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Will Biomarkers Save Prostate Cancer Screening?

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With the recent publication of its final grade D recommendation against prostate-specific antigen (PSA)–based screening [1], the influential US Preventive Services Task Force (USPSTF) has effectively laid siege to prostate cancer (PCa) early detection in the United States and threatens to condemn thousands of men with high-risk PCa to slow, painful, and avoidable deaths. There are many critical flaws in the USPSTF's analysis: It misinterprets and misrepresents key clinical trial evidence, focuses on outcomes at an insufficient duration of follow-up, and cherry-picks studies from the literature to overestimate the harms of treatment [1].

However, no matter how inappropriate the final grade D recommendation may have been, the kernel of truth in it that is beyond argument is that to date, PSA testing has not been used optimally in the United States and other countries. Too much screening and too many biopsies are done among older men with limited life expectancy [2], and too many men diagnosed with low-risk PCa receive unnecessary treatment that negatively affects their long-term quality of life. Conversely, many men with high-risk disease who should receive multimodal treatment never receive potentially curative local treatment [3]. The argument that the only solution to the problems of overdiagnosis and overtreatment is the wholesale cessation of screening [1] may be absurd, yet these problems persist and will only worsen, given an aging population.

The clear solution should be neither to stop screening nor to continue business as usual but rather to screen—and treat—smarter. Smarter screening implies testing men earlier and, for the majority with low baseline PSA levels, less often [4]. Screening should also be framed in terms of early diagnosis of high-risk PCa; most men diagnosed with low-risk cancer are better managed with at least an initial course of active surveillance rather than immediate treatment. In fact, any argument for screening men at younger ages must be accompanied by a willingness for surveillance of even young men if low-grade, low-volume tumors are identified. Finally, PSA test results clearly should not be used in a vacuum but should be considered in the context of age, family history, ethnicity, physical examination findings, prior biopsy history, and other factors. Several calculators for this purpose have been published and validated [5].

Many authors have expressed hope that novel biomarkers may help determine which men need prostate biopsy and which among the men diagnosed need urgent treatment. A plethora of markers have been proposed based on blood, urine, tissue, and imaging tests; to date, relatively few of these markers have been shown to contribute independent prognostic information beyond standard clinical information, and fewer still have been externally validated. This situation is starting to change, however, as candidate markers have been examined in increasingly rigorous clinical settings.

One challenge germane to the question of screening is how to manage men who have undergone at least one negative biopsy but have a persistently elevated and/or rising PSA. While the problem of false-negative biopsies is not highlighted in the USPSTF's critique of screening, it is a factor limiting the efficacy of screening and certainly a major source of anxiety for men in screening programs. In this issue of *European Urology*, Kader et al report the results of a large validation study of a proposed genetic signature intended help guide the decision whether to perform a second biopsy [6].

The investigators analyzed a set of germline single nucleotide polymorphisms (SNPs) determined from banked peripheral blood in a subset of patients in the placebo arm of the Reduction by Dutasteride of Prostate Cancer Events (REDUCE) chemoprevention trial, which included men with

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a prior negative biopsy and a PSA between 2.5 and 10 ng/ml. There are significant strengths to this analysis, including the use of a well-described study cohort with reliable follow-up and, perhaps most critically, the original REDUCE study design, which mandated biopsies at 2 and 4 yr of follow-up regardless of PSA levels. The statistical analysis was robust, including both net reclassification index (NRI) and decision analyses in addition to traditional area under the curve measurement. The focus was quite appropriately on what the novel genetic score can add to existing standard clinical information.

The cohort included men with a wide range of genetic scores derived from a signature of 33 SNPs. The genetic score was shown to contribute independent information, based on a variety of analyses, to a clinical model derived from age, PSA, prostate volume, prior biopsy extent, family history, and rectal examination [6]. However, despite the statistically significant superiority of the model incorporating the genetic score along with the clinical information, the absolute improvement realized through incorporation of the SNP data was fairly modest, as demonstrated in both the area under the curve and decision curve analyses. The NRI analysis indicated that in perhaps too many cases, addition of the genetic information resulted in incorrect reclassification of men, particularly with respect to their risk of high-grade cancer.

As the authors acknowledge, restriction of the analysis to Caucasian patients, who may have different germline predictors of cancer risk than members of other ethnic groups, is an important potential limitation to clinical applicability. Another issue, mentioned briefly at the end of the discussion, is that other approaches to the post–negative biopsy setting are being developed. Prominent examples include the use of multiparametric magnetic resonance imaging (MRI) and MRI-guided biopsy; extended-template biopsies, often via a transperineal approach; and analysis of blood and urine levels of emerging biomarkers. Indeed, the PCa risk calculator developed using data and specimens from the Prostate Cancer Prevention Trial now incorporates urinary levels of PCa antigen 3 gene (*PCA3*) or blood levels of [–2]proPSA to improve predictions for both the first biopsy and repeat biopsy settings [7,8]. Developments like these raise the bar of entry for novel candidate markers, which should be considered explicitly in the context of this rich emerging experience and literature, and ideally should be tested head to head in the same specimen sets.

Most of these candidate markers, including the SNP signature proposed in Kader et al's paper [6], are easily accessed through the blood or urine but ultimately may not be the best markers for the repeat—as opposed to the initial—biopsy setting, because in this setting only, prostate tissue is available for analysis. While germline genetic factors may still be relevant, it seems more likely that a better signal might be identified through evaluation of field effect changes in the "normal" prostate biopsy tissue [9].

Whether or not the SNP signature proposed by Kader et al [6] may ultimately prove clinically useful, the paper is emblematic of a rapidly rising level of methodological quality in PCa biomarker research. It is very reasonable to expect that in the near term, well-validated markers will be available to facilitate decision making both before and after PCa diagnosis. How exactly these emerging markers should be combined with clinical data and used in practice is an evolving question; another question is how to prove that the use of markers does in fact lead to better decision making, which will be necessary for cost effectiveness studies.

No biomarker has yet been proposed to be a replacement for PSA as a primary screening test, but many show promise as secondary screens for men considering a first or subsequent biopsy. Improving the accuracy of prebiopsy testing, and focusing on the end point of identifying high-risk PCa, would potentially go a long way toward ameliorating overdiagnosis and overtreatment of low-risk disease as well as delayed diagnosis and undertreatment of high-risk disease. Novel markers thus may play an important role in solving the screening controversy. But they are only one piece of the puzzle, and they can be of help only if the right men are screened, if the decision to screen is framed in terms of identifying those men with high-risk disease, and if immediate treatment is withheld in favor of initial active surveillance for the larger group of men with indolent, low-risk PCa.

Conflicts of interest: The author has nothing to disclose.

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