Screening for prostate cancer

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INTRODUCTION

Prostate cancer is common and is among the main causes of cancer-related death. At the same time, in many cases, prostate cancer grows so slowly that it does not impact survival; hence, routine screening is controversial.

This topic reviews the efficacy of screening and recommendations regarding screening for prostate cancer.

Risk factors, clinical manifestations, and diagnosis of prostate cancer are discussed separately. (See "Risk factors for prostate cancer" and "Clinical presentation and diagnosis of prostate cancer".)

Screening of patients at high risk for prostate cancer due to genetic syndromes (*BRCA1*/*BRCA2*) is described separately. (See "Cancer risks and management of BRCA1/2 carriers without cancer", section on 'Management of male BRCA1/2 carriers without cancer'.)

EPIDEMIOLOGY AND NATURAL HISTORY

- **Incidence** – Worldwide, there are an estimated 1,300,000 new cases of prostate cancer annually, making it the second most commonly diagnosed cancer in men [1]. In the United States, it is the third leading cause of cancer, with approximately 192,000 new diagnoses annually [2]. For an American male, there is a 12 percent lifetime risk of being diagnosed with prostate cancer [3].

- **Natural history** – Without screening, many cases of prostate cancer do not ever become clinically evident. Data suggest that prostate cancer often grows so slowly that most men die of other causes before the disease becomes clinically advanced [4-7]. At autopsy of men who died of other causes, prostate cancer detection rates, approximately 30 percent for men in their fifties and up to 70 percent for men in their seventies, are higher than the lifetime incidence of diagnosed prostate cancer in the population [4-7].

  Prostate cancer survival is related to many factors, especially the extent of tumor at the time of diagnosis. The five-year relative survival among men with cancer confined to the prostate (localized) or with regional spread is 100 percent, compared with 31 percent among those diagnosed with distant metastases [8]. While men with advanced stage disease may benefit from palliative treatment, their cancers are generally not curable.

- **Declining mortality rates** – Worldwide, there are an estimated 359,000 prostate cancer deaths annually, making it the fifth leading cause of male cancer death [1]. In the United States, prostate cancer is the second leading cause of cancer death among men, with about 33,000 deaths annually [2]. For an American male, the lifetime risk of dying of prostate cancer is 2.4 percent [3].

  Prostate cancer mortality rates have declined in the United States between 1992 and 2016, decreasing from 39 to 19 per 100,000 persons (figure 1) [9]. Simulation models suggest that prostate-specific antigen (PSA) screening could account for 45 to 70 percent of the decline, mainly by decreasing the incidence of distant-stage disease [10,11]. Some studies have noted a greater decline in prostate cancer mortality rates in a region where screening was implemented (ie, the United States) than in a region where it was not implemented (ie, the United Kingdom) during the same time period [12-14]. However, other studies have shown that mortality rates declined even in countries with less intensive screening than the United States [15]. Other factors that may explain the decline in mortality rates include advances in treatments for men with localized prostate cancer as well as for those with advanced-stage disease. For example, the use of androgen deprivation therapy or other chemotherapies could allow men with advanced-stage disease to live long enough to die from a concomitant condition, rather than from prostate cancer.

BENEFITS AND HARMS OF SCREENING

For prostate cancer screening to be valuable, it must reduce disease-specific morbidity and/or mortality by detecting cancer at an early stage. However, detection at an early stage does not necessarily correlate with a clinically beneficial outcome (eg, decline in morbidity or mortality due to prostate cancer). Increased detection of prostate cancer subjects some patients to the risks associated with treatments that may not prolong life and that have risks of morbidity.

Effect on incidence — Screening increases the detection of prostate cancer among men. Prostate cancer incidence in the United States increased sharply during the initial years following the advent of prostate-specific antigen (PSA) testing and has returned to levels seen prior to the onset of testing as the rate of PSA testing has declined (figure 1) [10]. In a meta-analysis of five randomized trials including 341,342 participants, cancer was diagnosed more often in men who were serially screened (risk ratio 1.30, 95% CI 1.02-1.65) compared with the control group [16]. In another study of just one-time screening, at 10-year follow-up, prostate cancer, particularly low-grade, was diagnosed more frequently in the one-time screening group than in the control group (rate ratio 1.19 [95% CI 1.14-1.25]) [17].

Screening may reduce the risk for advanced-stage prostate cancer. In a randomized trial of 76,813 men with median follow-up of 12 years, the cumulative incidence rate of metastatic disease among those who were in the regular screening group was 0.67 percent compared with the incidence rate in the control group of 0.86 percent [18]. The relative reduction of metastatic disease was 30 percent in the intention to screen group (hazard ratio [HR] 0.70; 95% CI 0.60-0.82), with a relative reduction of 42 percent for men actually screened. The absolute risk reduction of metastatic disease was 3.1 per 1000 men randomized.

Effect on mortality — While prostate cancer mortality rates have declined since the advent of PSA testing, it is uncertain what proportion of this is due to PSA screening. (See 'Epidemiology and natural history' above.)

The best available evidence from randomized trials found that screening has at most a small benefit in reducing prostate cancer mortality.

In a meta-analysis of randomized trials with follow-up periods ranging from 7 to 20 years, a prostate cancer mortality reduction was not found (relative risk [RR] 0.95, 95% CI 0.86-1.07). In this meta-analysis of five trials, participants were randomized to control groups or to screening that occurred at intervals ranging from one to seven years, except for one smaller study that used one-time screening [16].

However, the included studies each contained high or unclear risks of bias. In one included study, the European Randomized Study of Screening for Prostate Cancer (ERSPC), a small absolute survival benefit with PSA screening was reported; at 11 years, the prostate cancer mortality rate in the screening group was 0.41 percent compared with 0.52 percent in the control group [16,19]. Survival benefit increased over longer-term follow-up (RR for prostate cancer mortality 0.85 at 9 years, 0.79 at 13 years). At 13 years, the absolute risk reduction of prostate cancer death was 1.28 per 1000 men, meaning that to avert one prostate cancer death, 781 men needed to be invited to screening, of whom 27 were expected to be diagnosed with cancer, and at least 16 of those treated with surgery or radiation. While this trial was assessed to have the lowest risk of bias of those included in the meta-analysis, the risk of bias was unclear due to allocation concealment and completeness of outcome data. Another trial included in the meta-analysis, the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial, did not report a mortality benefit; however, the negative results have been largely discounted because so many patients randomized to the control group had screening as part of usual care [20,21].

A study performed subsequent to the meta-analysis (the Clustered Randomized Trial of PSA Testing for Prostate Cancer) looked at screening once rather than serially and found no survival benefit among the 400,000 men ages 50 to 69 years [17]. At median 10-year follow-up, there was no prostate cancer-specific survival difference (rate ratio 0.96, 95% CI 0.85-1.08) and no overall survival difference (rate ratio 0.99, 95% CI 0.94-1.03).

Calculations that take into account not only years of survival, but also the value of each potential benefit and harm associated with screening, suggest that screening does not clearly improve quality-adjusted life years (QALYs), even if mortality is reduced. In a simulation modeling study that used ERSPC data, annual screening between ages 55 and 69 years was projected to result in nine fewer prostate cancer deaths per 1000 men followed for their lifetime, with a total of 73 life-years gained [22,23]. However, the simulation model using the same data to calculate QALYs showed a gain of only 56 QALYs with a 95% confidence interval that ranged from a loss of 21 QALYs to a gain of 97 QALYs.

Risks of prostate biopsy — Men with abnormal results of screening may have a prostate biopsy to determine if prostate cancer is present. Complications of prostate biopsy (eg, infection, pain, bleeding, urinary obstruction) occur in up to 2 percent of men [24]. Risks of prostate biopsy are described in detail separately. (See "Prostate biopsy", section on 'Complications'.)

Overdiagnosis of prostate cancer — Overdiagnosis refers to the detection by screening of a condition that would not have become clinically significant in the patient's lifetime. When screening finds cancer that would never have become clinically significant, patients

have still been subjected to the risks of screening, confirmatory diagnostic testing, and potentially treatments that can result in side effects.

For prostate cancer screening, the potential for overdiagnosis appears to be substantial given the high prevalence of undiagnosed prostate cancer detected on autopsy series. Overdiagnosis is of particular concern because most men with screening-detected prostate cancers have early-stage disease and may be offered aggressive therapies that may produce long-lasting adverse effects (eg, impotence, urinary incontinence). However, the increased uptake of active surveillance rather than aggressive treatment may help to mitigate the treatment-related harms of overdiagnosis of prostate cancer [25].

Overdiagnosis by screening is suggested by studies showing an increased frequency of diagnosis of prostate cancer, particularly low-grade, but no survival difference between screening and non-screening groups [9,17]. Following the initial introduction of PSA testing, the lifetime risk of being diagnosed with prostate cancer increased from 1 in 11 to 1 in 6, while the lifetime risk of dying from prostate cancer remained around 1 in 34 [9]. Studies that applied computer-simulation models to study data from Surveillance, Epidemiology, and End Results (SEER) or ERSPC estimated that 23 to 50 percent of prostate cancer diagnoses were likely overdiagnosed [26-28]. The risk of overdiagnosis of prostate cancer appears to increase with increasing age [29].

False-positive PSA — In addition to potential overdiagnosis, some abnormal PSA results are false positives; no cancer will be found on follow-up evaluation. While such patients don't incur risks of therapy, they may have anxiety about their test result and/or they may incur risks related to prostate biopsy. The false-positive rate depends in part on the patient's baseline risk as well as the threshold chosen for PSA interpretation. (See 'PSA interpretation' below.)

Anxiety — Receiving a diagnosis of prostate cancer is psychologically distressing, whether it is at an early stage or at an advanced stage. Anticipating treatments and their potential side effects, as well as dealing with the side effects if they occur, may lead to anxiety.

Even patients with a biopsy result that is negative for prostate cancer may develop anxiety, since a negative result cannot completely rule out prostate cancer due to the false-negative biopsy rate [30-32]. This is described separately. (See "Interpretation of prostate biopsy", section on 'Sampling error'.)

Risks of prostate cancer therapy — Screening that results in a diagnosis of prostate cancer may lead to therapy that carries substantial risks. For example, undergoing radical prostatectomy or radiation therapy has risks for immediate complications (eg, operative mortality, urinary symptoms) as well as for long-term sequelae (eg, urinary incontinence, impotence, and bowel dysfunction);

these adverse effects are common and are described in detail separately. (See "Radical prostatectomy for localized prostate cancer", section on 'Complications and quality of life' and "External beam radiation therapy for localized prostate cancer", section on 'Complications'.)

APPROACH TO SCREENING

Shared decision-making — We engage in shared decision-making about prostate cancer screening. Although the randomized trials of screening all have important methodological limitations, the best available evidence suggests that screening confers a small absolute benefit for reducing prostate cancer mortality and the risk of developing metastatic disease. However, the potential harms from screening that arise from false-positive tests (eg, prostate biopsy, anxiety, overdiagnosis, and treatment complications) are common. (See 'Benefits and harms of screening' above.)

We encourage shared decision-making because it is not appropriate for clinicians to determine how a patient should weigh these potential outcomes. Patients are encouraged to decide for themselves whether the benefits of screening outweigh the harms. Patients and clinicians should engage in shared decision-making when initially discussing screening as well as during subsequent screening discussions (whether the patient has agreed or declined to be screened in the past) [33-47].

For men at average risk, many clinicians do not specifically advise in favor of or against screening. Other experts may advise screening, particularly for men at higher risk for prostate cancer. Shared decision-making is essential with either approach.

Points that may be useful in shared decision-making discussions include [33,42,48]:

- Whether to have prostate cancer screening is a challenging decision for eligible men; there are both potential benefits and harms.
    - Prostate cancer is one of the most frequently diagnosed cancers and a leading cause of cancer death in men.
    - Prostate cancer screening may reduce the chance of dying from prostate cancer. However, the absolute benefit is small. Most men who choose not to be screened with a prostate-specific antigen (PSA) test will not be diagnosed with prostate cancer and will die from some other cause. However, some of these unscreened men will die from prostate cancer. In the United States, the 10-year risk of death due to prostate cancer is 0.5 percent over 10 years and <3 percent over a lifetime [9].

- Screening is done with a PSA test which is repeated every one to two years.
  - The PSA test is not a test specifically for cancer. It may be abnormal even if there is no prostate cancer, and it may be normal even if there is prostate cancer.
  - Sometimes, additional tests may be done to assess the likelihood that an elevated PSA is due to prostate cancer. If the tests suggest a low likelihood of prostate cancer, the man may choose to avoid having a biopsy and instead have periodic follow-up.
- A prostate biopsy is needed to determine whether prostate cancer is present.
  - Biopsies can rarely cause serious infections or other complications.
  - Even if a man has a prostate cancer, a prostate biopsy may miss finding it.
- Patients who choose to be screened with a PSA test are much more likely than those who decline PSA screening testing to be diagnosed with prostate cancer.
  - Many prostate cancers detected by screening are considered "overdiagnosed," meaning that they never would have caused problems during a man's lifetime. Most men with prostate cancer will die from other causes, not from prostate cancer.
  - No available tests can accurately determine which men with a prostate cancer found by screening have a cancer that is destined to cause health problems and would be most likely to benefit from aggressive treatment.
  - Surgery and radiation therapies are the treatments most commonly offered to try to cure prostate cancer. These treatments can lead to problems with urinary incontinence, sexual dysfunction (eg, impotence), and bowel problems (eg, diarrhea). (See 'Risks of prostate cancer therapy' above.)

On-line patient decision aids are available at American Cancer Society (ACS), American Society of Clinical Oncology (ASCO), US Centers for Disease Control and Prevention (CDC), and Mayo Clinic [49].

Decision aids may help patients to make informed decisions about whether to be screened for prostate cancer, but their use does not clearly impact screening rates [50-53]. Systematic reviews have concluded that decision aids improve patient knowledge, increase participation in decision-making, decrease decisional conflict about screening, and make patients more confident about their decisions

[52,53]. One meta-analysis found that decision aids were associated with a somewhat lower rate of screening (relative risk [RR] 0.88, 95% CI 0.81-0.97) [52], whereas a more recent analysis found that screening rates were similar with and without the use of these aids (RR 0.96, 95% CI 0.88-1.03) [53]. Most included studies used decision aids developed before publication of mortality results from the European Randomized Study of Screening for Prostate Cancer (ERSPC) and Prostate, Lung, Colorectal, and Ovarian (PLCO) screening trials; thus, studies using updated decision aids are needed [53].

Age to begin discussing screening — There is some variability in recommendations by expert groups about the age to begin discussing screening for prostate cancer with men.

Assessing risk for prostate cancer — We use race, age, and family history to identify whether a man is at higher or average risk for prostate cancer. (See "Risk factors for prostate cancer".)

We do not stratify risk by obtaining a one-time measurement of PSA in men younger than age 50 years, although some experts do. Some observational studies found an association between PSA elevation before age 50 years and diagnosis of advanced-stage cancer or death due to cancer over the next 20 to 30 years, and one study estimated PSA measured before age 50 years would be more useful for risk stratification than family history or race. However, there is no clinical evidence that identifying and treating these men would lead to better outcomes, and early testing could increase anxiety and the number of false-positive results [54-56].

Risk-adjusted approach

- **Average-risk men** – We suggest initiating discussion of screening for prostate cancer at age 50 years for average-risk men as long as life expectancy is at least 10 years [33,57].

  There is some variability in the age at which expert guidelines recommend initiating discussion about screening for prostate cancer, mostly at age 50 or 55 years or, less commonly, age 45 years [33,39,42,47,58-61].

- ***BRCA* carriers** – Men known or likely to carry *BRCA1 or BRCA2* genetic mutations are at increased risk. Discussing screening for prostate cancer may begin as early as age 40 years, depending in part on the specific mutation, although data on the effectiveness of early screening are limited. Recommendations vary and are discussed separately. (See "Cancer risks and management of BRCA1/2 carriers without cancer", section on 'Management of male BRCA1/2 carriers without cancer'.)

- **Other higher-risk men** – We suggest initiating discussion of screening at age 40 to 45 years with other men at higher risk for prostate cancer, including [33,62-64]:

  - Black men
  - Men with a family history of prostate cancer, particularly in a first-degree relative who was diagnosed at age <65 years

  Men at higher risk may be more likely to benefit from screening. However, there is relatively little evidence addressing this, and these men should be informed that the potential benefits and risks of early screening are uncertain. (See 'Shared decision-making' above.)

  Among professional organizations, ACS guidelines recommend beginning screening discussions at age 40 to 45 in patients at high risk of developing prostate cancer (eg, black men and men with a first-degree relative with prostate cancer diagnosed before age 65) [33]. The US Preventive Services Task Force (USPSTF) concluded evidence was insufficient to make a specific recommendation regarding screening discussions for these higher-risk groups, and the American Urological Association (AUA) indicates that decisions should be individualized for higher-risk men ages 40 to 54 years [39,59].

Screening with prostate-specific antigen

PSA testing — For men who choose prostate cancer screening, we suggest screening with a PSA blood test alone. Digital rectal examination (DRE) is generally not used as a screening test for prostate cancer, either alone or in combination with a PSA test. (See 'Digital rectal examination' below.)

Studies have estimated that PSA elevations may precede clinical manifestations of prostate cancer by 5 to 10 or more years [28,65,66].

However, PSA may also be elevated in the absence of prostate cancer in men with ongoing benign conditions (eg, benign prostatic hyperplasia [BPH]) or transient conditions (eg, prostatitis) (table 1). (See "Clinical manifestations and diagnostic evaluation of benign prostatic hyperplasia" and "Acute bacterial prostatitis".)

PSA testing is discussed in detail separately. (See "Measurement of prostate-specific antigen".)

Reasons to temporarily defer PSA testing — Certain factors may transiently elevate PSA enough to affect its performance as a screening test. In the presence of any of these factors, it is appropriate to temporarily defer PSA screening long enough for a transient

PSA elevation to resolve [67-69]:

- Symptoms suggesting bacterial prostatitis; defer PSA testing until six to eight weeks after symptoms resolve
- Acute urinary retention or urethral instrumentation; defer PSA testing for at least two weeks
- Recent prostate biopsy or transurethral resection of the prostate (TURP); defer PSA testing for at least six weeks

The relationship between a PSA result and each of these conditions is discussed separately. (See "Measurement of prostate-specific antigen".)

Additionally, a patient who is repeating a PSA test to evaluate a result that was close to a cutoff that could prompt urologic evaluation should abstain for at least 48 hours from activities that induce perineal trauma (eg, ejaculation or bicycling).

If DRE was performed, PSA can be measured immediately afterwards because DRE leads to only minimal transient PSA elevations of 0.26 to 0.4 ng/mL [67,70].

In men with symptomatic benign prostatic hypertrophy, measurement of PSA does not need to be deferred while treatment is provided to improve BPH symptoms, unless the patient has had TURP within the past six weeks.

Frequency of PSA testing — For patients who choose to undergo PSA screening, some experts suggest repeating PSA testing every two years until it is appropriate to discontinue screening, whereas other experts repeat PSA testing annually. Studies that show a potential benefit of screening with PSA studied programs that screened regularly at intervals of one to a few years. No studies have shown a benefit of a one-time PSA test for screening [16].

Compared with one-time screening, serial PSA testing increases the overall sensitivity. Serial screening also increases the likelihood that detected tumors will be clinically organ-confined and be moderately or well differentiated, thus more amenable to successful treatment [71-74]. As an example, in the ERSPC with a four-year screening interval, the proportion of clinical stage I and II cancers increased from 81.5 during the first round to 96.3 percent during the second round, and the proportion of poorly differentiated cancers decreased from 8.1 to 3.3 percent [73].

With each round of PSA testing, detection rates for prostate cancer and positive predictive values of a PSA test decline substantially [72,73,75,76]. With screening at a four-year interval in the ERSPC, the cancer detection rate for PSA decreased from 5.1 percent in the

first round of screening to 4.4 percent in the second round, and the positive predictive value (PPV) for a PSA ≥3.0 ng/mL decreased from 29.2 to 19.9 percent [73].

Two- versus four-year screening intervals appeared to have similar efficacy in detecting potentially life-threatening cancers in one nonrandomized study. Although the overall 10-year incidence of prostate cancer was higher with a two-year versus a four-year interval (13.1 versus 8.4 percent), the cumulative rates of aggressive cancers were similar and low in both groups (0.11 versus 0.12 percent); follow-up was not long enough to compare mortality rates [77]. However, potentially important differences between the patients and screening methods at the two study centers limit the strength of this nonrandomized comparison of screening intervals.

An alternative strategy is to adjust the frequency of testing based on the prior PSA result, with less frequent retesting in men with lower initial PSA levels (eg, ≤1.0 ng/mL) and annual testing in those with higher PSA levels that are still below a cutoff for biopsy [78-80]. This strategy is supported by the observation that men with an initial PSA <1 ng/mL had low rates of conversion (0.9 to 1.5 percent) over five years to higher PSA rates (>3 to 4 ng/mL) in the PLCO and ERSPC studies [78,79]. Cancer detection rates over four to five years were also low (0.12 and 0.15 percent) in this subgroup. For the relatively few patients who did have cancer, the four-year screening interval was estimated to result in a delay in cancer diagnosis of 15.6 months [80]. The clinical consequences of delayed diagnosis on prostate cancer mortality and morbidity are unknown, although the majority of cancers detected after a four-year screening interval in the ERSPC were early-stage [81]. Similarly, a case-control study found that a PSA level ≤1 ng/mL at age 60 years was associated with an extremely low risk of prostate cancer metastasis (0.5 percent) or death from prostate cancer (0.2 percent) by age 85 years [82].

Expert guidelines vary as to screening interval recommendations. The AUA states that a screening interval of two years may be preferred to annual screening [64]. Some guidelines suggest that screening intervals be individualized based on a baseline PSA level. The range of adjustments varies among guidelines (from annual to every two, three, or four years) based on the prior PSA level [33,60].

Discontinuing screening — There is general agreement about not screening men who have substantial comorbidities that limit life expectancy to less than 10 years. There is less consensus about a precise age at which to discontinue screening.

- **Life expectancy** – We do not screen men for prostate cancer who have a life expectancy of <10 years. Screening is unlikely to benefit these men given the generally indolent course of prostate cancer.

  Professional society guidelines generally recommend not screening men who have less than 10-year [33,45] or 10- to 15-year [42,59] life expectancy.

- **Age** – For men with a life expectancy of at least 10 years, most clinicians offer screening up to age 70 years; some may continue screening until age 75 years if the patient desires it. Among guidelines, the suggested age to discontinue screening for prostate cancer varies from 69 to 75 years [39,42,47,58-60]. Actuarial tables suggest that among men in average health, only those ages 75 and younger have a 10-year life expectancy.

  Other data suggest that stopping screening in individuals as young as 65 years may be appropriate. The ERSPC found a screening survival benefit only among men ages 55 to 69 [83]. Further, a decision analysis using Medicare data found that aggressive treatment of prostate cancer in men age 70 years and older would decrease the quality-adjusted life expectancy [81].

  Another analysis found that discontinuing PSA testing at age 65 for men with PSA levels 0.5 ng/mL or less would still identify all cancers that would have been detected by age 75 [84]. If screening were discontinued for men with PSA levels of 1.0 ng/mL or less at age 65, then 94 percent of the cancers would still be detected.

INTERPRETATION AND FOLLOW-UP OF PSA RESULTS

Correction for 5-alpha reductase inhibitor — If the patient takes a 5-alpha reductase inhibitor (ARI]) such as finasteride or dutasteride, a correction factor must be applied to a prostate-specific antigen (PSA) result for accurate interpretation, because ARIs are known to lower PSA results. Specifics are described separately. (See "Measurement of prostate-specific antigen", section on 'Medications'.)

PSA interpretation — We use a PSA value of ≥4.0 ng/mL on a screening test (after applying a correction factor to the PSA result if the patient is using an ARI) to determine if further evaluation for prostate cancer is warranted. (See "Measurement of prostate-specific antigen".)

A PSA of ≥4.0 ng/mL has been the most widely accepted standard to balance tradeoffs between sensitivity and specificity. However, there is no single PSA value that avoids missing important cancers at a curable stage, avoids false-positives and detection of clinically insignificant disease, and avoids subjecting men to unnecessary prostate biopsies [57,85,86]. A PSA cutoff of 4.0 ng/mL had a sensitivity of 21 percent with specificity of 91 percent for detection of any prostate cancer; for detection of a high-grade cancer, sensitivity was 51 percent [33,71,87-89]. The low sensitivity means that some men with PSA levels <4 ng/mL will have prostate cancer

[82,90-92]. In the Prostate Cancer Prevention Trial (PCPT), 15.2 percent of men with PSA levels <4 ng/mL annually for seven years were found to have prostate cancer on end-of-study biopsy; 1.6 percent had high-grade prostate cancer [93].

Lowering the PSA cutoff improves test sensitivity somewhat. A PSA cutoff of 3.0 ng/mL had a sensitivity of 32 percent for detection of any prostate cancer; for detection of a high-grade cancer, sensitivity was 68 percent [33,71,87-89]. Among those with PSA between 2.1 and 4.0 ng/mL, prostate cancer was found in 24.7 percent (167 of 675 men) and 3.5 percent (four men) had high-grade cancers. Even a PSA cutoff as low as 1.1 ng/mL would have missed 17 percent of cancers, including 5 percent of poorly differentiated cancers [94].

However, lowering the PSA cutoff worsens specificity and overdiagnosis. A PSA cutoff of 3.0 ng/mL has a specificity of about 85 percent for detection of any prostate cancer [33,71,87-89]. It has been projected that if the PSA cutoff was lowered to 2.5 ng/mL, the number of men whose PSA is defined as abnormal would double to up to six million in the United States [95]. Additionally, many of the cancers that would be detected at these lower PSA levels may never have become clinically evident, so detecting them by using a lower PSA cutoff would lead to overdiagnosis and overtreatment [85]. (See 'Overdiagnosis of prostate cancer' above.)

Raising the PSA cutoff value increases the positive predictive value (PPV) for prostate cancer but lowers the likelihood that the cancer is organ-confined, thus potentially curable. For any PSA >4.0 ng/mL, the overall PPV for prostate cancer is approximately 30 percent [73,76,78]. However, for a PSA of 4.0 to 10.0 ng/mL, just somewhat above the cutoff, PPV is approximately 25 percent and nearly 75 percent of cancers are organ-confined [96], whereas for a higher cutoff of PSA >10 ng/mL, PPV increases to 42 to 64 percent, but less than 50 percent of cancers are organ-confined [76,79].

Some experts use age-specific reference ranges for PSA, rather than using the same cutoff for all ages. PSA levels generally increase with age, in part because older men are more likely to have a benign enlarged prostate producing larger amounts of PSA. However, there are limited data to support exact reference values for age cohorts.

There are several limitations to determining the accuracy of PSA screening. Most men with normal PSA values have not undergone biopsy unless they had a digital rectal examination (DRE) that was abnormal; this workup bias leads to overestimating sensitivity and underestimating specificity of PSA to detect prostate cancer [68]. Another limitation is the lack of consensus about which cancers are clinically important; PSA detects clinically unimportant cancers as well as important ones. Additionally, the false-negative rate of biopsy may have been as high as 10 to 20 percent in studies with <12 samples per prostate biopsy [97,98].

Referral to urology — Indications for a urology referral include:

- **PSA ≥4.0 ng/mL** – We refer patients for urology evaluation if the PSA is ≥4.0 ng/mL. Prior to referral, if the PSA is between 4.0 and 7.0 ng/mL, we repeat the testing in six to eight weeks, because PSA may be transiently elevated by certain modifiable benign factors (and any identified factors should be addressed prior to repeating the PSA test (see 'Reasons to temporarily defer PSA testing' above)), while some experts refer patients if the PSA level is ≥4.0 ng/m without first repeating a modestly elevated PSA.

- **Rise in PSA while on 5-alpha reductase inhibitor** – A man taking an ARI who has any rise in PSA should be referred for urology evaluation, even if the corrected PSA level is <4.0 ng/mL. Any PSA rise while on an ARI has been associated with an elevated risk for prostate cancer.

- **Abnormal DRE** – Although we do not suggest DRE for screening, if DRE is performed, men with nodules, induration, or asymmetry on prostate examination should be referred to a urologist for evaluation, regardless of the serum PSA level. However, symmetric enlargement and firmness of the prostate are frequent in men with BPH and do not typically warrant urologic evaluation unless the PSA is elevated or there are other concerns. (See "Risk factors for prostate cancer" and "Clinical manifestations and diagnostic evaluation of benign prostatic hyperplasia".)

Referral for urologic evaluation will not necessarily result in a prostate biopsy. Other tests (eg, free to total PSA ratio [f/T PSA], PCA3, 4Kscore test, and/or magnetic resonance imaging [MRI]) may be done by the urologist to help determine the likelihood that the PSA is elevated due to prostate cancer, the PSA may be followed over time, or a biopsy may be performed. Relevant considerations include the patient's health status, clinical likelihood for harboring significant disease, and personal wishes. (See "Clinical presentation and diagnosis of prostate cancer", section on 'Urologic evaluation'.)

METHODS NOT GENERALLY USED FOR SCREENING

Digital rectal examination — We suggest not performing digital rectal examination (DRE) for prostate cancer screening either as an adjunct to prostate-specific antigen (PSA) testing or as a standalone test.

DRE has low sensitivity and specificity for detecting prostate cancer. In one meta-analysis, DRE performed by primary care clinicians had an estimated sensitivity of 51 percent, a specificity of 59 percent, and a calculated overall positive predictive value (PPV) of 41

percent [99]. However, the quality of evidence was very low and there was substantial heterogeneity across studies. Additionally, urologists have been found to have relatively low interrater agreement for detecting prostate abnormalities [100].

The low sensitivity is due in part to the fact that DRE only detects palpable abnormalities in the posterior and lateral aspects of the prostate gland. Although this is where the majority of cancers arise, other areas of the prostate where cancer occurs are not reachable by a finger examination [101]. Additionally, stage T1 prostate cancers are nonpalpable by definition; thus, the majority of patients with cancers detected by DRE alone are not candidates for curative therapy [102]. In one study, an abnormal screening DRE was associated with a twofold increase in odds of detecting a clinically important cancer confined to the prostate gland; however, there was a three- to ninefold increase in the odds of finding extraprostatic extension of prostate cancer that presumably would not have been amenable to curative therapy [103].

Although DRE and PSA are somewhat complementary and their combined use may increase the overall rate of cancer detection, studies show that DRE has limited utility as an adjunctive test [57,96,104-106]. In a multicenter screening study of 6630 men, the prostate cancer detection rate was 3.2 percent for DRE, 4.6 percent for PSA, and 5.8 percent for the two methods combined [96,107]. Just 18 percent of cancers were detected only by DRE. In another study, the PPV of a suspicious DRE with a normal PSA level was 10 percent, whereas the PPV for a normal DRE with an elevated PSA level was 24 percent [108]. Among men with a normal PSA level, abnormalities on DRE appeared less likely to be from a cancer if the PSA concentration was below 1.0 ng/mL than if the PSA concentration was between 3.0 to 4.0 ng/mL.

Most specialty society guidelines do not suggest DRE for screening, although some [33,59,60] include DRE either to evaluate an elevated PSA, or as an option along with PSA testing.

Other tests — We do not routinely use any other testing or test interpretation strategies either for screening or for deciding which men to refer for urologic evaluation for an elevated PSA.

We do not use either the absolute change in PSA or the PSA velocity (ie, the rate of change of PSA over time) to determine whether to refer a patient [86]. PSA increases more rapidly in men with prostate cancer than in healthy men. However, PSA velocity adds little predictive information to PSA alone [109-115]. (See "Clinical presentation and diagnosis of prostate cancer", section on 'Evaluation'.)

Other methods have been developed to try to differentiate between higher-risk cancers and low-risk, indolent cancers. However, the clinical utility of these strategies is uncertain, there is no consensus on using any of these tests, and additional studies for clinical

effectiveness are needed. The American Urological Association (AUA) guideline noted the lack of evidence for using any tests other than PSA to determine the need for a referral for biopsy [59]. (See "Measurement of prostate-specific antigen", section on 'Advances in PSA testing' and "The role of magnetic resonance imaging in prostate cancer", section on 'Clinical applications'.)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Screening for prostate cancer".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient education: Prostate cancer screening (PSA tests) (The Basics)")
- Beyond the Basics topics (see "Patient education: Prostate cancer screening (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- The best available evidence from randomized trials found that screening has at most a small benefit in reducing prostate cancer mortality and the risk of developing metastatic disease.

The potential benefits of screening must be balanced against the potential harms to quality of life, including the risks of false-positive tests, prostate biopsy, anxiety, overdiagnosis, and treatment complications. (See 'Benefits and harms of screening' above.)

- For average-risk men, many clinicians do not specifically advise in favor of or against screening. Men who are candidates for screening should be engaged in shared decision-making about whether they choose to be screened. Individual patient preferences for specific health outcomes are a deciding factor in determining whether to screen for prostate cancer. Decision aids may help patients receive consistent, complete, objective information. (See 'Shared decision-making' above.)

- Men who are being screened for prostate cancer should have a life expectancy of at least 10 years. (See 'Age to begin discussing screening' above.)

- The age to initiate discussion about prostate cancer screening depends on the patient's risk for prostate cancer. We use race, age, and family history to identify whether a man is at higher or average risk for prostate cancer. (See 'Age to begin discussing screening' above.)

  - In average-risk men, we initiate discussion of screening at age 50 years. (See 'Age to begin discussing screening' above.)

  - Men known or likely to carry *BRCA1* or *BRCA2* genetic mutations are at increased risk. Initiating screening discussions for prostate cancer may begin as early as age 40 years, depending in part on the specific mutation, although data on the effectiveness of early screening are limited. Recommendations vary and are discussed separately. (See "Cancer risks and management of BRCA1/2 carriers without cancer", section on 'Management of male BRCA1/2 carriers without cancer'.)

  - For other men at higher risk for prostate cancer, including black men and men with a family history of prostate cancer, we suggest initiating discussion of screening at age 40 to 45 years. (See 'Age to begin discussing screening' above.)

- If a decision is made to screen for prostate cancer, prostate-specific antigen (PSA) testing alone is the most appropriate test for screening. We suggest a screening interval of one to two years. For most patients, we offer screening up to age 70 years, stopping earlier if comorbidities limit life expectancy to less than 10 years. (See 'Discontinuing screening' above.)

- A patient with an abnormal PSA value should be referred to urology for further evaluation. (See 'Referral to urology' above.)

  - Men with a PSA level above 7 ng/mL should be referred, without further testing, to a urologist for evaluation.

- For men with a PSA level between 4 and 7 ng/mL, we repeat the PSA testing several weeks later. Factors known to transiently increase PSA should be addressed prior to repeating the PSA test (see 'Reasons to temporarily defer PSA testing' above). Men with a repeat PSA level >4 ng/mL should be referred to a urologist for evaluation.

- For a man taking an 5-alpha reductase inhibitor (ARI) for benign prostatic hyperplasia (BPH), the PSA result needs to be corrected prior to interpretation. Additionally, any rise in PSA while taking an ARI should be evaluated by urology, even if the level is not ≥4.0 ng/mL. (See 'Correction for 5-alpha reductase inhibitor' above.)

- We do not perform digital rectal examination (DRE) as part of screening (see 'Digital rectal examination' above). However, if a DRE is performed, men with a nodule, induration, or asymmetry on prostate examination should be referred to a urologist, regardless of the PSA result. (See 'Referral to urology' above.)

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