Screening for Prostate Cancer

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This Journal feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author’s clinical recommendations.

A 50-year-old, non-Hispanic white man comes for a new-patient appointment and wants to discuss prostate-cancer screening. He has no family history of prostate cancer and says that he does not have any lower urinary tract symptoms. What would you advise?

Prostate cancer is the most frequently diagnosed cancer other than skin cancer and the second leading cause of death from cancer in men in the United States. In 2011, prostate cancer is expected to be diagnosed in an estimated 240,000 men and to cause nearly 34,000 deaths. After peaking in the early 1990s, by 2007 the age-adjusted incidence of prostate cancer had declined to 165.8 cases per 100,000 men and mortality rates had declined to 23.5 deaths per 100,000 men (Fig. 1). Between 1999 and 2006, at the time of diagnosis, about 80% of prostate cancers were clinically confined to the prostate, and only 4% had metastasized.

The strongest risk factors for prostate cancer are older age, a positive family history, and black race. The median age at diagnosis is 67 years, and the median age at death is 81 years. The risk of prostate cancer is two times as high among patients who have a first-degree relative with a prostate-cancer diagnosis as among patients who do not have a first-degree relative with this diagnosis. Black men have the highest incidence rate of prostate cancer in the United States and are more likely to receive a diagnosis of prostate cancer at an advanced stage than men in any other racial or ethnic group.

In the United States, approximately 90% of prostate cancers are detected by means of screening. After the introduction of prostate-specific antigen (PSA) testing, the lifetime risk of receiving a diagnosis of prostate cancer nearly doubled, increasing from approximately 9% in 1985 to 16% in 2007.

The great majority of men with a diagnosis of prostate cancer die from other causes. Autopsy series suggest that 30% of men older than 50 years of age and 70% of those older than 70 years of age have occult prostate cancer. An analysis of data from the Surveillance, Epidemiology, and End Results (SEER) registry and from Medicare claims evaluated outcomes of almost 90,000 older men who received a diagnosis of early-stage prostate cancer between 1992 and 2002 and who were cared for without attempted curative therapy. The 10-year risk of death from prostate cancer ranged from approximately 8% among men with well-differentiated tumors to 26% among those with poorly differentiated tumors. The 10-year risks of death from competing causes were consistently nearly 60%, regardless of the tumor grade.
**Screening Tests**

The rationale for screening is that early detection and treatment of asymptomatic cancers could extend life, as compared with treatment at the time of clinical diagnosis. Effective cancer screening requires an accurate, reliable, and easy-to-administer test that detects clinically important cancers at a preclinical stage and the availability of effective treatment that results in better outcomes when administered early, rather than after signs or symptoms of disease have developed.

For many years, the digital rectal examination was the primary screening test for prostate cancer. However, this test has considerable interexaminer variability, and the majority of cancers detected by means of digital rectal examination are at an advanced stage. In the late 1980s, PSA testing, which was initially developed for prostate-cancer surveillance, was rapidly and widely adopted for screening; by 2001, a population-based survey in the United States showed that 75% of men 50 years of age or older had undergone PSA testing. The widespread use of PSA testing was based on its increased detection of early-stage cancer, as compared with digital rectal examination; there was no evidence that testing reduced the risk of death from prostate cancer.

Initially, PSA values above 4.0 ng per milliliter were considered abnormal, though lower cutoff levels have subsequently been proposed. The estimated diagnostic performance of PSA testing according to the cutoff level is shown in Table 1. Most abnormal PSA values are false positive results that can be caused by benign prostatic hyperplasia, prostatitis or cystitis, ejaculation, perineal trauma, or the recent use of instruments for testing or surgery in the urinary tract. Moreover, a normal PSA value does not rule out prostate cancer; in the control group in the Prostate Cancer Prevention Trial, prostate cancer was detected in 15% of men with normal results on digital rectal examination and PSA values of 4.0 ng per milliliter or less (and in 9% of men with normal results on digital rectal examination and PSA values ≤1.0 ng per milliliter) who underwent a prostate biopsy at the end of the study.

Numerous approaches have been proposed to improve the diagnostic accuracy of the PSA test, including measuring PSA velocity (change over time), levels of free and protein-bound PSA, PSA density (the PSA level divided by the prostate volume), and the use of cutoff values for PSA levels that are specific to the patient’s age and race or ethnic group. However, the clinical usefulness of these strategies remains unproved.

**Potential Benefits of Screening**

Ecologic and case–control data have suggested associations between PSA testing and a decrease in mortality from prostate cancer, but the findings are conflicting. SEER data show steadily declining age-adjusted mortality rates from prostate cancer since 1994, though an absolute decrease of only 10.4 deaths per 100,000 men (Fig. 1). Mathematical models have estimated that 45 to 70% of the observed decrease in mortality could be attributable to PSA screening.

Results of recently reported randomized trials, however, have not convincingly established the value of PSA screening (see Table 1 in the Supple-
mentary Appendix, available with the full text of this article at NEJM.org). Although the European Randomized Study of Screening for Prostate Cancer (ERSPC; Current Controlled Trials number, ISRCTN49127736) showed that screening resulted in a moderately reduced mortality from prostate cancer,\textsuperscript{19} the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial (ClinicalTrials.gov number, NCT00002540) showed no benefit.\textsuperscript{20}

The ERSPC, conducted in seven European centers, randomly assigned 182,160 men who were between the ages of 50 and 74 years to PSA screening every 4 years (except every 2 years in Sweden) or usual care (no PSA screening).\textsuperscript{19} The initial mortality findings were based on data for 162,243 men who were between the ages of 55 and 69 years. During a median follow-up of 9 years, prostate cancer was detected in 8.2% of the screened subjects as compared with 4.8% of the control subjects (a 71% increase). Mortality from prostate cancer was 20% (95% confidence interval [CI], 2 to 35) lower in the screening group. However, the absolute difference was only 0.7 deaths per 1000 men, suggesting that 1410 men would need to be screened approximately twice over a period of 9 years to prevent 1 death from prostate cancer. Furthermore, prostate cancer would need to be diagnosed in 48 men to prevent that 1 death. Screening did not result in decreased overall or prostate-cancer mortality among men between the ages of 50 and 54 years or those between the ages of 70 and 74 years.

Subsequent analyses of these data have suggested that the benefit of regular screening might be higher after adjustment for nonadherence (estimated relative reduction in mortality, 27%) and after additional adjustment for contamination (PSA screening in persons not randomly assigned to screening; estimated relative reduction in mortality, 31%).\textsuperscript{21} However, even these post hoc analyses, which are more susceptible to bias than the primary intention-to-treat analysis, suggested only a small absolute survival benefit.

Results from the Göteborg, Sweden, randomized screening trial, which included ERSPC subjects, showed a greater reduction in the risk of death from prostate cancer with screening (44%; 95% CI, 18 to 61) among men 50 to 64 years of age who were followed for a median of 14 years.\textsuperscript{22} This finding corresponds to a number needed to screen of 293 and a number needed to diagnose of 12 to prevent one death from prostate cancer. Possible explanations for this finding include more frequent PSA testing, younger age range, longer follow-up at this site, and simply chance (the 95% confidence interval for this site-specific estimate included the point estimate for the multicenter analysis). Studies have estimated that PSA screening detects cancers 5 to 10 years before they can be detected clinically (the lead time),\textsuperscript{23} and survival curves after treatment for clinically detected cancers did not diverge significantly for at least 5 years.\textsuperscript{24} Accordingly, a modeling study extrapolating ERSPC data from all sites over a longer follow-up period projected an increasing screening benefit over time;\textsuperscript{25} by year 12, the estimated number needed to screen to prevent one death from prostate cancer would be 503, and the number needed to diagnose would be 18.

In contrast, the PLCO trial, which randomly assigned 76,693 men, who were between the ages of 55 and 74 years at enrollment, to annual PSA testing for 6 years and annual digital rectal examination for 4 years or to no screening, did not show any reduction in overall or prostate-cancer mortality with screening.\textsuperscript{20} Screening resulted in a significant increase in cancer detection, with 22% more cancers diagnosed in the screened group than in the control group (2820 vs. 2322) at 7-year follow-up. Cancers in the screening group had more favorable tumor characteristics than cancers in the control group, including earlier stages and lower Gleason scores (the Gleason score is the sum of the two most common histologic
patterns or grades in a prostate tumor, each of which is graded on a scale of 1 to 5, with 5 indicating the most aggressive pattern). Nonetheless, prostate-cancer mortality was not reduced in the screening group as compared with the control group (rate ratio, 1.13; 95% CI, 0.75 to 1.70).

However, several factors could have biased the results of the PLCO trial toward the null hypothesis. More than 40% of enrolled subjects had undergone at least one PSA test in the 3 years before study enrollment. Serial PSA testing is associated with reduced rates of prostate-cancer detection as well as an earlier stage and less aggressive tumor characteristics at the time of diagnosis. Given the long lead time associated with PSA testing, the 7-year follow-up might have been insufficient to show a survival benefit. The study also had substantial contamination, with more than half of the subjects in the control group reporting PSA testing in year 6. In addition, only 40% of men in the screening group who had abnormal initial PSA values actually underwent prostate biopsy, and the proportions were even lower during subsequent screening rounds.

POTENTIAL HARMs OF SCREENING
Abnormal PSA tests lead to biopsies, which can infrequently cause bleeding, pain, or infection. Undergoing biopsy can be stressful, and some men have persistent anxiety regarding possible cancer, despite negative biopsy results. Mathematical models estimate that 23 to 42% of PSA-detected cancers are overdiagnosed, because on the basis of life expectancy at the time of diagnosis and the natural history of the cancer in the absence of screening, it would not be expected to cause clinical problems during the patient’s lifetime. Aggressive treatment of these cancers is associated with unnecessary risks of urinary, sexual, and bowel dysfunction, which can adversely affect the quality of life.

TREATMENT TRIALS
Paradoxically, PSA testing became widespread before any data supported the benefit of aggressively treating early-stage cancer. In 2002, the Scandinavian Prostate Cancer Group Study Number 4, which randomly assigned 695 men younger than 75 years of age who had early-stage prostate cancer to radical prostatectomy or watchful waiting, showed a relative hazard reduction for death from prostate cancer of 50% among those assigned to prostatectomy (4.6% vs. 8.9%), during a median follow-up of 6.2 years. The mortality benefit persisted through 15 years of follow-up. However, no survival benefit was seen for men who were older than 65 years of age at the time of diagnosis and treatment. Since only about 5% of the tumors were detected by screening, and more than 75% were palpable, it is questionable whether these results are applicable to patients in the United States.

The Prostate Cancer Intervention versus Observation Trial (NCT00007644) randomly assigned 731 men with early-stage prostate cancer to either radical prostatectomy or watchful waiting. Three fourths of tumors were diagnosed primarily on the basis of abnormal PSA values, and about half were palpable. Preliminary results showed no significant differences in overall or prostate-cancer mortality after 12 years of follow-up, particularly among men with low-risk cancers. In other randomized trials, the combination of external-beam radiotherapy and androgen-deprivation therapy was associated with increased overall and disease-specific survival, as compared with radiotherapy alone in men with intermediate- or high-risk early-stage prostate cancers and as compared with androgen-deprivation therapy alone in men with locally advanced cancers. Data are lacking from randomized trials comparing radiotherapy with either surgery or watchful waiting for early-stage prostate cancer.

INFORMED DECISION MAKING
Given the complexity of issues regarding prostate-cancer screening, experts recommend that men receive support in making informed decisions. However, PSA testing is often performed without discussion of the benefits and harms of screening. Competing clinical demands and the challenge of providing sufficient information to sup-

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Table 1. Diagnostic Performance Characteristics of PSA Testing, According to Cutoff Level.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>PSA Cutoff Level</th>
<th>percent</th>
<th>percent</th>
</tr>
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<tr>
<td></td>
<td>≥4.0 ng/ml</td>
<td>≥3.0 ng/ml</td>
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<tr>
<td>Test positivity</td>
<td>12</td>
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<td>Cancer-detection rate</td>
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<td>4</td>
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<td>Sensitivity</td>
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<td>Specificity</td>
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<tr>
<td>Positive predictive value</td>
<td>30</td>
<td>28</td>
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</table>

* Data are from Wolf et al. PSA denotes prostate-specific antigen.
port decision making present important barriers to having this discussion. A strategy for conveying relevant information is to use “decision aids,” defined as interventions that “help individuals make specific and deliberative choices among options by providing information on the options and outcomes relevant to an individual’s health status.” A meta-analysis of 18 randomized trials of screening decision aids, which included video, written, and Internet-based materials, showed that they significantly increased patients’ knowledge and confidence in their screening decisions and also decreased PSA screening.

Men undergoing regular PSA screening are much more likely than unscreened men to receive a diagnosis of prostate cancer. However, a substantial proportion of PSA-detected prostate cancers are considered to be overdiagnosed. Although the PSA level, the findings on digital rectal examination, and the Gleason score on biopsy can be used to stratify patients into risk groups, they cannot perfectly predict which cancers are destined to cause future illness. Consequently, the majority of men with an early-stage cancer opt for a potentially curative treatment such as surgery or radiotherapy. Biomarkers that may better identify high-risk cancers (and avert unnecessary treatment) are being evaluated, including ones targeting hypermethylation and gene expression, but their clinical usefulness is currently unclear.

An alternative approach that is intended to minimize the harms of overdiagnosis is a strategy of active surveillance for men with low-risk cancers (a PSA level of ≤10 ng per milliliter and a Gleason score of ≤6) with the use of serial PSA tests, digital rectal examinations, and prostate biopsies. Aggressive treatment is offered only for signs of clinical progression on surveillance testing — although criteria for defining progression remain controversial — or at the patient’s request. Pooled results from seven observational studies involving 2130 subjects showed a very low risk of death from prostate cancer (0.3%), with 64% of men who continued to undergo active surveillance rather than receive active treatment throughout a median follow-up period of 43 months. The randomized Prostate Testing for Cancer and Treatment trial (NCT00632983) is enrolling 2050 men between the ages of 50 and 69 years who have early-stage prostate cancer and following them at least through 2013 to compare rates of survival and disease progression between active surveillance and aggressive treatment.

Although screening decision aids are recommended to support informed decision making, more research is needed to determine the optimal formats, timing, and settings for providing them and their effects on clinical outcomes.

### Areas of Uncertainty

Whereas early American Urological Association and American Cancer Society guidelines strongly supported routine, annual prostate-cancer screening, subsequent guidelines have taken into account the uncertainties regarding the outcomes of screening. Current American Urological Association and American Cancer Society guidelines, updated after the publication of the results of the ERSPC and PLCO trials, are summarized in Table 2. Both organizations encourage shared decision making between patients and clinicians and periodic PSA testing when the patient’s life expectancy is at least 10 years. However, guidelines differ with respect to the recommended age at which to begin routinely discussing screening and the criteria for biopsy referral. The American Cancer Society guidelines also recognize the challenges in helping men achieve informed decision making and list a number of publicly available written and Web-based screening decision aids.

The U.S. Preventive Services Task Force recently issued a draft recommendation against PSA screening for asymptomatic men, regardless of their age, racial or ethnic group, or family history (Table 2). The task force concluded that the harms of screening outweigh the benefits. The task force’s final recommendation will be released after publication of this article.

### Conclusions and Recommendations

Decisions about prostate-cancer screening should be based on the preferences of an informed patient. The man in the vignette should be engaged in a shared decision-making process that elicits his values and preferences for the potential consequences of testing. Supporting his decision making requires informing him of his cancer risk (which is average) and educating him about the often indolent natural history of prostate cancer, the limited accuracy of screening and diagnostic tests, and the potential...
benefits and harms of screening and treatment. He should be informed that there is inconsistent evidence thus far from the major screening trials regarding whether screening decreases mortality from prostate cancer. Although articles on the initial trial results may have underestimated the potential benefit of screening with respect to prostate-cancer mortality, screening has not been shown to improve survival overall. In addition, the small absolute disease-specific survival benefit must be balanced against the potential harms of over-diagnosis and complications of treatment, including urinary, sexual, and bowel dysfunction. Moreover, the optimal treatment for early-stage cancer, if any, is uncertain. Having the patient review a decision aid (see, for example, www.cdc.gov/cancer/prostate/pdf/prosguide.pdf, or, for black men, www.cdc.gov/cancer/prostate/pdf/aaprosguide.pdf) might facilitate a more efficient and effective discussion that helps him reach his best decision.

The views expressed in this article are those of the author and do not necessarily represent the official positions of the Department of Veterans Affairs.

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Table 2. Prostate-Cancer Screening Guidelines.

<table>
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<tr>
<th>Recommendation</th>
<th>American Urological Association</th>
<th>American Cancer Society</th>
<th>U.S. Preventive Services Task Force</th>
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<tr>
<td>Shared decision making between patient and clinician</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Age to begin offering screening — yr</td>
<td>40</td>
<td>50</td>
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<tr>
<td>Average-risk patients</td>
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<tr>
<td>High-risk patients (black patients and those with first-degree relative with prostate cancer)</td>
<td>40</td>
<td>40-45</td>
<td>Not applicable</td>
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<td>Discontinuation of screening</td>
<td>Life expectancy &lt;10 yr</td>
<td>Life expectancy &lt;10 yr</td>
<td>Not applicable</td>
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<tr>
<td>Screening tests</td>
<td>PSA, digital rectal examination</td>
<td>PSA, optional digital rectal examination</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Frequency of screening</td>
<td>Annual (possibly less often for men in their 40s)†</td>
<td>Annual (every other year when PSA &lt;2.5 ng/ml)</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Criteria for biopsy referral</td>
<td>Age, family history, race or ethnic group, findings on digital rectal examination, total PSA, free PSA, PSA velocity, PSA density, previous biopsy findings, coexisting conditions</td>
<td>PSA ≥4.0 ng/ml, abnormal digital rectal examination; individualized risk assessment if PSA is 2.5–4.0 ng/ml</td>
<td>Not applicable</td>
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</tbody>
</table>

† The guidelines indicate that the initial PSA value at 40 years of age (relative to the median value of 0.6 to 0.7 ng per milliliter for this age group) would determine subsequent (but unspecified) screening intervals. The National Comprehensive Cancer Network recommends using a PSA cutoff level to determine whether subsequent testing should be performed annually or at 45 years of age (and then at 50 years of age). However, these recommendations are not evidence-based.
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