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Focusing PSA Testing on Detection of High-Risk Prostate Cancers by Incorporating Patient Preferences Into Decision Making

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In the mid-1980s, the discovery that prostate-specific antigen (PSA) testing, coupled with prostate biopsy, could identify silent prostate cancers that would otherwise be present as metastatic disease led to substantial increases in cancer detection and subsequent treatment. With time, more intensive screening and biopsy led to significant increases in detection of low-grade tumors that are almost ubiquitous at autopsy in older men. Although during the ensuing 2 decades there was a 44% decline in prostate cancer mortality (likely attributable, in part, to early detection with PSA testing), the effect of detection and treatment as well as the complications from treatment (erectile dysfunction, urinary obstruction or incontinence, and gastrointestinal adverse effects) led the US Preventive Services Task Force to recommend against PSA screening in the general population.¹ Results from 2 large randomized clinical trials (RCTs) of PSA screening, in which a European RCT reported a modest reduction in prostate cancer mortality and a US trial found no change in mortality, reinforced this conclusion.^{2,3}

Data suggest that PSA levels should no longer be referred to as “normal” or “elevated” but should be incorporated into a multivariable risk assessment to provide individualized risk information for decision making.

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Increasing numbers of RCTs and observational studies demonstrate that multimodality treatment of high-grade, larger, and more aggressive prostate cancers reduces the risk of prostate cancer death, whereas for small, low-grade, potentially indolent tumors, high rates of survival can be achieved with active surveillance in which treatment is deferred, often for years, unless an aggressive cancer is subsequently detected.⁴ For these lower-grade tumors, there is little evidence that detection and immediate treatment will benefit the patient, whereas early detection and treatment may significantly reduce quality of life through adverse effects of treatment or anxiety.⁵ A risk of sepsis approaching 4% after biopsy⁶ further adds to the potential harm of immediate biopsy in men who are then found to have low-grade cancer.

A risk assessment tool was developed in 2006 based on 5519 men in the Prostate Cancer Prevention Trial (PCPT), all of whom had undergone a prostate biopsy regardless of PSA level and in whom other risk variables (age, race/ethnicity, family history of prostate cancer, prior biopsy information, and rectal examination findings) were known.⁷ Using individual patient information, this assessment tool predicts 3 outcomes: negative biopsy result, low-grade cancer, or high-grade cancer. This tool has subsequently been validated in several populations, was recently updated with contemporary data, and now includes a simplified patient display.^{8,9}

During clinical interactions, it has become apparent that when PSA test results are incorporated in this risk assessment tool, a new calculus develops as the patient weighs the risks and benefits of the decision to undergo prostate biopsy. Much of the decision making is related to the risks of the 3 outcomes (negative biopsy result, low-grade cancer risk, high-grade cancer risk) as well as patient comorbidities and, importantly, the values that the patient places on the different outcomes, some of which occur immediately and some of which may occur years in the future. Clinical interactions using the risk calculator have improved and enhanced individualized patient decision making; importantly, before biopsy is performed, patients are empowered to consider not only short-term outcomes but long-term consequences of their decision.

Two patient examples are illustrative. Neither patient had previously undergone a prostate biopsy. The first patient, a 55-year-old white man, had a prostate nodule; his PSA level was 0.8 ng/mL, and he had no family history of prostate cancer. His risks were 89% for a negative biopsy result, 10% for low-grade cancer, and 1% for high-grade cancer. By contrast, the second patient, a 69-year-old African American man, had a prostate nodule; his PSA level was 7.5 ng/mL, and his father had prostate cancer. His risks were 42% for a negative biopsy result, 19% for low-grade cancer, and 39% for high-grade cancer. The risk calculator graphically displays these rates along with a randomly distributed 2% to 4% of individuals developing sepsis after biopsy (eFigure in the Supplement).

In a conversation with the first patient, it can be stressed that although there is a 1-in-100 risk that he may have an aggressive prostate cancer for which a biopsy now and early treatment may prevent a future prostate cancer death, there is a 10-in-100 risk that a low-

grade tumor would be found, a tumor that is often inconsequential and that even with an active surveillance strategy would involve years of repeated PSA testing, examinations, and repeated prostate biopsies. If the patient opts for treatment instead of surveillance, there is a risk of erectile dysfunction and a risk of urinary adverse effects (incontinence or obstruction). There is also a 4% risk of sepsis with biopsy. In this patient, the risk of detection of a low-grade, potentially inconsequential tumor is 10 times the likelihood of finding a high-grade cancer. In practice, patients empowered with this information often opt to repeat the assessment in 6 to 12 months rather than undergo an immediate prostate biopsy.

The second patient has an entirely different calculus. Although he has a 42-in-100 chance of a negative biopsy result and a 19-in-100 chance of detection of a potentially inconsequential low-grade tumor, his likelihood of a potentially life-threatening, high-grade cancer (39 in 100) is double the risk of a low-grade tumor. Although some men may still opt for deferring biopsy, most with a reasonable life expectancy decide to undergo biopsy.

Although some observers (including the US Preventive Services Task Force) have concluded that PSA testing should be summarily dismissed, advances in understanding disease risks and outcomes now allow physicians and patients to make more intelligent, personalized decisions regarding PSA findings. Data suggest that PSA levels should no longer be referred to as “normal” or “elevated” but should be incorporated into a multivariable risk assessment to provide individualized risk information for decision making.¹⁰ Although it remains to be proven that such a targeted approach to prostate cancer detection will maintain the continued reduction in prostate cancer mortality, inclusion of a targeted approach in clinical practice has the potential to reduce the detection of small, low-grade tumors. Future improvements in decision-making tools may include incorporation of comorbidities, life expectancy, and validated measures of patient preferences.

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