Prostate-Cancer Screening — What the U.S. Preventive Services Task Force Left Out
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Forty years after prostate-specific antigen (PSA) was identified and nearly 20 years after it became available for prostate-cancer screening, the U.S. Preventive Services Task Force (USPSTF) recently recommended against PSA-based screening.\(^1\) In the interim, untold millions of men have been tested. Because PSA is not cancer-specific and because prostate cancer's aggressiveness varies widely, controversy and debate about PSA screening were predictable from the outset.

Although we agree fully with the task force's analysis, there are three issues that the panel did not address but that are relevant to primary care clinicians, who initiate most PSA screening. (One of us is a general internist who has discussed the pros and cons of PSA screening with hundreds of patients over two decades; the other discovered PSA in 1970.)

The first issue pertains to office-based decisions about whether to initiate PSA screening. Virtually all guidelines call on clinicians to discuss the benefits and harms of screening and to individualize screening decisions according to patients' values and preferences. For example, the American Urological Association states that decisions "should be individualized, and benefits and consequences should be discussed . . . before PSA testing occurs."\(^2\) The American Cancer Society advises clinicians to provide "information about the uncertainties, risks, and potential benefits" to help men "reach a screening decision based on their personal values."\(^3\)

At first glance, these guidelines appear exemplary, because they embrace the idea of patient-centered informed decision making. However, before 2009 — when results from two large screening trials were finally published — an evidence-based discussion of benefits was impossible because no convincing data existed to support screening. To be sure, clinicians could speculate loosely about potential benefit ("We might catch prostate cancer early enough to save your life") and potential harm ("Screening might result in burdensome interventions with serious complications"). But the idea that physicians could initiate truly informed discussion was wishful thinking, because clinicians and
patients had to consider an enormous list of probability estimates and uncertainties: What PSA cutoff is best? What level should trigger repeat PSA testing or biopsy? How often should we repeat either one? What is the patient's pretest probability of cancer? What is the chance that a PSA test plus a biopsy will find cancer, if it's present? If cancer is found, will it be clinically important? Will this patient prefer surgery, radiation therapy, or watchful waiting? What are the probabilities of serious side effects from each treatment, and how will this patient weigh them? Most important, will screening reduce this patient's risk of death from prostate cancer?

All these factors are relevant to discussions of benefits and harms, harmonized with patients' values or preferences. But it was impossible to address so many probabilities and uncertainties coherently during routine office visits. Thus, patients were not really making informed decisions, and office-based discussion of the pros and cons of PSA testing was essentially a charade. Instead, most patients' decisions reflected their general concerns about cancer or their general inclination to accept (or resist) medical interventions.

In March 2009, initial results of the two major screening trials were finally available. Unfortunately, they created more confusion than clarity. A U.S. trial showed no mortality benefit from screening; a European trial showed a small reduction in prostate-cancer–related mortality, but large numbers of men received aggressive treatment to benefit few. Both trials had important methodologic limitations (which are addressed by the USPSTF). Discussions with patients about the benefits and harms of screening have therefore become even more difficult since 2009, since clinicians must now add another layer of uncertainty: explaining why two huge randomized trials were less than definitive and why experts disagree about their interpretation.

The second issue is the variable and often idiosyncratic management of PSA levels in primary care and urology practices. Many PSA levels fall near the commonly used action thresholds in the range of 2.5 to 4.0 ng per milliliter. Men are tested and retested — sometimes several times per year — hoping to hear that their PSA levels “went down” or at least “didn't go up.” Patients undergo repeated biopsies, often at arbitrary intervals, after small spikes in PSA levels. PSA screening has even contributed to overuse of quinolone antibiotics, which many clinicians prescribe for lowering mildly elevated PSA levels in asymptomatic men with presumed prostatitis, even though a recent trial showed no difference between the PSA response to antibiotics and placebo.
These approaches to managing serial PSA levels reflect either a fundamental misunderstanding of — or an unwillingness to acknowledge — PSA’s limitations as a marker for early prostate cancer. Observational studies show clearly that PSA levels fluctuate spontaneously, moving above or below whatever threshold clinicians deem worrisome. In addition, random biopsies can detect prostate cancer in 12% of men with PSA levels below 2 ng per milliliter and in 25% of men with levels between 2.1 and 4.0 ng per milliliter; the latter figure approximates the prevalence often reported for men with levels between 4.0 and 10.0 ng per milliliter. When the PSA goes up — for example, from 3.0 to 4.0 ng per milliliter — and triggers a biopsy that reveals cancer, clinicians refer to “PSA-detected cancer.” But many of these cancers are not really detected by PSA screening; they are incidental findings against a background of randomly fluctuating PSA levels and an age-related increase in prostate-cancer incidence.

The substantial variability in how clinicians manage serial PSA levels is understandable, since published guidelines are vague and offer little guidance. But the guidelines are vague precisely because the limitations of PSA screening preclude the kind of rational, standardized, evidence-based algorithm that should inform any routine preventive intervention.

The third issue lies at the interface of clinical practice, public health, and responsible stewardship of health care resources. Although the USPSTF explicitly does not consider costs, policymakers cannot ignore economic aspects of screening. Using data from the European screening trial, researchers have estimated that $5.2 million would have to be spent on screening (and the interventions that follow it) to prevent one death from prostate cancer. That estimate does not appear to include the costs of excessive serial PSA testing and repeated office-based encounters devoted to discussions about screening or interpretation of fluctuating PSA results. The extraordinary time, effort, and costs associated with the PSA-screening enterprise must be evaluated against other claims on health care spending and physicians’ time and energy. We believe that the current PSA-based screening paradigm does not compare favorably with competing health care priorities.

Some people have argued that PSA screening should at least be available for black men, because the incidence and aggressiveness of prostate cancer are greater in black than in white Americans. This proposal, however well intentioned, is misguided. In 2007, the proportion of deaths among U.S. men that were attributed to prostate cancer was 3.3% among blacks and 2.3% among
whites; these rates are close enough that race-specific distinctions for screening are unwarranted. Furthermore, there is no evidence that the balance of benefits and harms from PSA screening differs for blacks and whites. If PSA screening is worthwhile, it should be applied universally; if it is not, selective screening would be a disservice to black men. Eliminating the unconscionable racial gap in overall access to essential health care services would be a far better way to address disparities than promoting a questionably effective cancer-screening program: the percentage of blacks without medical insurance is nearly twice that of whites.5

For two decades, primary care physicians have been expected to present a flawed screening test to patients, cloaking the flaws in an elaborate ritual of informed decision making. In turn, men have been expected to make sense of a confusing mix of hypothetical outcomes. Although the USPSTF recommendation is unlikely to end the PSA controversy, a document finally exists that should provide guidance to clinicians and policymakers.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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SOURCE INFORMATION

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