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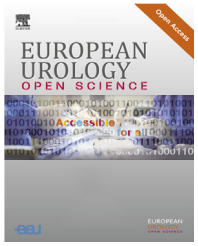


European Association of Urology

Brief Correspondence

# Implementation of 4Kscore as a Secondary Test Before Prostate Biopsy: Impact on US Population Trends for Prostate Cancer

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**Abstract**

Prostate cancer screening using prostate-specific antigen (PSA) reduces prostate cancer mortality at the cost of unnecessary prostate biopsy, overdiagnosis, and overtreatment. Several secondary tests have been developed to restrict biopsy to men at the greatest risk of high-grade disease. 4Kscore is a widely used secondary test that has been shown to reduce biopsy rates by approximately two-thirds in routine clinical practice. We estimated how 4Kscore implementation has affected cancer trends in the US population. We combined data from the US validation study of 4Kscore with data from the diagnostic test impact study, using a basis of 70 000 on-label 4Kscore tests performed annually. We estimate that each year, 4Kscore leads to 45 200 fewer biopsies and 9400 fewer overdiagnoses of low-grade cancer, at the cost of delayed diagnosis of high-grade prostate cancer for 3450 patients, of whom two-thirds have International Society of Urological Pathology grade group 2 disease. These findings need to be taken into consideration when studying epidemiologic trends in prostate cancer. They also suggest that high levels of overdiagnosis and overtreatment are not inevitable characteristics of PSA screening, but can be mitigated by additional tests.

***Patient summary:*** We estimate that use of a test called 4Kscore to predict the probability that a patient has high-grade prostate cancer has significantly reduced the number of unnecessary biopsies and overdiagnosis of low-grade cancer in the USA. These decisions may result in delayed diagnosis of high-grade cancer in some patients. 4Kscore is a useful additional test in the management of prostate cancer.



Prostate-specific antigen (PSA) screening for prostate cancer reduces cancer-specific mortality [1] at the cost of some unnecessary prostate biopsies, overdiagnosis, and overtreatment. 4Kscore, a secondary test for men with elevated PSA, was developed to predict the risk of high-grade cancer on biopsy and reduce overdiagnosis of low-grade disease. It combines a panel of four blood kallikreins with clinical variables to give an individual percentage risk (from 0% to 100%) of having International Society of Urological Pathology grade group (GG) ≥2 prostate cancer [2]. Numerous studies have demonstrated that 4Kscore can accurately predict the risk of GG ≥2 disease and if used to determine the indication for biopsy, would dramatically reduce the number of benign biopsies and overdiagnosis of GG 1 disease [3].

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Approximately one million prostate biopsies are performed annually [4], with a total of 288 300 new cancer diagnoses [5] and ~75 000 4Kscore tests administered each year [6]. Konety et al. [7] conducted a diagnostic test impact study involving 611 men being considered for biopsy at a range of academic and community practices. The authors made a causal claim that 4Kscore led to a 64.6% reduction in the number of patients referred for prostate biopsy. This claim seems justified on the grounds that the study carefully assessed clinicians' pretest intentions regarding biopsy and their perceptions of whether the test results influenced their decision. In this study we modeled the effect of the 4Kscore test on the overall number of patients biopsied and diagnosed with low- or high-grade cancer in the US population.

First, we analyzed a cohort of 1012 patients from the prospective US validation study [8]. To estimate the reduction in US biopsy numbers on 4Kscore implementation, we started from the overall number of 4Kscore tests (70 000, slightly reduced from the number of tests sold to take into account off-label use, including when 4Kscore is ordered for a patient who the urologist might not otherwise biopsy) and multiplied by the percentage reduction in patients not referred for biopsy from the Konety data set (64.6%, with a 95% confidence interval [CI] estimated as 60–69%) [7]. To estimate the reduction in the number of low-grade cancers related to 4Kscore use, we created a logistic regression model using the US validation study data to predict the risk of low-grade disease according to 4Kscore results. The relationship between 4Kscore and low-grade cancer risk is nonlinear: it will be small at low 4Kscores (owing to an overall decrease in cancer risk) and also at high 4Kscores (because most men will have high-grade disease). Inclusion of a square root as a nonlinear term resulted in an excellent model fit in comparison to locally weighted scatterplot smoothing (Supplementary Fig. 1). The model coefficients were then used in the Konety data set to calculate the predicted probability of low-grade cancer among patients not referred for biopsy. The mean risk of low-grade cancer for men not referred to biopsy (along with the 95% CI) was then multiplied by our estimate of the mean number of patients not referred for biopsy each year in the USA to give the total reduction in low-grade cancers. To estimate the reduction in the number of high-grade cancers associated with 4Kscore use, we repeated the methodology described above for low-grade cancers, except that we used the 4Kscore result directly, as this gives the probability of high-grade disease and is known to be well calibrated [8].

Figure 1 shows a plot of the cumulative incidence of high- and low-grade prostate cancer as a function of the 4Kscore centile. The incidence of low-grade cancer follows an almost linear relationship with the 4Kscore centile: a given percentage reduction in biopsy rate related to the 4Kscore will give an equivalent percentage reduction in detection of low-grade cancers. By contrast, the effect on high-grade cancer is nonlinear, with a very small reduction in detection of high-grade cancers up to approximately the 50th centile, and increasing rapidly thereafter. Rounding to the nearest 50, our principal estimates are that 4Kscore implementation leads to 45 200 (95% CI 42 000–48 300),

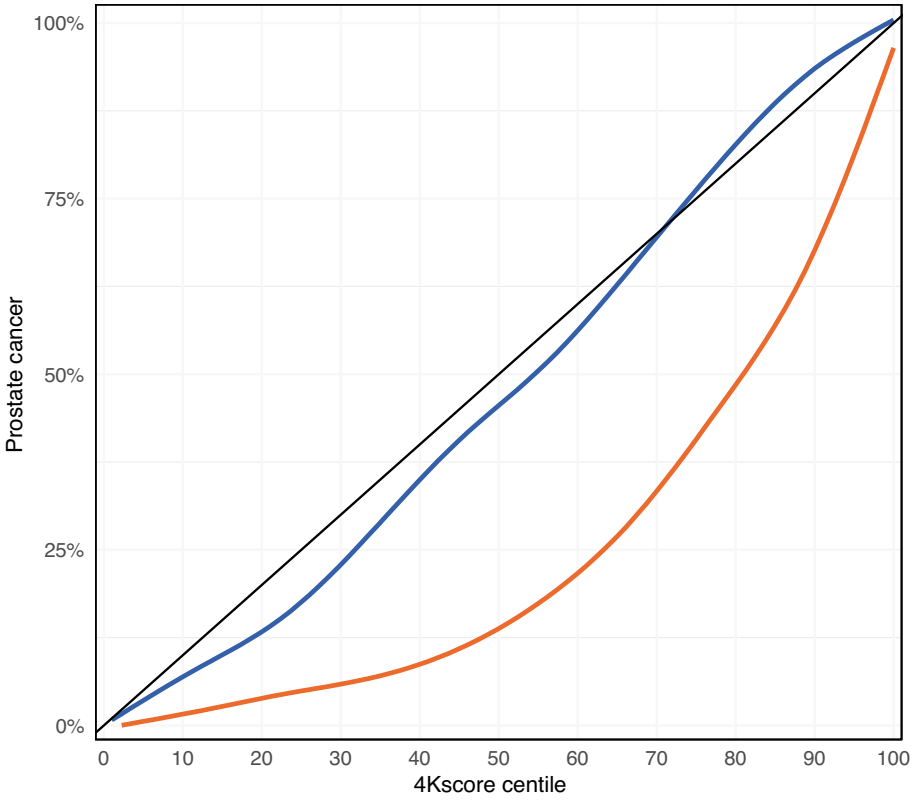


**Fig. 1 – Cumulative incidence of low-grade (blue line) and high-grade (red line) prostate cancer by 4Kscore centile.**

fewer biopsies and 9400 (95% CI 8700–10 050) fewer overdiagnoses of low-grade cancer each year at the cost of delayed diagnosis of high-grade prostate cancer for 3450 patients (95% CI 3200–3700). We can further estimate that as 66% of the delayed high-grade cancers will be GG 2, clinical use of 4Kscore will delay diagnosis for 1150 GG $\geq$3 cancers (95% CI 1050–1250; Supplementary Table 1).

Our study has several limitations. First, we assumed that the 4Kscore distribution in the overall population of men undergoing 4Kscore testing and consequent biopsy decisions is the same as in the Konety study population. We feel that this is justified by a complementary paper: in a study of more than 10 000 Medicare patients [9], 4Kscore was followed by biopsy in 31% of cases, a result very similar to that of Konety et al. [7]. The second limitation is that our results are based on cross-sectional data. For example, some men not biopsied because of a low 4Kscore result would subsequently undergo biopsy because of rising PSA and their 4Kscore result. Hence, we may have overestimated both the reduction in biopsies and overdiagnosed cancers and the number of diagnoses of high-grade cancer delayed. Given that both 4Kscore and PSA are strongly predictive of high-grade disease, we hypothesize a smaller effect of the former than of the latter: men with high-grade disease who are not biopsied are still likely to be diagnosed at a curable stage, whereas those with low-grade will avoid biopsy in the long term. That said, research is clearly warranted to determine the effect of 4Kscore on biopsy rates over time.

In conclusion, clinical implementation of 4Kscore has had a large impact on US urologic practice, leading to an estimated 45 000 fewer biopsies and nearly 13 000 fewer cancer diagnoses. Given that 4Kscore is only one of several secondary markers and imaging tests, the total effect of all secondary tests on prostate cancer trends will be greater. These findings need to be taken into consideration when studying epidemiologic trends in prostate cancer. Moreover, they suggest that high levels of overdiagnosis and overtreatment are not inevitable characteristics of PSA screening but can be mitigated by additional testing.

***Author contributions:*** Simone Scuderi had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

*Study concept and design*: Vickers, Scuderi.
*Acquisition of data*: Scuderi.
*Analysis and interpretation of data*: Scuderi, Tin, Vickers.
*Drafting of the manuscript*: Scuderi, Vickers.
*Critical revision of the manuscript for important intellectual content*: Vickers, Montorsi, Briganti, Gandaglia, Stabile.
*Statistical analysis*: Scuderi, Tin, Vickers.
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## Appendix A. Supplementary data

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