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The Benefits of Risk Assessment Tools for Prostate Cancer

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We share the take-home message of Zhu et al. and applaud their synthesis of the evidence in support of current prostate cancer (PCa) screening strategies, in particular, the central role played by risk assessment tools [1]. In addition to the very important clinical impact of risk assessment tools, which are increasingly used day in and day out in the clinical setting, there have been five salutary benefits to these tools.

The first has been to dispel the notion that a prostate-specific antigen (PSA) level of <4.0 ng/ml is “normal.” It is a tragedy that many laboratory reports continue to list a “normal range” for PSA of 0–4.0 ng/ml on the right side of the report. We have demonstrated clearly that if the goal of PSA testing is to detect disease when it is curable and a threshold of 4.0 ng/ml is used, at least 26% of men will no longer be curable at diagnosis [2]. For some men, the illustration of risk at a lower level of PSA may be a life-saving revelation.

The second important impact of these tools has been to illustrate the ubiquity of detectable PCa in the general population and the importance of focusing on the risk of high-grade disease. Simply showing a 55-yr-old man with PSA of 2.0 and no other risk factors for cancer that his risk of PCa is 23% (using the Prostate Cancer Prevention Trial [PCPT] Prostate Cancer Risk Calculator [3]) illustrates that overall risk of cancer simply cannot be the focus [4]. In contrast, this same man’s risk of high-grade disease is 2.5%. Given that the risk of a serious infection from a prostate biopsy in the United States has been estimated at between 2% and 4%—the risk of the potentially lethal variant of PCa may be less than the risk of a complication of biopsy—one can now focus on this element of risk prediction. In our own practice, we have increasingly relied on the risk of high-grade disease to help focus decision making as to the appropriateness of a prostate biopsy. The reasons are two-fold. First, high-grade disease poses the greatest risk of morbidity and mortality for the patient. Second, the diagnosis of low-grade PCa has a very major negative impact, especially on a young man: It will lead to a lifetime of anxiety and repeated biopsies, and in the United States, it can even affect his ability to obtain health or life insurance and can have a major impact on premiums for such coverage.

A third extremely important contribution of risk assessment tools has been that they facilitate the understanding of how combinations of other risk factors can affect risk of cancer and especially risk of high-grade cancer. As noted, our impression is that the most

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important piece of information that flows from a risk assessment tool is the risk of high-grade cancer. In our PCPT risk calculator [3], we found that the factors that affected risk of high-grade disease were PSA, digital rectal examination (DRE) findings, age, and African American ethnicity. The revelations that have followed this seemingly simple observation have been profound. African Americans have some of the highest risks of PCa death in the world; the risk calculator enables the adjustment of PSA for these men to allow similar access to further diagnostic testing options. For example, in men with no other risk factors for PCa, such as a 60-yr-old white man with a PSA of 4.5 ng/ml, the risk of high-grade disease is about 8%. That same PSA in an identical man whose only difference is his African American race results in an 18% risk of high-grade disease. The 8% risk of high-grade disease in the African American man is reached at a PSA of only 2.5 ng/ml.

A fourth important observation that has flowed from these risk assessment tools is related to the interaction of age and risk of PCa and, more important, risk of high-grade disease. We have previously observed that, through natural intuition, our colleagues often recommend using lower PSA thresholds in younger men and higher levels in older men, that is, *age-adjusted* PSA values. Commonly used values are 3.5 ng/ml for men in their 50 s, 4.5 ng/ml for men in their 60 s, and 6.5 ng/ml for men in their 70 s. Because of the “perfect storm” effect of PSA and age (as both of these increase, independently, the risk for high-grade disease increases), there is a multiplier effect on the risk of high-grade disease. As such, the risk of high-grade disease in a 55-yr-old white man with a PSA of 3.5 ng/ml is 5%, whereas the 75-yr-old white man with a PSA of 6.5 ng/ml has an 18% risk of high-grade disease (the 75-yr-old man achieved a 5% risk of high-grade disease at a PSA of 1.0 ng/ml). A provocative implication of this well-intentioned clinical action is that we have substantially increased detection of indolent tumors in young men while “ignoring” lethal tumors in older men until they are incurable. It is informative that the median age of death from PCa in the United States is 80 [5] (ie, half of the deaths from PCa occur after this age).

Perhaps the most important effect of risk assessment tools has been on the science of detection of PCa with new biomarkers. As illustrated by the US Preventive Services Task Force’s recent announcement of draft guidelines for PSA screening, changing them to a “D” recommendation (not recommended), it is incumbent on our specialty to reduce the burden of overdiagnosis of indolent disease as well as to improve our ability to identify lethal tumors early, when treatment would be most successful. In the Early Detection Research Network (EDRN) of the National Cancer Institute, the Prostate Collaborative Group’s biomarker validation programs have embedded plans to determine how novel markers can be used in combination as well as how they can be used in combination with other biometrics (e.g., age, race, family history, DRE findings) to improve on our existing biomarkers. Our recent experience with [–2] proPSA in a formal EDRN validation trial found a significant improvement of the combination of %free PSA with [–2] proPSA in the prediction of PCa [6]. Importantly, these new biomarkers improved the detection of high-grade disease. A similar assessment is ongoing in both the PCA3 and *TMPRSS2:ERG* validation trials. We strongly encourage all analyses of putative PCa biomarkers to adopt this approach, building on the knowledge of risk factors, biometrics, and biomarkers related to PCa and, most important, to high-grade disease.

The greatest remaining challenge is for the clinician. The most common question we receive is, “At what level of risk should I recommend a prostate biopsy?” Unfortunately, we do not have a precise answer. One general piece of guidance, however, is that if the risk of high-grade disease is 2–4% or less, one could inform the patient that his risk of a serious infectious complication from the biopsy (which he would suffer immediately) may be as high or greater than the risk of detection of a potentially lethal cancer (from which he may suffer consequences years into the future). A second piece of guidance is to compare the risk of detection of low-grade cancer with the risk of detection of high-grade cancer. As there is growing consensus that there may be a net negative impact of a detection of a Gleason 3 + 3 tumor in most men, if the risk of low-grade cancer is 20% and the risk of high-grade cancer is < 2%, the patient could be told that he has a 10-fold greater risk of potential detection of an indolent tumor than of one of consequence. The final guidance is that there should not be a single level of risk that prompts biopsy in all men; their aversion to risk of cancer will be different, as will their life expectancy, their aversion to risk of overdiagnosis, and all other consequences of detection.

Ideally, in the future, a biomarker will be discovered that will say “normal” in some men and “cancer” in others. Given the heterogeneity of PCa and the experience in the science of biomarkers, this is unlikely in the near term. Until that ideal future, clinicians should regularly use risk assessment tools and become familiar with discussing risk with their patients. We must remember that our patients are comfortable with risk: When they purchase a washing machine, they rely on *Consumer Reports* to assess reliability. If they can use risk for consumer purchases, they can certainly do likewise for their health.

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