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Value of a Statistical Model Based on Four Kallikrein Markers in Blood, Commercially Available as 4Kscore, in All Reasonable Prostate Biopsy Subgroups

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The 4Kscore is a commercially available test to aid prostate biopsy decision-making for men with moderately elevated prostate-specific antigen (PSA). Zappala et al [1] conducted a meta-analysis of 12 studies including close to 17 000 patients and reported a pooled discrimination of 0.81 for Gleason grade group (GGG) 2. Several guideline groups have, however, criticized the 4Kscore data on the basis that the patients included in the studies were “outside the intended use population” [2] or that the results for a specific PSA range were not cited.

We reanalyzed data from a recent meta-analysis of individual patient data across a wide variety of subgroups [3]. GGG 2 was the endpoint. Only data from completely independent validation studies were included, involving 8396 biopsies from eight cohorts. The PLCO study [4] was excluded because of the unusual sampling design; the Rotterdam Repeat Biopsy [5] cohort had an insufficient number of events. The base model consisted of age, total PSA, and digital rectal examination (DRE) result, if available. We varied the upper and lower limits for PSA and age, all patients or only those with negative DRE, and all cohorts or only contemporary cohorts on the basis of ten or more biopsy cores and post-2005 grading. Cohorts were excluded from any given analysis if there were fewer than 20 events or non-events.

We first conducted a total of 1792 different analyses reflecting different combinations of the most common age, PSA, DRE, and cohort criteria. In general, the results did not vary importantly. The mean increase in area under the receiver operating characteristic curve (AUC) for the kallikrein panel was 0.097. The smallest increase was 0.063, seen in two subgroups. There were only 14 analyses for which the upper bound of the confidence

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Conflicts of interest: Andrew J. Vickers is named on a patent for a statistical method to detect prostate cancer, commercialized as the 4Kscore by OPKO Health; he receives royalties from sales of the test and has stock options in OPKO Health. The remaining authors have nothing to disclose.

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interval excluded the overall estimate of the effect, a finding that might well be expected by chance. All improvements in AUC were statistically significant ($p = 0.004$).

We then repeated analyses across all plausible subgroups of age, PSA, DRE, and cohort. This resulted in 180 224 analyses. For 20 377 of these, there were not enough data to conduct an analysis (eg, age 48–61 yr, PSA 8–15 ng/ml, negative DRE). The mean increment in discrimination for the remaining 159 847 analyses was 0.113, with the lowest increment being 0.024 (age 53–60 yr, PSA 1–25 ng/ml, any DRE, contemporary cohorts).

To assess clinical utility, we calculated the net benefit for the panel and base model at threshold probabilities of 6%, 9%, 12%, and 15%. Although the panel was sometimes not of benefit at low threshold probabilities if the PSA or age range was restricted or unusual, we were unable to find any reasonable combination of age or PSA in contemporary cohorts for which the decision curve did not support clinical utility of the panel.

We compiled all the results into an app (available in the Supplementary material) that allows a user to specify age, PSA, DRE, and cohort type and obtain a full range of results.

In conclusion, we present data on the properties of the 4Kscore across an extremely wide range of subgroups. The value of the 4Kscore is not sensitive to different definitions of eligible subpopulations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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