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New Prostate Cancer Biomarkers: The Search Continues

Devin N. Patel, Stephen J. Freedland *

Department of Surgery, Division of Urology, Cedars-Sinai Medical Center, Los Angeles, CA, USA

Although prostate-specific antigen (PSA) was originally introduced as a tumor marker for detection of prostate cancer recurrence or progression, its wider adoption in the late 1980s and early 1990s changed prostate cancer screening forever. PSA has been very useful for prostate cancer screening; however, owing to limitations of poor specificity and predictive values of total PSA assays, the search for better biomarkers is an area of active research. Towards this end, this issue of *European Urology* highlights the work by Klein et al [1] in developing the IsoPSA assay. The authors, recognizing the benefits afforded by the specificity of PSA to prostate tissue, explored the diagnostic potential of its structural variants for detection of prostate cancer.

PSA exists in the blood in multiple forms known as isoforms. Some of these forms are more cancer-specific, while others are less related to cancer. IsoPSA takes advantage of these differences to detect isoform structures that are more cancer-specific. While in concept this is similar to free PSA and -2[Pro]PSA, the IsoPSA test analyzes all PSA isoforms, both known and unknown, to categorize the PSA isoform mixture into cancer and benign phenotypes.

Using this novel technology, Klein et al examined the diagnostic accuracy of IsoPSA among 261 men scheduled for prostate biopsy in a multicenter setting. For detection of any cancer on biopsy, the IsoPSA assay had significantly better receiver operating characteristics (area under the curve [AUC] 0.79) compared to total PSA (AUC 0.61; $p < 0.001$). Similarly, for detecting high-grade prostate cancer (Gleason ≥ 7), the IsoPSA assay (AUC 0.81) outperformed total PSA (AUC 0.69; $p < 0.005$). Moreover, relative to the Prostate Cancer Prevention Trial Risk Calculator (PCPTRC) 2.0 risk calculator, the IsoPSA assay had significant improvements in decision curve analysis, showing that it offers net clinical

benefits relative to currently available calculators that use only clinical features. Finally, use of an optimized cutoff point for decision-making for biopsy would decrease unnecessary biopsies by 45% while missing only 1.9% of high-grade cancers.

While this study included men with prebiopsy PSA as low as 2 ng/ml, the authors found less robust benefits of IsoPSA in detecting high-risk cancer in these men with lower risk. Specifically, unless the prebiopsy threshold probability was >10% for high-grade disease, there was no net benefit of using IsoPSA versus biopsying all men. In the PCPT trial, the incidence of high-grade cancer among men with PSA <4 ng/ml was approximately 6%, suggesting that the IsoPSA assay may be most useful for patients with higher PSA levels rather than those at the lower end of the diagnostic "grey zone" [2].

Although the authors clearly showed that IsoPSA outperforms currently used parameters, such as PSA, age, race, and physical examination findings, their study also clearly reveals the limitations of current risk calculators that rely on these same clinical parameters. Indeed, in this study the PCPTRC 2.0 calculator was worse than simply biopsying all men. IsoPSA, along with other biomarkers, provides the potential to improve these risk calculators in the future.

While IsoPSA provided important information, it should be noted that there are numerous commercially available biomarkers, all of which have been shown to offer improved detection over PSA. These include PSA-based biomarkers such as the Prostate Health Index (PHI) and the 4KScore [3], RNA-based biomarkers such as PCA3, SelectMDX and the Mi-Prostate Score [4–6], tissue-based biomarkers including ConfirmMDx and the Prostate Core Mitomic test [7,8], and immune-based assays such as the APIFINY blood test designed to detect prostate tumor–related autoantibodies

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[9]. Despite their merits individually and aside from a limited number of studies comparing PHI and 4KScore, the merits of one particular biomarker over any other remains unknown. Thus, while all of these biomarkers appear to "work", it is not known which one works best for which populations.

Beyond serum- and tissue-based biomarkers, another key tool in the diagnostic armamentarium that has emerged in the past few years is magnetic resonance imaging (MRI) [10]. Whether MRI gives additional or identical information to these biomarkers remains unclear. Unfortunately, without comparative data, clinicians are left to use the test they are most comfortable with, or even resort to using multiple assays combined with imaging to accomplish the same end goal, thereby reducing the potential cost-effectiveness these new tests afford.

We applaud efforts such as these to improve the detection of prostate cancer in the most clinically optimum manner. However, how these new biomarkers should be used is not clear, as the "gold" standard (ie, PSA) against which it was tested is no longer golden. Many biomarkers exist today and while all outperform PSA, they are not widely used for several possible reasons: (1) there are too many biomarkers, leading to confusion about the best biomarker; (2) the new biomarkers, while better than PSA, are still not good enough; and (3) there is a lack of high-quality comparative effectiveness studies. While we believe that all three are reasons for the limited use of these biomarkers in practice, the lack of comparative studies is a particular major limitation.

Thus, while IsoPSA represents a new and intriguing option, until well-conducted comparative effectiveness studies are carried out, the field of prostate cancer biology will continue in the unfettered pursuit of more novel biomarkers and the medicine of diagnosing prostate cancer will be unmethodical in its use of these new tests. As prostate cancer continues to evolve from a disease of overdiagnosis and overtreatment, it is important that we maintain the paradigm of maximizing patient benefit while minimizing patient harm in the most economic manner. New tools for optimizing diagnosis, such as biomarkers and imaging, serve this aim in part; however, without comparative data, the creation and implementation of both clinically effective and cost-effective utilization parameters among providers will continue to be elusive.

Conflicts of interest: Stephen J. Freedland serves as a consultant with stock options for Armune BioScience, the manufacturer of the APIFINY blood test. Devin N. Patel has nothing to disclose.

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