



Prostate-Specific Antigen Screening for Prostate Cancer: Yes, No, or Maybe?

Moderated by **Richard Hoffman, MD, MPH¹**

Discussants: **David Penson, MD²; Robert J. Volk, PhD³; Andrew M.D. Wolf, MD⁴**

DR. HOFFMAN: Prostate-specific antigen (PSA) testing was introduced in the 1980s as a tumor marker for cancer surveillance. However, it was rapidly and widely adopted for prostate cancer screening. From the beginning, PSA screening has been controversial. Based largely on diagnostic performance data, The American Uro-

logical Association (AUA)¹ and the American Cancer Society (ACS)² began recommending routine PSA screening and digital rectal examination (DRE) in the early 1990s. In contrast, the US Preventive Services Task Force (USPSTF) did not endorse screening because they believed that the available evidence was insufficient to either recommend or oppose screening. Large randomized screening trials were initiated in Europe (the European Randomized Study of Screening for Prostate Cancer [ERSPC]³) and in America (the Prostate, Lung, Colorectal, and Ovarian [PLCO] Cancer Screening Trial⁴).

The introduction of PSA screening was associated with a decreased incidence of advanced stage disease and a slight decrease in prostate cancer mortality. However, screening often detected indolent localized cancers that did not require treatment. Observational studies also suggested that treating localized cancers could

adversely affect urinary, bowel, and sexual function.⁵ Consequently, while awaiting results from the randomized trials, the guidelines began acknowledging the complexity of screening decisions and encouraging clinicians to help patients make informed decisions.

In 2009, the publication of the long-awaited mortality results from 2 large randomized prostate cancer screening trials did not provide sufficient data to resolve controversies. The ERSPC showed a small benefit from screening after 9 years, but the American PLCO Cancer Screening Trial reported only negative findings. Recent updates with longer follow-ups confirmed the original findings.^{6,7} Revised guidelines have actually heightened the controversies.⁸ The ACS and AUA still recommend helping men make informed decisions regarding screening, though the 2009 AUA guideline expanded the age range for screening as well as criteria for biopsy referral.⁹

ABSTRACT

The discussion focused primarily on: 1) The effects of prostate-specific antigen screening on prostate cancer incidence and mortality; 2) strengths and weaknesses of The European Randomized Study of Screening for Prostate Cancer (ERSPC) and comparisons with the United States Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial; 3) American Urological Association and American Cancer Society guidelines for prostate cancer screening; 4) US Preventive Services Task Force recommendations for prostate cancer screening; 5) informed decision-making in prostate cancer screening and the use of decision aids; and 6) the future of prostate cancer screening. Updated with new evidence-based medicine guidance from The American Urological Association. *Med Roundtable Gen Med Ed*. 2014;1(4):290-300.

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Meanwhile, the USPSTF recently recommended against prostate screening under any circumstances.¹⁰ Regardless of this, after more than 20 years of use, PSA testing is not going to be suddenly discontinued. Patients and physicians will still face the challenging decisions of whether and how to screen for prostate cancer. We've assembled a panel of experts to discuss clinical trial results, guideline controversies, and strategies for supporting informed decision making for prostate cancer screening.

DR. HOFFMAN: I'm Dr. Richard Hoffman, Professor of Medicine at the University of New Mexico and a staff physician at the Albuquerque VA Medical Center. I'll be moderating this discussion.

DR. PENSON: I am David Penson; I'm Professor of Urologic Surgery at Vanderbilt University. I direct our Center for Surgical Quality and Outcomes Research.

DR. VOLK: I'm Bob Volk. I'm a professor in the Department of General Internal Medicine at the MD Anderson Cancer Center. I'm a decision scientist and a developer of patient decision aids.

DR. WOLF: I'm Andy Wolf. I am an Associate Professor of Medicine at the University of Virginia School of Medicine. I was the first author of the ACS Guideline for the Early Detection of Prostate Cancer that came out in 2010.

DR. HOFFMAN: I want to start briefly by talking about the epidemiology of prostate cancer with regard to PSA screening. We've seen a large and persistent increase in cancer incidence rates. Cancer mortality rates initially increased slightly after the introduction of PSA testing followed by a decrease in mortality rates. Dr. Penson, can you comment on this?

DR. PENSON: When we assess prostate cancer mortality rates in the United States, interestingly, we see a spike in the early 1990s, which we have alluded to, that's consistent with the introduction of PSA testing. We also see a spike for incidence,

Proponents of screening will tell you this is proof that screening works and that we're catching cancers earlier and treating them earlier. However, although it certainly makes those of us who believe that screening is a positive thing feel optimistic, it isn't conclusive evidence.

The problem is that there are other possible influences that may reduce mortality. The first is the change in the way we treat prostate cancer. There was an increase in the use of hormone therapy in the late 1990s and early 2000s, and some people have said that this may be the cause of the decline in mortality.

Some models have tried to account for changing patterns of treatment and for the potential benefit of hormone therapy. Most of the work has been done by a group called the Cancer Intervention and Surveillance Modeling Network (CISNET), which is a group of

biostatisticians and modelers who are funded by the National Cancer Institute (NCI).

I've actually participated in that group, and there was a paper in *Cancer Causes and Control*¹² approximately 3 or 4 years ago that is often quoted. We were able to show that even after accounting for these changes in treatment, over time, you're going to see that PSA screening or prostate cancer screening is responsible for anywhere from 40% to 70% of the observed drop in mortality.

"Over the last 2 decades, professional organizations have issued a number of screening guidelines. Initially, the AUA and ACS were very pro-screening. However, over time, they have acknowledged the fact that screening decisions are complicated, involving tradeoffs between benefits and harms, and that we need to help men make informed decisions."

Richard Hoffman

and as we examine that spike, we see that incidence remains higher than it was before the introduction of PSA testing.

Certainly, that's what you'd expect with a new screening test, but what's interesting is that when we follow-up the patients into the late 90s and the early 21st century, we see a decline in prostate cancer mortality when we look at the Surveillance Epidemiology and End Results (SEER) data.¹¹ This gives rise to the question of why we are seeing this decline in mortality.

Again, this is a model. It's not a randomized clinical trial, so it is looked at quite skeptically. That being said, we are definitely seeing a decline in mortality. There is some preliminary evidence showing that this may be due to screening, but it's not conclusive.¹³

DR. WOLF: Dr. Penson, interestingly, when you review the European Randomized trial data, which shows a potential reduction in mortality due to screening, it seemed that the benefit was observed approximately 10 years after the onset of screening.¹⁴ And yet, the initial decline in prostate cancer mortality seemed to begin only 2 or 3 years following the advent of PSA screening. The critics of screening say that the mortality decline occurred too soon after the advent of PSA for it to be attributed to PSA screening. I'm sure you've thought about that, but is that a legitimate criticism of PSA screening?

DR. PENSON: I think it is a legitimate criticism to some degree. If you only observed a decline in the first few years after screening was introduced, which then dissipated, it would be a very valid criticism, but here, you continue to see the decline. A recently published study from Austria observed a decline within 1 to 2 years of prostate cancer screening.¹⁵ No one gives that result credit because of exactly what you said: It occurs too early. When you look at these models that Ruth Etzioni and Alex Tso-

dikov have developed,¹⁶ you notice that some of the decline in mortality, but not all of it, is attributed to screening. The former change may be related directly to treatment that was stopped after the first 2 or 3 years as patients were receiving hormonal treatments earlier. I think that's what accounts for that initial drop, but the fact is, you see a prolonged drop over time.

When I look at that decline in mortality—and again, this is an opinion because it has not been shown in a randomized clinical trial—my opinion is that prostate cancer screening has an effect, but

"There may be a real role for following those patients [patients who have been diagnosed with prostate cancer] closely, with regard to monitoring their PSA levels, repeating biopsies over time, and effectively and actively surveying them. This reduces the complications associated with aggressive intervention and potentially improves the efficacy of screening."

David Penson

we can't say that the entire decline in mortality is due to screening. It's probably due to other reasons as well, and that's why the models make more sense to me when you say, "Somewhere between 40% and 70% of the decline can be attributed to screening."

DR. HOFFMAN: Dr. Wolf, that's actually a good lead in, because clearly, the epidemiologic data are not going to be conclusive with regard to whether screening accounts for a decline in mortality. We awaited publication of the results from the ERSPC and PLCO randomized screening trials for many years.

Can you tell us about the ERSPC study design and results and how you have interpreted the findings?

DR. WOLF: The European trial was more of a meta-analysis of multiple trials going on simultaneously because it involved 7 European countries. It started in 1991 and included randomized 162,000 men who were between the ages of 55 and 69 years, to PSA screening or routine care.

However, this trial was being conducted in 7 different European countries, and there were some real differences in the methodologies between the countries. In addition, there were differences in the PSA level cutoffs that prompted further evaluation and also differences in screening intervals. Therefore, it wasn't a pure randomized trial; it was more of a meta-

analysis. Nonetheless, it provided a very large cohort of men who were randomized. They were followed up for a mean period of approximately 11 years at the most recent update, which was published in 2012.

In that study, there was a statistically significant difference in prostate cancer mortality in the men who underwent PSA screening compared with those who received routine care. There was a 21% relative risk reduction in prostate cancer death in the screened group as compared to the unscreened group at 11 years of follow-up. Thus, approximately 1000 men needed to be screened

to save 1 life and approximately 37 men needed to be diagnosed with prostate cancer to save 1 life over 11 years. These findings highlight an important limitation of prostate cancer screening: overdiagnosis and overtreatment. Although screening may reduce cancer mortality overall, many men who undergo screening will be diagnosed with and treated for prostate cancer, who never would have developed clinically apparent disease if they had not been screened. In other words, they would have lived a normal life and died of an unrelated cause before their prostate cancer became apparent. This is an issue with many conditions that are screened for, but it is a particularly prominent issue for prostate cancer screening, because of the often long latency between cancer onset and the development of clinical illness.

Of note, the European trial did not show any impact on overall all-cause mortality, although this is often the case in most cancer screening trials. They're aimed at assessing cancer-specific mortality reduction. Therefore, this study did show a statistically significant decline in prostate cancer-specific mortality.

The European study has been criticized for a number of reasons. Perhaps the most serious criticism is that there was some concern that the men in whom prostate cancer was diagnosed in the screening arm were more likely to receive treatment in university settings than those in whom prostate cancer was diagnosed in the routine care arm

or control arm, who may have been more likely to receive care in community hospitals. That difference, if big enough, may have affected the outcome.

Another criticism is that the study is, in fact, a meta-analysis and that the methodologies differed significantly between the countries. In fact, one of the concerns of the USPSTF was that only 2 of the countries—Sweden and the Netherlands—showed a statistically significant mortality reduction that was not seen in the other 5 countries. This raised the question of whether the reduction in mortality was a generalizable finding.

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Robert Volk

The contamination rate, referring to the number of patients who were in the control arm and who were actually screened, was relatively low; it was only 10% compared to an approximately 40% to 50% contamination rate in the American study, which we will discuss further on.

DR. HOFFMAN: Dr. Penson, the American PLCO Cancer Screening Trial is essentially negative. Can you comment on that study?

DR. PENSON: It's really nice to follow that great discussion of the ERSPC trial. At the same time that ERSPC

was being conducted, there was a similar trial in the United States—the PLCO Cancer Screening Trial—involving prostate, lung, colorectal, and ovarian cancer screening.

In the prostate arm of that trial, the researchers randomized just over 76,000 men for either screening or routine care. This was accomplished at 10 centers from 1993 through 2001, and they originally published their results in *The New England Journal of Medicine*.¹⁷ They have published a longer-term follow-up earlier this year in the *Journal of the National Cancer Institute*.¹⁸ This study was essentially a negative study. With 13 years of follow-up, there was no difference between the intervention arm and the control arm.

However, I don't view this study as a screening versus no-screening one. This is a study of a little bit of screening ver-

sus a lot of screening. In the intervention arm, there were patients undergoing annual screening as would be suggested if a patient decided to undergo screening via various guidelines. However, there is high contamination in the control arm because at 3 years of the study, just over 40% of the men in the control arm underwent a PSA screening test, and by the end of the study, more than half the men—I believe it was 52%—had a PSA screening test. So, it's not really a fair comparison of screening versus no screening, but the study does provide us with some important information.

Screening is not to be performed for everyone. For example, in an older patient who has more comorbid diseases, screening is probably not worth it because, as was discussed earlier, the life expectancy should be adequate in order to see a benefit (if one exists). You have to live long enough to get that benefit—I would say, at least 10 years.

There was another analysis of PLCO Cancer Screening Trial that was published in *The Journal of Clinical Oncology*, with David Crawford as the lead author, that looked at the subgroup of patients in the PLCO Cancer Screening Trial who were younger and healthier.¹⁹ In that subgroup, they found prostate cancer screening to have a benefit. We should keep in mind that this study was a subgroup analysis, but I think it starts influencing our decision making because it helps us understand which patients are going to benefit from the screening.

DR. HOFFMAN: Dr. Penson, as a urologist, what do you think about the potential biases in ERSPC in that screened patients were more likely to be treated at university centers? Is that a real concern?

DR. PENSON: I think that's a very fair criticism of the study. One of the problems that you have with the European study—and to some degree, even the American study—is that there was really no protocol for treatment once a diagnosis was

made. There are treatment differences not only in the European study but also in the American study. For example, we know for a fact that there are differences in the quality of surgical interventions between high-volume and low-volume hospitals. I suspect that the same differences exist for radiation therapy. Therefore, I think there are differences with regard to who underwent treatment and where the patients were treated in the European study.

People wish to compare the European study to the American study, but as stated earlier, the European study is a meta-analysis

"The problems associated with treating screen-detected prostate cancer are well known and include sexual dysfunction, urinary incontinence, bowel injury from radiation, death on the operating table, and postoperative death. Patients should be aware of these elements before they launch into the screening process."

Andrew Wolf

with a number of different screening protocols, and the patients involved in those screening protocols aren't necessarily a representative population of the United States. So, my take-home message is that we should not generalize the results of either study to all patients. Results of each study can only be applied to patients that reflect those enrolled in that particular study.

DR. HOFFMAN: Over the last 2 decades, professional organizations have issued a number of screening guidelines. Initially, the AUA and ACS were very pro-

screening. However, over time, they have acknowledged the fact that screening decisions are complicated, involving tradeoffs between benefits and harms, and that we need to help men make informed decisions. The USPSTF argued for years that there was insufficient evidence either for or against screening.

After the long-awaited publication of the randomized screening trial results, the AUA revised their guidelines. Dr. Penson, can you tell us about these guidelines?

DR. PENSON: As a urologist, I am affiliated with the AUA, which is the primary specialty organization for urology. The AUA's guidelines are more of best practice statements than guidelines, per se, because they were released immediately after the randomized clinical trials were completed;

thus, these trials didn't have a prominent role in the document as they should have. So, now, AUA is revising the guidelines again, as they do every few years.

DR. HOFFMAN: Dr. Wolf, you were the lead author on the recently revised ACS guidelines. Can you highlight your recommendations and talk about how they contrasted with the AUA guidelines?

DR. WOLF: The ACS guideline, similar to that of the AUA, calls for informed decision making as the centerpiece of the guideline. I think the exact wording was, "Men should

have an opportunity to make an informed decision with their health-care provider about whether to be screened for prostate cancer.” It really does highlight the importance of informed decision making. In fact, in the guideline, it specifically states, “Prostate cancer screening should not occur without an informed decision-making process.”

One difference is the age at which that informed discussion begins. The ACS recommends that the discussion between doctor and patient about whether to screen begin at the age of 50 years. We also recommend that men whose life expectancy is below 10 years not be engaged in that discussion. In other words, the ACS determined that if the patient does not have a 10-year life expectancy, he would not benefit from early detection. In contrast, the AUA guideline, which was just published in 2013, recommends initiating the informed decision-making process at the age of 55 years in average-risk men.²⁰ For men who choose to be screened, they recommend screening until the age of 69 years, rather than following the 10-year life expectancy guideline. In general, the AUA appears to be adhering more strictly to the protocol of the ERSPC.

Other elements of the ACS guideline are also risk-based in the sense that for men whose initial PSA level is below 2.5 ng/mL, the recommendation is now to conduct screening every 2 years rather than annually. If a man's PSA level is between 2.5 and 4.0 ng/mL, the ACS still calls for annual screening. The AUA guideline, again adhering closely to the European trial protocol, calls for screening every 2 to 4 years.

The ACS guideline also indicates that community-based screening

should be discouraged, unless thorough informed decision making can be done at the time of the screening. If that cannot be established, then community-based screening should not be offered. By community-based, I mean in public settings or hospital-based settings where there is a significant chance that decision making would not occur. Such screening should be discouraged.

The ACS guideline includes a delineation of the core elements that should be included in the discussion to assure that informed decision making occurs. These include the potential benefits; for example, prostate cancer can be found earlier with screening than without screening, and early detection may reduce the chance of dying from prostate cancer. However, we also included the disadvantages of screening, including the significant risk of overdiagnosis and overtreatment; the risk of false-positive and false-negative results; the risks of prostate biopsy; and the significant risk of sexual dysfunction, urinary incontinence, and bowel injury that are associated with treatment of screen-detected cancer: these are the key elements.

Another new aspect of the ACS guideline included our recommendation that the DRE be included only as an optional component of screening. This is just based on the lack of data to suggest that it's an effective screening tool at the population level. The European study did not include the DRE as a part of the screening in most countries, and this study showed a mortality benefit. The PLCO Cancer Screening Trial included the DRE, and it was a negative study. Therefore, on the basis of the randomized trial evidence and

other evidence, the ACS elected to make the DRE an optional element of the screening process.

DR. HOFFMAN: To lead the discussion into the last guideline from the USPSTF, I'd like to turn to Dr. Volk, who's written a number of very thoughtful commentaries on this topic. Dr. Volk, can you summarize the USPSTF recommendation and explain why you question it?

DR. VOLK: First, I'd like to spend a moment describing the Task Force. I think the USPSTF is often misunderstood with respect to their composition, function, etc. The USPSTF was authorized by Congress in 1984 to make evidence-based recommendations about clinical preventive services, including, but not limited to, cancer screening. Members of the USPSTF belong to fields of preventive medicine and primary care, and they volunteer their time to serve on the Task Force. They make these recommendations based on a careful assessment of evidence regarding the benefits and harms of a particular preventive health service.

In 2010, the Affordable Care Act legislation authorized the Agency for Healthcare Research and Quality (AHRQ) to provide administrative, research, and communications support to the USPSTF. The current prostate cancer-screening recommendation from the Task Force is a result of a careful comparative effectiveness review that was commissioned by the AHRQ.

The USPSTF functions autonomously from other government agencies. Their guidelines are not vetted by the AHRQ or any other entity with the Department of Health and Human Services. They have independent authority to make recommendations.

A couple of things to keep in mind: The recommendations are evidence-based, and the Task Force is looking at the same evidence that the other organizations are considering. The USPSTF does function autonomously, as I mentioned earlier, and an interesting aspect of their work is that they consider the cost of an intervention only because that cost relates to people's ability to partake in the intervention.

In July 2012, the USPSTF issued its recommendation about screening for prostate cancer, and we did have a heads up about the update. The USPSTF has implemented a new process in which they post drafts of their recommendations and have a comment period where people can indicate their reactions to an upcoming recommendation. Therefore, we knew that this guideline was going to be released.

This is a "D" level recommendation from the Task Force, and it reads, "The Task Force recommends against PSA-based screening for prostate cancer. This recommendation applies to all men in the general US population, regardless of age."

They go on to talk about the guidelines not addressing issues such as using PSA for surveillance.

In summary, what the USPSTF has done is review the evidence largely from the 2 screening trials that have been mentioned previously. They have concluded that the harms of screening, which are well known and well documented, exceed the potential benefit of screening; in effect, they recommend against prostate cancer screening.

This is different from their recommendation of 2008 where the

USPSTF issued an "I" recommendation, arguing that the evidence was insufficient to recommend for or against screening. Therefore, the USPSTF is a bit of an outlier when considering the recommendations of other groups.

This is a controversial recommendation, and there have been quite a few comments and criticisms about it. We've talked about the concerns regarding the PLCO Cancer Screening Trial, and perhaps, the USPSTF gave too much importance to the PLCO Cancer Screening Trial findings, especially considering the high (>50%) contamination rate among the control men.

Additionally, there have been concerns about the USPSTF not giving enough importance to the European trial. In particular, the trial from Goteborg²¹ showed a significant benefit in terms of prostate cancer mortality and a much lower number needed to be screened as compared to the overall trial.

Then again, they released a "D" level recommendation. People would have been much more comfortable with the recommendation if it had been a "C." A "C" recommendation would recommend against routine screening, which would be very much in line with the recommendation of other groups that endorse an informed or a shared decision-making process.

DR. HOFFMAN: Dr. Wolf, regarding the informed decision-making process, ACS has consistently supported this concept. Can you define informed decision making and explain its importance?

DR. WOLF: In general, whenever there is an intervention or a diagnostic tool where the balance between the benefits and potential

harms is too close to call, it is really incumbent on physicians to engage patients in an informed decision as to whether they wish to proceed.

This is particularly relevant to the prostate issue. Because prostate cancer screening, by definition, involves men who are asymptomatic at the time that we're proposing it, and given that there's clearly uncertainty regarding the overall balance between benefits and harms, it really is vital to allow the patient to be part of the decision.

This is essentially an ethical issue. Before we potentially cause harm, we should certainly have the patient's agreement; we should know that they want to proceed with the intervention—in this case, prostate cancer screening. That's the reason why informed decision making—and in this case, shared decision making—is so important.

Shared decision making implies not only that the patient is informed but also that the health-care provider is engaged in the decision-making process by assisting the patient in making the decision whether or not to be tested for prostate cancer.

One element of this process is that the patient has the information to understand why screening is controversial. The patient should understand the potential benefits of screening, which, of course, include potentially preventing death from prostate cancer.

There are many potential harms, including harms related to the initial PSA screening with or without the DRE, which are negligible risks; however, the problems associated with biopsy are not insubstantial, primarily in terms of the infection risk and bleeding risk. One Medicare

database study reported a hospitalization rate of up to 0.45% for urinary or prostate infection in men who have had a prostate biopsy.²²

The problems associated with treating screen-detected prostate cancer are well known and include sexual dysfunction, urinary incontinence, bowel injury from radiation, death on the operating table, and postoperative death. Patients should be aware of these elements before they launch into the screening process.

Since this is such a value-dependent decision, physicians can play a critical role in helping patients to articulate their values and subsequently integrate these values into the screening decision. For example, is it more important to the patient to try to avert death due to prostate cancer or to avoid complications such as sexual dysfunction, urinary incontinence, or bowel injury incurred while treating a cancer that might never have harmed them?

DR. HOFFMAN: One thing that I really appreciate about the ACS guidelines is that while encouraging informed decision making, they recognize that physicians and patients often don't have the time to adequately discuss screening. The physicians may also not have readily available information on benefits and harms; therefore, the ACS recommends using decision aids. Dr. Volk, could you describe decision aids and how we should use them? Do we know whether they're effective?

DR. VOLK: The question really is that with all this wonderful evidence, how can we expect clinicians to have a conversation with patients about the potential harms and benefits of screening, all within the context of a very limited encounter? It just

takes a lot of time, and decision aids can be quite helpful in this situation.

Decision aids are tools that help patients think about their choices. They provide patients with information about their options in a balanced way. They help people to deliberate or think about their options, pursue more information, and consider what it would be like if they decided to choose either option.

For prostate cancer screening, some very useful tools have been developed. We mentioned that the ACS developed a prostate cancer-screening decision aid after its guidelines were released, and there are other aids too. The Informed Medical Decisions Foundation has a very useful tool, and the Centers for Disease Control and Prevention has a tool as well. Thus, there are some very helpful decision aids that are available.²³⁻²⁵

Decision aids are developed to help move some of the educational burden off the clinician and help the patient to have a meaningful conversation about what their values and preferences are so that they can make a decision in collaboration with their health care provider that's best for them.

A large number of randomized trials examining patient decision aids have been completed. Many are specific to prostate cancer screening, and invariably, they show that men learn a lot about the harms and benefits of screening. The tools don't make men more anxious about cancer or making a decision, and they become more assured about the choices they make.

DR. HOFFMAN: I wanted to get everyone's thoughts on what the future of screening is. Dr. Penson,

STUDIES DISCUSSED:

European Randomized Study of Screening for Prostate Cancer (ERSPC), Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial, the Prostate Cancer Intervention versus Observation Trial (PIVOT), the Göteborg randomized population-based prostate-cancer screening trial

what do you think lies ahead for prostate cancer screening?

DR. PENSION: This concept of risk-based screening is the future of prostate cancer screening. Eventually, we are probably performing too many PSA tests. We probably don't need them on an annual basis, and we need to develop a more intelligent way to approach this topic in the men who want to undergo PSA testing. The biggest problem with screening, which we alluded to earlier, is the problem of overdiagnosis and overtreatment. We know that probably, one-third of the patients who are screened and in whom prostate cancer is detected have an overdiagnosed cancer. So, potentially, screening less often and screening only the patients who are most likely to have an increased risk for prostate cancer may reduce the overdiagnosis rate.

The other point that we really haven't talked about—and I do think this is important for the future—is the concept of divorcing screening from treatment. We discussed about the harms of screening a little, and people tend to clump the harms of screening and treatment together.

There are harms to screening, specifically the harms of a biopsy if the screening test is positive. However, the harms of treatment (if the biopsy is positive) are avoidable by increasing the use of active surveillance as a treatment strategy. In other words, instead of taking a patient who has been diagnosed with prostate cancer, particularly a low-grade prostate cancer, and immediately operating on him or performing a radiation treatment for him, we manage him with active surveillance. There may be a real role for following those patients closely, with regard to monitoring their PSA levels, repeating biopsies over time, and effectively and actively surveying them. This reduces the complications associated with aggressive intervention and potentially improves the efficacy of screening.

DR. HOFFMAN: Dr. Volk, you have actually worked on a decision aid for prostate cancer treatment. Can you discuss the challenges of convincing men to select active surveillance?

DR. VOLK: I have done some work with the Eisenberg Center and the AHRQ on a web-based decision aid for prostate cancer treatment.²⁶ We released this decision aid before the results of the Prostate Cancer Intervention Versus Observation Trial (PIVOT) were published, but we were certainly aware of the main findings from that important study.²⁷

It takes some rethinking about prostate cancer. For example, a challenging idea for patients is that there is a spectrum of risk: some cancers can have a lesser chance of progressing than others. What we've done with our decision aid tool is try to emphasize that patients should understand this spectrum of risk and talk with their healthcare provider about their

options, including the option of careful monitoring of their cancer, if the risk is really low.

Active surveillance is more than watchful waiting—it is carefully monitoring the cancer for progression. Thus, it is a challenge to communicate the idea of a spectrum of risk and how this is related to treatment or management decision making. Active surveillance

involves carefully monitoring, and if there is progression, there is still time to act.

DR. HOFFMAN: Finally, Dr. Wolf, do you have any other thoughts on the future of prostate cancer screening?

DR. WOLF: I have concerns about it, just because there is now such a divergence of national recommendations. When you have competing

Clinical Implications

- ▶ The improvement in survival could also be attributed to improved techniques for surgery and radiotherapy.
- ▶ The European Randomized Study of Screening for Prostate Cancer (ERSPC) showed a 21% relative risk reduction in prostate cancer death in the screened vs. the unscreened group at 11 years of follow-up.
- ▶ The contamination rate in the ERSPC was only 10% compared to an approximately 40% to 50% contamination rate in the US Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial.
- ▶ Although screening may reduce cancer mortality, many men who undergo screening are being diagnosed and treated for low-risk cancers that are unlikely to ever progress.
- ▶ Screening decisions are complicated and involve tradeoffs between benefits and harms, and prostate cancer screening should not occur without an informed decision-making process.
- ▶ The potential benefits of prostate cancer screening include earlier detection, which may reduce mortality due to prostate cancer. Disadvantages of screening include the significant risk of overdiagnosis and overtreatment; the risk of false-positive and false-negative results; the risks of prostate biopsy; and the significant risk of sexual dysfunction, urinary incontinence, and bowel injury that are associated with the treatment of screen-detected cancer.

recommendations, which is the situation we are now in, physicians understandably don't know what to do and they tend to continue whatever they were doing before. We don't want physicians to be conducting blanket screening without informed decision making; on the other hand, we may lose opportunities to target screening for men who might want it and benefit from it but won't be offered screening based on the USPSTF recommendation.

I think that the USPSTF made an important error in giving prostate can-

cer screening a "D" recommendation. My feeling is that the evidence would best support a "C" recommendation, meaning that men should not be routinely screened but instead should be informed of the risks and benefits and allowed to decide for themselves.

I also agree with the others in that active surveillance should be part of what is offered if a low- or moderate-grade prostate cancer is detected. That approach is used much more readily in Europe and may partly explain why the Goteborg European trial

demonstrated such a low "number needed to treat" (12 men with screen-detected prostate cancer treated to avert one cancer death over 14 years of follow-up).²¹ This number is much lower than that in the European study overall and compares favorably with other cancer screens such as mammography and even colorectal cancer screening.

DR. HOFFMAN: Thank you, everyone. I really appreciate your participation and very insightful comments.

UPDATE

The AUA recently updated their position on PSA screening.²⁰ The previous AUA recommendations were based upon expert opinion and the consensus process, while the new guidelines are evidence-based developed using a process based upon the Institute of Medicine's recommendations on guideline development. In short, the AUA guidelines now recommend informed decision making for PSA screening for men aged 55-69 years at average risk for the disease. In this setting, men should be informed of the risks and benefits of screening and should undergo screening if they feel it is in their best interests after this discussion. In men over age 70 years at average risk or those with less than a 10-year life expectancy, the guidelines recommend against routine screening, although they do acknowledge that there may be a role for informed decision making in particularly healthy men over the age of 70 years. Perhaps, the most controversial element of the new AUA guidelines is the fact that they do not recommend routine screening in men aged 40-54 years at average risk for prostate cancer. This is somewhat different from explicitly recommending against screening. The panel felt that because there was currently no evidence showing a significant benefit to screening in this age group, while there were some documented harms associated with screening, it could not endorse routine population-wide screening. However, the panel did note some evidence showing a relationship between elevated PSA levels in men in their 40s and increased risk of prostate cancer metastases and death later in life. Because of this, the panel felt that "the absence of evidence does not mean an evidence of absence" and stopped short of explicitly recommending against screening in this younger age group. It is important to remember that the AUA guidelines only apply to men at average risk and that men at an increased risk of disease (strong family history and African-American race) are encouraged to discuss screening with their provider and make an informed decision regarding testing, regardless of their age.

The American College of Physicians (ACP) also recently issued a guidance statement based on their review of screening guidelines developed by other organizations.²⁸ The ACP also supported shared decision making for men between the ages of 50 and 69 years, advising clinicians to inform these men about "the limited potential benefits and substantial harms of [PSA] screening for prostate cancer." They also recommended against PSA testing for average-risk men under the age of 50 years or over the age of 69 years and for men with a life expectancy less than 10 years. With these new publications, there is now a consensus among professional organizations against routine screening. Instead, men between the ages of 50 and 69 years should be supported in making informed decisions that reflect their preferences.

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