorithm.

Patients were excluded from the trial if they had had a previous diagnosis of prostate cancer or underwent DRE within 96 hours of phlebotomy. Patients were also excluded if they had undergone an invasive prostate procedure or had received an α-reductase inhibitor within the last 3 months. There were no exclusions for PSA level or age.

Histopathology of biopsy specimens was performed according to the established practice at each Veterans Affairs hospital. The 4Kscore calculation and the interpretation of histopathology findings were performed independently with each party blinded to the results of the other party. Demographic and clinical information were collected in a standard format.

Institutional review board approval was obtained at each site and all men provided written informed consent prior to study enrollment. The primary end point was to assess the ability of the 4Kscore test to predict significant prostate cancer on biopsy, defined as GG2 or higher adenocarcinoma of the prostate.

Statistical Analysis

Based on the initial 4Kscore validation trial[1] we estimated that 300 samples would be enough to achieve an AUC 95% CI band width of ± 0.05 or less. We assumed an AA-to-nonAA ratio of 1:1. With 180 AA and 180 nonAA men we estimated that there would be 80% power to detect an AUC difference of 0.04 between the 2 groups at a significance level of 0.05. Assuming 10% exclusion due to missing data or inadequate samples, we planned to prospectively enroll a total of 400 men at the 8 participating sites.

Demographic and clinical differences between men who had no or GG1 cancer and those with GG2 or higher cancer were compared with the Kruskal-Wallis test for continuous variables and the chi-square test for categorical variables. The accuracy level of 4Kscore to discriminate GG2 or higher cancer from GG1 or no cancer was calculated using ROC characteristic analysis. The 4Kscore AUC was compared to the AUC of a base model consisting of age, DRE and total PSA using the chi-square test and the Stata® romcomp command to compare AUCs. Calibration plots were used to illustrate the level of agreement between 4Kscore predictions and the true observed rates of GG2 or higher prostate cancer in the cohort. Decision curve analysis was done to show the clinical usefulness of using the 4Kscore to determine the need for prostate biopsy. This was explored across a wide range of threshold probabilities.

The clinical usefulness or net benefit of using 4Kscore was compared to a strategy of biopsying all men or no men as well as a strategy of using the base clinical model to determine the need for biopsy. In this cohort in which all men had already been referred for biopsy the all biopsy strategy represented the current standard of care at these Veterans Affairs hospitals.

Finally, we explored the number of biopsies that could have potentially been avoided and the number of clinically significant cancers that would have been missed based on various 4Kscore cutoffs to decide on biopsy. We also compared the discrimination of the 4Kscore test to the base model for detecting clinically significant prostate cancer in AA and nonAA men separately. Finally, we compared the 4Kscore AUC between AA and nonAA men to determine whether test performance differed by race.

All analyses were specified prior to starting the trial and performed with Stata, version 13.0.