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Would You Recommend Prostate-Specific Antigen Screening for This Patient?

Grand Rounds Discussion From Beth Israel Deaconess Medical Center

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Prostate cancer is the third most common cancer type in the United States overall, accounting for 9.5% of new cancer cases and 5% of cancer deaths. The goal of prostate-specific antigen (PSA)–based screening is to identify early-stage disease that can be treated successfully. The U.S. Preventive Services Task Force (USPSTF) reviewed evidence on the benefits and harms of PSA-based screening and treatment of screen-detected prostate cancer. It found that PSA-based screening in men aged 55 to 69 years prevents approximately 1.3 deaths from prostate cancer over 13 years per 1000 men screened and 3 cases of metastatic cancer per 1000 men screened, with no reduction in all-cause mortality. No benefit was found for PSA-based screening in men aged 70 years and older. On the basis of its review, the USPSTF concluded that the decision for men aged 55 to 69 years to have PSA-based screening should be an individual one and should include a discussion of the potential benefits and harms. Here, 2 experts—an internist and a urologist—discuss the key points of a shared decision-making conversation about PSA-based prostate cancer screening, the PSA-based screening strategy that optimizes benefit and minimizes harm, and the PSA threshold at which they would recommend further diagnostic testing.

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ABOUT BEYOND THE GUIDELINES

Beyond the Guidelines is a multimedia feature based on selected clinical conferences at Beth Israel Deaconess Medical Center (BIDMC). Each educational feature focuses on the care of a patient who "falls between the cracks" in available evidence and for whom the optimal clinical management is unclear. Such situations include those in which a guideline finds evidence insufficient to make a recommendation, a patient does not fit criteria mapped out in recommendations, or different organizations provide conflicting recommendations. Clinical experts provide opinions and comment on how they would approach the patient's care. Videos of the patient and conference, the slide presentation, and a CME/MOC activity accompany each article. For more information, visit www.annals.org/GrandRounds.

This article is based on the Department of Medicine Grand Rounds conference held on 24 January 2019.

Mr. W is a 64-year-old man who had normal results (range, 2.5 to 3.4 μg/L) on a series of prostate-specific antigen (PSA) tests between 2009 and 2013. In 2008, he had an elevated PSA level on a single test after a prolonged bicycle ride, but on repeated testing 6 months later, his PSA value was normal. In August 2018, he established care with a new primary care provider, who suggested repeated PSA testing. This time, his level was 7.8 μg/L and was still elevated (6.2 μg/L) 1 month later. Mr. W was referred to a urologist, who noted an enlarged, 30- to 40-g prostate on digital rectal examination. His percentage of free PSA was 11%, with an estimated probability of cancer of 28% (1). The urologist suggested a biopsy, but Mr. W opted to wait 6 months and repeat the PSA evaluation.

Mr. W has a history of left ventricular outflow tract obstruction, gastroesophageal reflux disease, hyperlipidemia, chronic sinusitis, prediabetes, and anxiety. His current medications include citalopram, diltiazem, pantoprazole, rosuvastatin, and zolpidem as needed for sleep. He has no known drug allergies. He is retired and lives with his wife.

Mr. W's Story

I had my first PSA back in the 1990s. My understanding is that it was standard procedure. Subse-

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quently, in 2008, I had a high PSA. I saw a urologist, and it was still high. I had participated in a 100-mile bicycle ride and was experiencing pain, so I figured that was the problem. I didn't take the doctor's advice and did not get a biopsy. Six months later, I had another PSA and it was normal, so I think I definitely made the right decision.

After having several PSAs, I was advised that it was no longer considered necessary, because the diagnosis of prostate cancer often led to unnecessary treatment and the gain from early detection wasn't that great. So I went along and didn't have any done for a while.

This summer, I got a new doctor, and she recommended I get a PSA. So I did, and I found out it was elevated. I was getting my blood drawn anyway—zero cost, why not? I just didn't think to object.

She called me and recommended I see a urologist. I went and had another blood test done, which also showed an elevated PSA. They looked at the free PSA, and my probability of having cancer is 28%, as I understand it.

I have decided, after much hemming and hawing, to wait 6 months and have another PSA. I actually constructed a decision model. I drew out a decision chart, looking at the 2 options of getting a biopsy now versus waiting 6 months, and then calculated as best as I could what the change in probability of 10-year survival would be, depending on how I made that choice. So, that was how I arrived at what I think is a reasonable ballpark estimate: that there's probably only about 1% to 2% of prostate cancers that I would have to worry about a 6-month delay in diagnosis.

The biggest cost that I am paying from screening would be anxiety related to it. I recognize that there has been a little bit of anxiety, but for the most part I just go on with my life and I deal with it when I have to deal with it. At this point, I have made the decision to wait until my next appointment to get another PSA. So, I am fairly comfortable with that.

See the **Patient Video** (available at Annals.org) to view the patient telling his story.

CONTEXT, EVIDENCE, AND GUIDELINES

Prostate cancer is the third most common cancer type in the United States overall, accounting for 9.5% of new cancer cases and 5% of cancer deaths. Approximately 11% of men will receive a diagnosis of prostate cancer during their lifetime, with 98% surviving 5 years or longer. Prostate cancer is more common in older than younger men, in men with a family history of prostate cancer, and in men of African American descent, all of whom also have higher mortality rates (2).

The goal of PSA-based prostate cancer screening is to identify early-stage disease that can be treated successfully. The U.S. Preventive Services Task Force (USPSTF) reviewed evidence on the benefits and harms of PSA-based screening and treatment of screen-detected prostate cancer (3). The evidence review found that PSA-based screening programs in men aged 55 to 69 years may prevent 1.3 deaths from prostate cancer over 13 years per 1000 men screened (4, 5) and 3 cases of metastatic prostate cancer per 1000 men screened (4), with no reduction in all-cause mortality. Data were inadequate to determine whether the benefits for men at highest risk differed from those at average risk, or whether those at highest risk should begin screening before age 55. Finally, the review found adequate evidence that men aged 70 years and older receive no benefit from PSA-based screening.

Harms of PSA testing include those resulting from the screening test itself as well as from subsequent diagnosis and treatment. Harms from screening include false-positive results and psychological effects. False-positive results are common; 1 study showed that among men screened every 2 to 4 years for 10 years, more than 15% have 1 false-positive result (6). Harms from diagnostic procedures (transrectal ultrasound-guided core needle prostate biopsy) include pain, hematospermia, bleeding, infection, and hospitalization.

Other harms include overdiagnosis (the diagnosis of prostate cancer in men whose cancer would never have become symptomatic during their lifetime and for whom treatment would provide no benefit) and overtreatment. Data from randomized controlled trials suggest that 20% to 50% of prostate cancer cases diagnosed through screening may be overdiagnosed (4). Treatment with surgery or radiation may result in major adverse effects, including death, urinary incontinence, erectile dysfunction, and rectal and fecal incontinence (3). For men with low-risk prostate cancer, active surveillance and watchful waiting offer the option to forgo treatment in favor of ongoing monitoring. With active surveillance, the patient is followed closely according to a defined protocol with the intention of receiving active treatment if deemed necessary. In contrast, watchful waiting does not include the intention of active treatment unless symptoms develop.

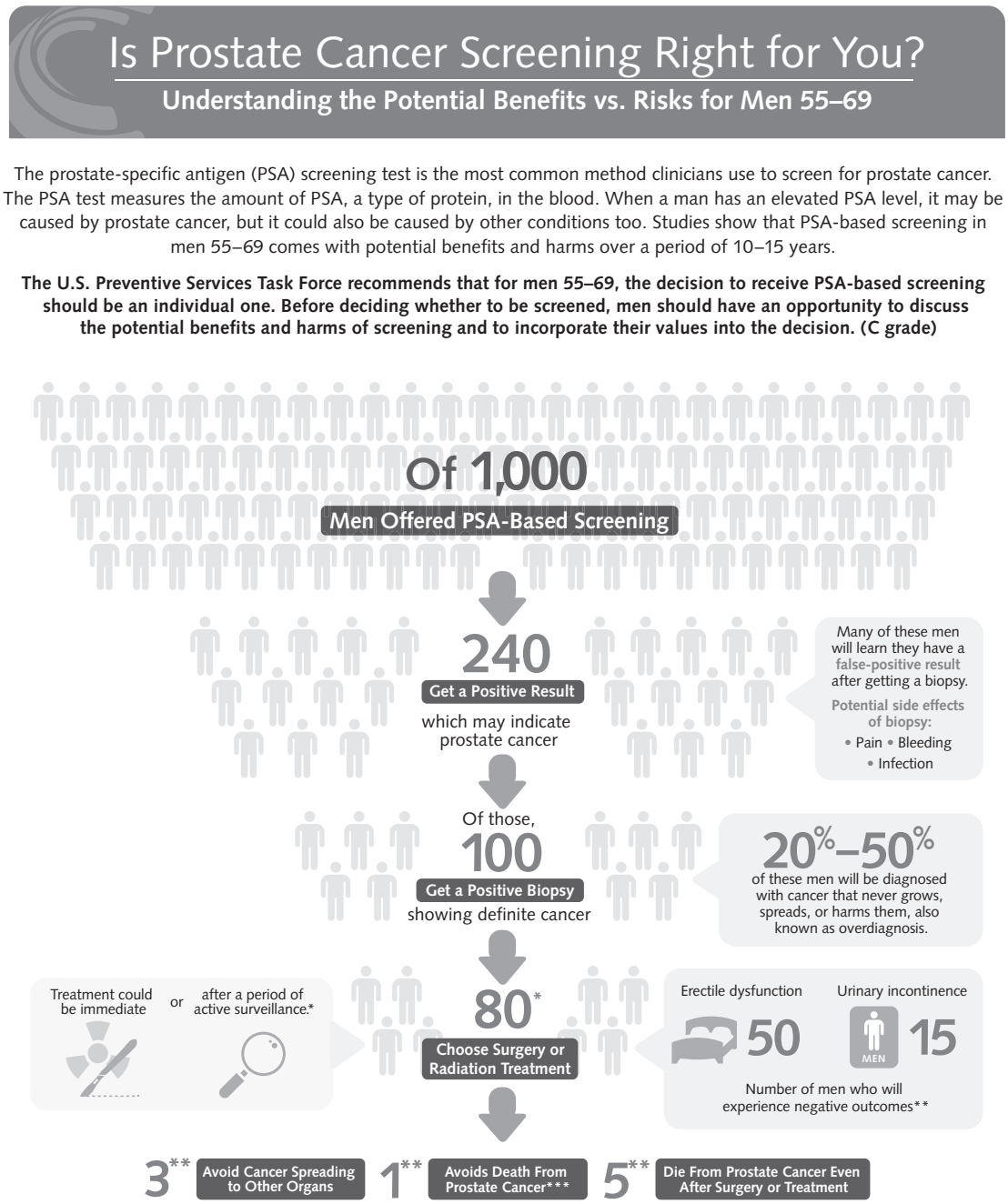
The USPSTF considered whether certain screening and follow-up procedures could reduce overdiagnosis by lowering the age at which to stop screening or extending the interval between screenings, or by using a higher PSA threshold for biopsy. Although no strategy completely eliminated overdiagnosis, PSA-based screening every 2 to 4 years instead of annually seemed to reduce overdiagnosis, with a small reduction in mortality benefit (7).

The USPSTF concluded that the decision for men aged 55 to 69 years to have PSA-based screening should be an individual one and should include a discussion of the potential benefits and harms, as shown in the **Figure** (8). The American Urological Association (AUA) offers similar guidance (9). Furthermore, the AUA concurs that a routine screening interval of 2 years or longer may be preferred over annual screening.

CLINICAL QUESTIONS

To structure a debate between our 2 discussants, we mutually agreed on the following key questions to consider when applying this guideline to clinical practice and to Mr. W in particular.

Figure. Potential outcomes for men who choose to be screened for prostate cancer.



Men who are considering prostate cancer screening should talk with a health care professional and become informed about the potential benefits and harms of prostate-specific antigen–based screening. (Reproduced from U.S. Preventive Services Task Force [8]; a color PDF version of the figure is available at www.uspreventiveservicestaskforce.org/Home/GetFileByID/3795.). ERSPC = European Randomized Study of Screening for Prostate Cancer; PIVOT = Prostate Cancer Intervention Versus Observation Trial; ProtecT = Prostate Testing for Cancer and Treatment; PSA = prostate-specific antigen; SPCG-4 = Scandinavian Prostate Cancer Group Study Number 4.

1. What are the key points of a shared decision-making conversation about the potential benefits and harms of PSA-based screening?

2. What PSA-based screening strategy optimizes benefit and minimizes harm?

3. At what PSA threshold would you recommend further diagnostic testing, and what would you recommend for Mr. W?

DISCUSSION

An Internist's Viewpoint (Dr. Douglas K. Owens)

Question 1: What are the key points of a shared decision-making conversation about the potential benefits and harms of PSA-based screening?

A decision regarding screening for prostate cancer is one of the most challenging in cancer screening. Although a few men with aggressive prostate cancer may benefit, many more are likely to be harmed from overdiagnosis, overtreatment, and adverse effects of treatment. Thus, the goal of shared decision making is to help men understand the potential benefits and harms of screening and to clarify their preferences (10–12). How a man weighs these benefits and harms is important in determining whether screening is appropriate. For a man who strongly values the reduction in prostate cancer mortality and has less concern about adverse outcomes of diagnosis and treatment, screening may be the best choice. For a man who is concerned about adverse effects, such as erectile dysfunction or incontinence, and does not value as highly the modest reduction in mortality (at best, about 1.3 fewer men per 1000 screened over 13 years die of prostate cancer [12]), forgoing screening is a reasonable choice.

To understand the challenge of prostate cancer screening, it's helpful to compare it with other cancer screening. Screening for colorectal cancer prevents 20 to 25 deaths per 1000 persons screened (13) and has only small harms. Breast cancer screening every 2 years from ages 50 to 75 prevents about 7 deaths per 1000 women screened, and starting screening at age 40 may prevent 1 additional death per 1000 women screened. Like prostate cancer, breast cancer screening is associated with overdiagnosis and overtreatment (14). Screening for cervical cancer prevents about 8 deaths per 1000 women screened and has small harms (15). Thus, prostate cancer screening has substantially less benefit relative to these other screening interventions (at least until 13 years of follow-up), and the harms are substantial, making the decision whether to be screened difficult and anxiety provoking for many men, including Mr. W. Understanding which men will benefit from prostate cancer screening is complex, and shared decision making can sometimes help men decide whether screening is the right choice for them.

Important topics to include in a shared decision-making discussion about prostate cancer screening are summarized in Table 1 (10–12). Men need to understand that there is no single best decision that applies to everyone (10). Rather, the decision to screen depends on how men value the potential outcomes. Men need to be informed about the natural history of prostate cancer, the meaning of PSA test results, the evaluation (and potential complications) that may occur if they are found to have an elevated PSA level, the main treatment choices (watchful waiting, active surveillance, prostatectomy, and radiation therapy), and the beneficial and harmful outcomes that can occur with treatment. In addition, African American men and men with a family history of prostate cancer, who are at higher risk for prostate cancer (12), need to understand their elevated risk for cancer and the potential for cancer to occur at a younger age.

The natural history of prostate cancer is important, because many such cancer cases will not cause important clinical disease during a man's lifetime, a concept that may be unfamiliar to many men. In these circumstances, active surveillance is an approach for delaying

Table 1. Important Points for Shared Decision-Making Conversations*

Whether to have prostate cancer screening is a personal decision based on how a man values the potential benefits and harms of screening and treatment. Before making a decision, each man should understand the benefits and harms of prostate cancer screening. After a discussion with their clinicians about what decision best fits their circumstances and preferences, some men will choose to be screened and others will choose not to.
A small proportion of prostate cancer cases may cause death, but most are slow growing and do not result in death. PSA testing does not clearly distinguish between these kinds of cancer.
An elevated PSA level may be a result of prostate cancer or other causes. Most men who have an elevated PSA level do not have prostate cancer.
Some men who have prostate cancer do not have an elevated PSA level.
Having a PSA test substantially increases the likelihood that a man will receive a prostate cancer diagnosis.
An elevated PSA level may lead to further testing, including a biopsy. A biopsy is how prostate cancer is diagnosed. It involves the insertion of needles into the prostate and carries a risk for infection, substantial bleeding, and hospitalization.
Several options are available for managing prostate cancer. Some men with low-risk cancer may be candidates for active surveillance, which involves repeated blood tests and biopsies. Active surveillance may postpone or prevent treatment that would not be helpful. Watchful waiting is a more passive strategy sometimes used for men who want treatment only if symptoms develop. Active treatment involves surgical removal of the prostate or radiation therapy. Treatment provides benefit for some men with aggressive cancer but is associated with substantial harms, including loss of sexual function and incontinence.
Approximately 1.3 men aged 55–69 y who are screened periodically will avoid death from prostate cancer after 13 y per 1000 men screened. Approximately 35%–50% of men who receive treatment will have sexual dysfunction, and approximately 15% will have some degree of urinary incontinence. Men who value the reduction in mortality more than avoiding complications may be more suitable candidates for screening.
African American men are more likely than white men to have prostate cancer and more than twice as likely as white men to die of prostate cancer. They also may develop prostate cancer earlier than average-risk men. Whether earlier or more intensive screening for African American men is helpful is not known, but informing African American men of their increased risk may help them decide whether and when to be screened.
Men with a family history of prostate cancer are at increased risk. Whether earlier or more intensive screening is beneficial is not known. Men who have a first-degree relative who had advanced prostate cancer at diagnosis, had metastatic prostate cancer, or died of prostate cancer are probably the most likely to benefit from screening.

PSA = prostate-specific antigen.
* Based on references 10–12.

or avoiding surgery or radiation, and the associated morbidity, in men whose cancer is indolent. The use of active surveillance has increased substantially in the past 10 years.

False-positive PSA results are relatively common, and biopsy has substantial morbidity. Men should be informed that PSA does not always distinguish between prostate cancer cases that are aggressive versus those that are indolent. How to use prostate biopsy more selectively to make this distinction is an active area of research, as discussed later.

Men at increased risk for prostate cancer include African American men and those with a family history of prostate cancer. African American men are more likely to develop prostate cancer than white men and are almost twice as likely as white men to die of it (12). Unfortunately, there are virtually no empirical data to inform whether earlier or more aggressive screening is helpful or harmful in such men. Screening may offer additional benefit, but it could also lead to men being exposed to potential harms. A discussion of the epidemiology, as outlined in Table 1, may be useful to men at higher risk as they make decisions about screening. For example, African American men may decide to begin screening earlier. For men with a family history, those most likely to benefit from screening are those who have a first-degree relative who had advanced prostate cancer at diagnosis, developed metastatic cancer, or died of prostate cancer (12).

Many decision aids have been designed to help men understand the benefits and harms of screening (10); examples can be found at https://decisionaid.ohri.ca/azlist.html. It is important to note that these tools are designed to supplement conversations with clinicians, not to replace them (10). In a review of 13 studies of decision aids, men who used such tools were modestly less likely to choose screening when compared with usual care (16).

Question 2: What PSA-based screening strategy optimizes benefit and minimizes harm?

An ideal screening strategy would identify men who would benefit from early detection and treatment but not result in overdiagnosis and overtreatment of men whose prostate cancer would not become clinically important. How best to do this is uncertain and is a very active area of research. More frequent screening intervals or use of lower PSA thresholds for diagnostic biopsy may modestly increase prostate cancer–specific survival but will result in a higher number of false-positive results, more biopsies, and more overdiagnosis (12).

The multisite ERSPC (European Randomized Study of Screening for Prostate Cancer), 1 of the 3 large trials to study PSA-based screening, screened men at intervals from 2 to 7 years, with no site screening more frequently than every 2 years (12). The ERSPC trial showed a reduction in prostate cancer mortality of 1.3 men per 1000 screened over 13 years. In general, screening intervals of 2 to 4 years are probably reasonable, but further research would be helpful to identify optimum screening intervals.

Question 3: At what PSA threshold would you recommend further diagnostic testing, and what would you recommend for Mr. W?

Mr. W has taken a very thoughtful approach to his situation. He carefully considered the pros and cons of waiting and estimated the chance that delay could result in adverse outcomes. The optimal PSA threshold to warrant biopsy and whether other parameters, such as PSA velocity or percentage of free PSA, can improve outcomes remain active areas of research without definitive answers, so individualized decision making with Mr. W is reasonable. In ERSPC, the threshold for biopsy ranged from 2.5 to 4 μg/L during the later years of the trial; higher thresholds were used at some sites early in the study (12).

Going forward, I would recommend another shared decision-making discussion when Mr. W receives his next PSA test result. Such a conversation should confirm that he would be willing to undergo treatment if he has prostate cancer. If he is not willing to have treatment under any circumstances, further evaluation is unnecessary. The most relevant topics for shared decision making, as shown in Table 1, would include information about the process of undergoing a biopsy, the adverse events that may occur from biopsy, and benefits and harms of the different treatment options. With this information, Mr. W can make a decision that best reflects his preferences and circumstance.

A Urologist's Viewpoint (Dr. Aria Olumi)

Question 1: What are the key points of a shared decision-making conversation about the potential benefits and harms of PSA-based screening?

Since its discovery in 1979 as a prostate-specific marker that is secreted in the blood (17) and its implementation into clinical practice for prostate cancer screening in the 1990s (1), PSA-based screening has had a substantial impact on management of patients with prostatic diseases. Because of widespread use of PSA testing, the lifetime risk for being diagnosed with prostate cancer increased from 7.3% to 17% (18), whereas the lifetime risk for death from prostate cancer decreased by 20%, from 3% to 2.4%, over the past 3 decades (19). Although PSA-based screening may have lifetime benefits in select patients, the interventions may come at substantial risk for others (20–22). Therefore, shared decision making should be undertaken with all men deciding whether to undergo prostate cancer screening (23).

The key points to include in shared decision making are covered in Table 1. It is important to review what occurs after detecting an abnormal PSA level. First, patients should be informed about the changing definition of an elevated PSA value. Historically, the cut point was 4.0 μg/L (1). Now, with lower cut points ranging from 2.5 to 4.0 μg/L, approximately 80% of PSA tests will yield false-positive results. Estimates from the ERSPC trial, which used a cut point of 3.0 μg/L, suggest that the likelihood of detecting prostate cancer is approximately 25% (24). Second, it is important to review other physiologic factors that contribute to an elevated

Table 2. Biomarkers for Early Detection of Prostate Cancer*

Biomarker	Source	Description
%fPSA	Blood	Ratio between fPSA and tPSA
Prostate Health Index	Blood	Combines 3 PSA subforms (tPSA, %fPSA, and p2PSA) into a single mathematical score
4K score	Blood	Combines 4 kallikrein markers (tPSA, %fPSA, intact PSA, and hK2) with age and prostate examination findings
SelectMDx (MDxHealth)	Urine + clinical risk factors	Measures post-DRE mRNA levels of a 2-gene panel (*DLX1* and *HOXC6*)
Michigan Prostate Score	Urine + blood	Combines findings of fusion gene *TMPRSS2* and *ERG* (*TMPRSS2*:*ERG*) along with PCA3 and the PCPT risk calculator†
PCA3	Urine	Measures PCA3 mRNA in first-void urine after DRE with prostatic massage
ExoDx (Exosome Diagnostics)	Urine	Exosomes are small membranous vesicles secreted from cells and assessed in urine collected during routine evaluation; urine sample does not have to be obtained after DRE prostate examination
ConfirmMDx (MDxHealth)	Prostate biopsy	Evaluates epigenetic alterations (methylation status) of *GSTP1*, *APC*, and *RASSF1* to look for a field defect
mpMRI	Prostate imaging	MRI can be programmed for several different pulse sequences, or parameters, that highlight specific diffusion of contrast differences based on vascularity of healthy and unhealthy tissue; MRI using ≥2 parameters is called mpMRI

APC = adenomatous polyposis coli; *DLX1* = distal-less homeobox 1; DRE = digital rectal examination; *ERG* = v-ets erythroblastosis virus E26 oncogene homolog transcription factor ERG; fPSA = free PSA; *GSTP1* = glutathione *S*-transferase Pi 1; hK2 = hexokinase 2; *HOXC6* = homeobox C6; mpMRI = multiparametric MRI; MRI = magnetic resonance imaging; mRNA = messenger RNA; p2PSA = [−2]proPSA; PCA3 = prostate cancer antigen 3; PCPT = Prostate Cancer Prevention Trial; PSA = prostate-specific antigen; *RASSF1* = Ras association domain family member 1; *TMPRSS2* = transmembrane serine protease 2; tPSA = total PSA.
* Based on references 33 and 34.
† The PCPT risk calculator is available at http://riskcalc.org/PCPTRC.

PSA value, including age, prostate volume, prostate manipulation, inflammation, or infection (25).

For men who have an elevated PSA level and for whom prostate biopsy is recommended, the immediate physical harms include hematuria, hematochezia, hematospermia, dysuria, urine retention, pain, and infection. The 30-day risk for hospitalization for any cause after prostate biopsy is 4%, of which 75% is the result of infection (20). The psychological harms of screening should not be overlooked, as demonstrated by Mr. W.

Treatment options for early and late prostate cancer, and the associated potential complications, should be discussed (21, 22). Patients should be informed that the longest randomized trial comparing radical prostatectomy with watchful waiting has shown that men with a long life expectancy benefited from treatment with 2.9 years of life gained. At 23 years of follow-up, 8.4 patients needed to be treated to avert 1 death from any cause (24). Therefore, it is clear that although treatment reduces the likelihood of death from prostate cancer, there are many other competing risks for death in this age group. Each man needs to weigh the risks and benefits of screening and treatment individually.

Question 2: What PSA-based screening strategy optimizes benefit and minimizes harm?

The USPSTF recommendations in 2012 led to a decrease in PSA testing, prostate biopsy, and diagnosis of prostate cancer (26). However, along with the decline in diagnosis of localized prostate cancer was a concomitant increase in diagnosis of more advanced and metastatic prostate cancer, raising concern for a reverse-stage migration (27, 28). We have learned from this experience that a single PSA test versus no screening has no significant effect on prostate cancer mortality (29), whereas annual prostate cancer screening is probably no more effective than screening every 2 to 4 years, because a 2- to 4-year interval is unlikely to miss a curable window for prostate cancer (30).

The Physicians' Health Study (31) and Southern Community Cohort Study among black men (32), which focused on personalization of PSA testing, found that PSA values during the fourth and fifth decades of life are highly predictive of aggressive and lethal prostate cancer. Therefore, men with very low PSA levels during midlife may not require PSA screening as frequently, whereas those with higher baseline PSA levels may benefit from more frequent testing.

If an abnormal PSA level is detected, several secondary tests exist to refine the risk estimate of detecting prostate cancer, as shown in Table 2 (33, 34). Another important method is multiparametric magnetic resonance imaging (mpMRI), which may be used as a tool for screening and detection of clinically relevant disease (35). Although secondary tests are designed to reduce unnecessary biopsies while maintaining the ability to detect clinically significant prostate cancer, more research is needed to confirm which test is best capable of achieving this goal. In the near term, mpMRI probably holds the greatest promise in helping identify clinically relevant prostate cancer (36).

Question 3: At what PSA threshold would you recommend further diagnostic testing, and what would you recommend for Mr. W?

Prostate-specific antigen thresholds that would lead me to recommend additional testing vary for men depending on their age, comorbid conditions, and historical PSA values. Before making a decision about further testing, I make certain the PSA value was not obtained at a time when the patient may have had any inflammatory, infectious, or traumatic process that would account for a falsely elevated PSA level.

Prostate-specific antigen should be collected after the man has been abstinent from any sexual or ejaculatory activity (at least 3 days), because ejaculation causes false elevation of PSA levels. In addition, PSA levels are falsely elevated in the setting of a urinary tract

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Dr. Owens is a general internist and investigator at the Center for Innovation to Implementation at the Veterans Affairs Palo Alto Health Care System. He is the Henry J. Kaiser Jr. professor at Stanford University, where he is also a professor of medicine, health research, and policy (by courtesy) and of management science and engineering (by courtesy).

Dr. Smetana is a member of the Division of General Medicine and Primary Care at Beth Israel Deaconess Medical Center and Professor of Medicine at Harvard Medical School in Boston, Massachusetts.

infection or acute urine retention; therefore, I wait at least 2 to 3 months after resolution of a urinary tract infection before repeating the PSA test, and I look for a downward trend. In the setting of acute urine retention, the underlying cause needs to be determined and PSA values need to be judged individually to help guide treatment decisions.

For Mr. W, whose prostate size is age appropriate, the PSA trajectory—a PSA value of 2 to 3 μg/L from 2009 to 2013 that doubled in 5 years to 6 to 7 μg/L—is concerning. In addition, his 11% free PSA and PSA density of 0.18 μg/L per mL are abnormal (33). Therefore, I would recommend a prostate biopsy. However, if he is reluctant to accept that recommendation, it would be reasonable to obtain an mpMRI scan to assess for abnormal foci raising concern for prostate cancer. In fact, in the United Kingdom prostate biopsy is not recommended in the absence of an abnormal finding on mpMRI, a practice that may be appropriate although not fully adopted in the United States yet. The role of additional biomarkers where high-quality mpMRI is available remains unclear. However, for patients and centers that do not have access to mpMRI and expertise to obtain high-quality images, additional biomarkers may have a role (**Table 2**).

Prostate biopsy techniques are also evolving. With advances in mpMRI technology, some European centers biopsy only the lesions detectable on MRI and forgo the systematic biopsy of the different zones of the prostate. Biopsy of the MRI-targeted lesions identifies more clinically relevant cancer cases while reducing the rate of detection of well-differentiated cancer that will remain dormant and may not require treatment during a patient's lifetime (36).

Active surveillance strategies have gained acceptance among health care providers for patients with low-grade or well-differentiated prostate cancer (37). By appropriately selecting patients who are diagnosed with low-risk prostate cancer, fewer treatment-related side effects are encountered; with appropriate follow-up, if there are changes that suggest cancer progression, treatment with curative intent would then be possible (38). The best candidates for active surveillance are those with Gleason 3 + 3 (group grade 1) prostate cancer; however, patients with low-volume Gleason 3 + 4 (group grade 2) may also be considered (39).

Prostate cancer screening and treatment reduce the risk for prostate cancer metastasis and death from disease. With increased longevity, the benefits of screening and treatment have become more evident. However, strategies for management of prostate cancer come at a cost, and the risks and potential benefits are weighed differently by each patient, highlighting shared decision making as a critical component of prostate cancer management.

SUMMARY

Our discussants agree that the decision to have PSA-based prostate cancer screening is challenging because of the need to balance competing benefits and harms. Dr. Owens reviewed the key components of a shared decision-making conversation and the importance of understanding how each patient values these benefits and harms. Dr. Olumi pointed out that although PSA-based screening creates risk for overdiagnosis and overtreatment, not screening carries the risk for missing men with intermediate- and high-risk disease, who would benefit from early detection and treatment.

Our discussants concur with both the USPSTF and AUA guidelines that if the decision is made to proceed with PSA-based screening, it should be done every 2 to 4 years rather than annually. They also agree that the PSA threshold at which to proceed with biopsy is unclear and depends on several factors, including age, life expectancy, prior PSA values, and recent infection. In the setting of an elevated PSA level, Dr. Olumi discussed the role of genomic markers and mpMRI to minimize overdiagnosis and overtreatment, as well as the role of active surveillance for patients with low-risk disease.

Regarding Mr. W, the discussants were concerned about the increase in his PSA level, and both would recommend a biopsy. However, Dr. Owens would proceed only after a shared decision-making conversation to be certain that Mr. W would accept treatment if he had prostate cancer. Dr. Olumi suggested that if Mr. W remained reluctant to have a biopsy, mpMRI would be an option to establish the diagnosis.

A transcript of the audience question-and-answer period is available in the **Appendix** (available at Annals.org).

To view the conference video, including the question-and-answer session, go to Annals.org.

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Appendix: Comments and Questions

Dr. Gerald W. Smetana: There is a lot of information to cover in this shared decision-making discussion. We frequently have 15 or 20 minutes for a visit, and we are trying to discuss other things during the same visit. I wonder if there are any types of support tools for patients to understand shared decision making, so that some of it could perhaps happen outside the context of our visit to help patients be better prepared.

Dr. Owens: There are, and the paper that we're doing is part of this. We give a reference for a site that contains a number of decision tools for prostate cancer screening decisions. So, there are some that are available.

Dr. Olumi: There are risk calculators from different institutions to help as well. Most of the risk calculators have focused on the likelihood of diagnosis or the likelihood of intermediate- or high-grade cancer, which can be useful sometimes.

Dr. Bruce Landon: I think this question is more for Doug, but it could be for either of you. I am not exactly following how you get the estimates of overdiagnosis. If you screen 1000 men, 100 get diagnosed. Of those, 5 are going to die and there are 3 fewer cases of metastatic disease. I will assume that is over a base of somewhere between 20 and 30; 35 from 100 is 65. So, what's in that number for saying that the rate of overdiagnosis is only 20% to 50%?

Dr. Owens: Good question. No one knows what the rate of overdiagnosis is. Let's start with that, because you have to have the counterfactual, but the randomized trials do help, and you can compare the different arms in them. The estimates of 20% to 50% come from the trials, and the notion is, Would that cancer have caused trouble during that person's lifetime or not? You can make the comparison between the intervention and control arms to get some estimates of that, but there is uncertainty about it. The overdiagnosis rate is substantial because prostate cancer is slow growing in many men. So, it's just something that we have to attend to, and the exact number is hard to know for sure.

Dr. Olumi: I would say how overdiagnosis actually gets labeled is by the type of cancer that's detected. Gleason 6 cancer nowadays is often felt to be overdiagnosed and not needing therapy.

Dr. James Jacques Carter: The state health department has been working on some tools to help primary care physicians deal with the information issue with patients coming in—we have a short period of time to deal with patients. So, they put together some shared decision-making tools that are very good for this particular instance. The point I have to make is that the current thinking is that we are still living with the old Task Force D recommendations. What has the Task Force done to help promote the fact that there should be more screening in the shared decision-making way? Most people think that you shouldn't screen.

Dr. Owens: Well, the guideline came out in May 2018, published in *JAMA*, and we do the usual things to try and disseminate that and get it out as best we can. I hope that word filters out, because it is a significant change from the prior recommendations, and *JAMA*, of course, also has efforts to publicize it.

Dr. Olumi: Can I make a comment as far as the new recommendations? I think an important piece that we have focused on is patients who should be screened, but patients we think should definitely not be screened, as clearly stated in the new guidelines, are those over the age of 70, who probably do not benefit from PSA screening. I had a patient referred to me yesterday: a 79-year-old gentleman with several comorbid conditions, referred to me for an elevated PSA level. So, I think that it is important not to have a routine, knee-jerk reaction of checking off the PSA testing box in our routine clinical visits for our older patients.

Dr. Lewis Lipsitz: Many patients get PSA tests because they seek help from their physicians for symptoms—symptoms of prostatism, usually. Do these symptoms help in any way to determine whether the patient might have prostate cancer?

Dr. Owens: I am going to defer that to Aria, but I will just say one thing about our guideline: It is for people who are asymptomatic. So, if you're having prostate symptoms, our guideline doesn't apply, and that would be case finding or evaluation or work-up. In terms of how you interpret those, I'd be interested in hearing from Aria.

Dr. Olumi: In this day and age in the United States, I think symptoms associated with diagnosis of prostate cancer are extremely rare. However, if patients are having symptoms, just checking off PSA testing does not replace a complete physical examination. Oftentimes what I hear from our residents in the internal medicine department is, "They are teaching us not to even do a prostate exam anymore." So, I would say that for a patient who may have some symptoms, it is more important to do a prostate examination as opposed to simply sending him for a PSA blood test evaluation.

Dr. Jacqueline Wolf: You have a number of people who have had PSA testing in the past, so they have a baseline. Then they request a repeated test, maybe several years later. Let's say that they are under the age of 70. At what value do you say, "Okay, we now need an MRI. It's gone up 1, it's gone up 2. We're worried now

that there may be something going on." Or do you have a level at which you say, "Forget it. We're going to keep following you."

Dr. Olumi: That's a loaded question, but I would say that it's clearly shown that PSA testing annually is too much. I think a good place to focus on is every 2 to 4 years. Checking every 3 years is reasonable. For a patient who is 58 years old and has a gradual rise in PSA level, whether to proceed with a prostate biopsy or do MRI before a biopsy, I think that those practices are evolving. As I mentioned, in the United Kingdom, generally they don't do a biopsy for patients who do not have a targetable lesion on MRI. As a society, they decided that is a good way to go. I would say that in most urologic practices in the United States, that is not the way we do it because we are not comfortable with that yet.

Dr. Owens: I would add that if someone asks that question, even if they've had a prior PSA test, I'd still want to have a shared decision-making conversation. For most people, that probably hasn't happened. They should understand what the implications are, and most of the things that we've talked about in terms of shared decision making would be applicable, even if they've had a prior PSA test, if they've never had those conversations.

Dr. William DeWolf: One of the terms that bothers me is *insignificant prostate cancer*. We don't know which insignificant prostate cancer cases will become significant, or is it called insignificant simply based on error of biopsy? How does this fit into your algorithm, the tendency for errors to occur in our system?

Dr. Owens: Our guideline for the Task Force is really focused on that initial decision about whether to get a PSA test, and that is the recommendation about do you get a PSA test or not? Once somebody has a PSA test, we would actually defer its interpretation to the urology colleagues in terms of the biopsy and so on. We did, of course, look at the harms of biopsy, which we've talked about here, but the focus of the USPSTF guideline is really on whether to get a PSA test. To make that decision, we want to incorporate information about the biopsy, both false-positives and potential false-negatives—although false-positives get more attention—and then about what happens subsequently.