The Controversial Prostate Specific Antigen (PSA) Test


Oyer


Lin


Sieber

A Roundtable Discussion of its Indications and Uses

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Dr. Oyer: In the U.S., the lifetime risk of a man receiving a diagnosis of prostate cancer is 16%, or 1 in 6. The lifetime risk of dying of prostate cancer is 3.3%, or 1 in 33. Prostate cancer is the 5th leading cause of death in the U.S. at 3.3%, with heart disease #1 at 33.2%.

We have been trained that early detection and early treatment of cancer is key to decreasing cancer-related deaths. This seems to be true for some types of cancer, and perhaps even for some types of prostate cancer, but prostate cancer is a heterogenous disease, which can be aggressive and fatal or slow-growing and harmless. Currently, the most accepted method of early detection of prostate cancer is the PSA blood test, which is not cancer-specific but detects a protein released by both cancerous and noncancerous prostate cells. Of 100 men over the age of 50, 15 will have an abnormal PSA. Only 3 of those 15 with an abnormal PSA will have prostate cancer, and 12 will not, so of those who have an elevated PSA, only a small number of prostate cancer deaths will be prevented. *The New England Journal of Medicine* noted that $5.2 million would have to be spent on screening and the interventions that follow to prevent one death from prostate cancer.

In October of 2011, the U.S. Preventive Services Task Force published a scientific review of the evidence and made a clear recommendation against prostate cancer screening that has created great controversy. This influential group assigned a grade D to the evidence, noting that "there is moderate or high certainty that this service has no net benefit or that the harms outweigh the benefit."

To discuss this controversial issue we are fortunate to have 2 experts, one a urologist, and the other a family physician with a special interest in preventive care who has participated in the work of the Preventive Services Task Force.

Dr. Paul Sieber obtained his medical degree from Indiana University, and completed his residency at Hershey Medical Center of Penn State University. He has been the principle investigator in over 60 trials in prostate cancer and is the author of 25 articles on prostate cancer. He was a principle investigator for over 15 years of CaPSURE, the longest long-term database on prostate cancer outcomes. Dr. Sieber is a Diplomate of the American Board of Urology, a fellow of the American College of Surgeons, and a member of the American Urological Association and the Society for Urologic Oncology.

Dr. Kenneth Lin obtained his medical degree from NYU School of Medicine and completed a family medicine residency at Lancaster General Hospital and a fellowship in faculty development and medical editing at Georgetown University School of Medicine. He formerly served as a medical officer at the Agency for Healthcare Research and Quality, where he co-authored 2 systematic reviews of the evidence of benefits and harms of prostate cancer for the U.S. Preventive Services Task Force.

Dr. Oyer: Would you explain to us who the Task Force is, how they prepared their report, and what the scope of the report was?

Dr. Lin: The Task Force was originally established in 1984 by an Act of Congress as an independent panel of nonfederal experts to make recommendations on preventive services. It is a group of 16 primary care clinicians whose membership shifts approximately every 4 years, and consists of internists, pediatricians, family physicians, OB/GYNs, nurses, and health behavior specialists. The intent was that they would make recommendations for primary care, so though they often have specialists advising them on different issues, there are no regular members who are subspecialists. Their recommendations are widely used by primary care medical societies and now influence coverage decisions under the Affordable Care Act which covers services that the Task Force has determined to be clinically beneficial.

The Task Force looks for answers by soliciting an independent literature review which in this case was done by me and my colleagues at the Agency for Healthcare Research and Quality. The review of evidence is separate from the recommendations. Since the Task Force does not collect the evidence, the reviewers' opinions have no influence over the ultimate recommendation grade. The scope of the report was actually fairly narrow because the Task Force had made a recommendation only a few years before in 2008, and they just wanted to look at the intervening 3 years of literature, which included, of course, the 2 major trials that we will discuss later.

Dr. Oyer: The primary question asked by the Task Force was "Does PSA-based screening decrease prostate cancer specific or all-cause mortality?" Dr. Lin, what does this question mean, and is this the only question that matters to primary care physicians and their patients?

Dr. Lin: For this review, PSA-based screening meant any kind of screening for prostate cancer that involved measurement of a PSA level, but different studies used different levels at which the PSA was considered abnormal. Clinicians often also do a rectal exam, and in some screening trials they have done rectal ultrasonography. As a result, the Task Force looked at this whole body of data, even though the protocols may have varied between trials.

Prostate cancer-specific mortality is a death that was determined to have been caused by prostate cancer, and of course it is the purpose of prostate cancer screening to try to avert such deaths. But a larger and more important goal would be to determine if PSA screening could decrease total deaths, or all-cause mortality. This is difficult to show in any trial of prostate cancer screening because, as noted earlier, prostate cancer is only the 5th leading cause of death and it is often a secondary cause that is outweighed by a cardiovascular cause of death.

Other questions that were asked included: "What harms might result from the screening service itself? What diagnostic and treatment options follow from an abnormal screening test?

Dr. Oyer: Dr. Sieber, what about the scientific evidence supporting the Task Force recommendations? Would you tell us about the major clinical trials that were reviewed, and give us your opinion about the level of evidence that was used.

Dr. Sieber: The striking thing about the Task Force is its composition, as a result of which they look at things from a primary care perspective. That is their Achilles heel, since specialists are going to have a different slant. They primarily based their conclusions on 2 trials, an American trial, PLCO (The Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial), and a European study, ERSPC (The European Randomized Study of Screening for Prostate Cancer). In terms of the mortality benefit from screening, the American trial really did not show any advantage at all. The European trial, as time has gone on, has shown a marked advantage overall, but it has some difficulties in that it was conducted in a number of different European countries and there were differences between some countries that showed benefit and others that did not.

The American PLCO trial bothers me a lot because it included so many people who were screened outside of the study protocol, yet the study group is described as an unscreened population. As I interpret what I have read, about ½ of the population ultimately had a PSA test anyway, so it is not exactly an unscreened population. So probably the European trial is the one that comes closest to giving us an absolute estimate of the influence of PSA screening on mortality. The European study also looked at metastasis, which the Task Force did not place much emphasis on. They seemed to write it off as not much of an issue since their charge was to look at the effect of PSA screening on mortality, not metastases. Yet we as specialists might have a different perspective versus primary care because we are looking at a different issue when we see that patient.

In defense of the Task Force, they did not have ideal data to help them come to an easy decision. What bothers us as specialists is that the Task Force came out with a firm stance that the screening may do more harm than good, rather than saying we are not really sure about the benefit of screening so we will take a neutral stance. They made a pretty strong statement based on the available studies.

Dr. Oyer: How many men must be screened to prevent one death from prostate cancer?

Dr. Sieber: The number has fallen as we have accumulated more long-term follow-up. It was originally 1400 but is lower now that we have 11-year data.

Dr. Lin: That is correct. The European study reported the number needed as 1,055 in their March 2012 publication in NEJM. The number 800 has been offered as what one could theoretically get if there was perfect compliance in the screening and control groups.

Dr. Oyer: Do you think that it is reasonable to screen 1,100 men over an 11-year period to prevent one prostate cancer death?

Dr. Sieber: It is always easier to talk at the population level, but on an individual basis it is tough to have a discussion that says it is not worth screening Mr. Jones because it is too expensive for the whole population. Still, I recognize the restrictions of Accountable Care and cost concerns of healthcare in general, which may eventually require us to pick a number for everything we do. We may have to decide what number is reasonable to determine whether we are going to screen or not. Since the European ERSPC study is still ongoing, and since the numbers seem to change with longer follow-up, when the 15-year data becomes available the urology community may have to make a determination of an absolute number that decides at what point screening is worthwhile. And if we decide it isn't worth doing because too many people would have to be screened, will we say it is reasonable for people who are willing to pay for the test to have that option, or do we say it is unreasonable for anyone to have it? I am not sure.

Dr. Oyer: Dr. Sieber mentioned the limitations of the trials the USPSTF examined. Dr. Lin, what caused those limitations and could other types of trials overcome them? Dr. Sieber mentioned extending the followup time, and we have already seen the difference that made a when the ERSPC extended its followup from 9 years to 11 years. With prostate cancer being a slowly growing cancer, there is some expectation that longer followup will make a difference. What are your thoughts?

Dr. Lin: I agree with Dr. Sieber about the flaws in both large trials, and certainly the PLCO's greatest problem, as he noted, was that alot of opportunistic screening was initiated by the patient's physicians outside of the study. This happened in the ERSPC too, although to a smaller degree. The interpretation of the studies really depends on whom you talk to because I think a lot of people in the urology community sort of dismissed the PLCO and said it was hopelessly contaminated and we should just pay attention to the ERSPC; conversely, there might be people saying "we should only pay attention to the PLCO because it is the U.S. study." I think both studies have things to tell us, and the truth is somewhere in between.

It's important to emphasize that in the PLCO study, the "contamination" caused by opportunistic screening in the control group would have narrowed any apparent differences between the controls and the study group, and would have minimized any apparent benefit in the study group. Also, "contamination" would not cause what the PLCO continues to show, namely that there seems to be more harm from the screening than good. Furthermore, you would think that even if "contamination" made the benefit seem smaller than it really is, if you followed the groups long enough any real benefit would show up. But that hasn't happened.

With the ERSPC, there are, as Dr. Sieber said, concerns about the variation among individual countries in the trial. A few had very impressive results while several of the others didn't show a statistically significant benefit. The variation is problematic because, at least in the Goteborg Sweden portion of the ERSPC, which was published separately because its results were so impressive, men in the group assigned to screening were—for obscure reasons—more likely to get their treatment from university centers. That doesn't necessarily mean they got better care, but it is a little bit problematic.

Since neither of the trials was perfect, the Task Force took the best case scenario for prostate cancer in terms of reducing mortality, and decided that they would accept the ERSPC as the best possible case and then weigh it against the harms from treatments. They felt that even if you assume that the PLCO—which showed no benefit—was completely wrong, and only

the ERSPC was correct, and even if the benefits may even be a little more than were apparent, they still felt that on a population level, the benefits were not outweighed by the harms of treatment.

Dr. Oyer: Were there any other differences in the Goteborg subset, other than the site of treatment? The screening interval was 2 years.

Dr. Lin: The screening intervals in the ERSPC varied between 2 and 7 years, and the most common was 4 years.

The PLCO screened annually, which is interesting because one possibility for its finding of increased prostate cancer mortality in the screened patients was perhaps over-diagnosis; the more often you screen, the more often you are going to diagnose prostate cancer that might not be clinically significant, yet you can cause harm by all the follow-up testing and treatment. So some people have said that maybe the 4-year screening interval in most of the ERSPC patients is a better plan. The Goteborg study had a 2-year screening interval, which was shorter than the majority of the ERSPC sites, yet showed screening to be beneficial. That would seem to contradict the hypothesis that screening less often would lower harms while maintaining the benefits.

Dr. Oyer: Dr. Sieber, a paper in the Journal of Urology in August indicated that the routine use of PSA screening resulted in earlier and more sensitive detection of prostate cancer. What does this widely cited study tell us about survival, and are there other new studies we should be considering?

Dr. Sieber: From a urology perspective, the bulk of our patients who come through the door now have early stage disease. In contrast, when I finished my residency in 1988, probably two-thirds came in with what we thought was either stage C or D disease at that time, or advanced disease that was probably incurable. So the PSA era has dramatically changed the profile of patients we see initially. The question is how to treat these people, because there is a fair amount of overtreatment and patients treated unnecessarily skew our results towards not showing benefit because they inevitably die from their disease anyway. So I think that in urology, we have not so much the problem of making a diagnosis, as a concern about overtreatment. To try to sort that out, we don't get help from the U.S. Preventive Task Force, because they aren't looking at the changes occurring in patient profiles in the first place.

I think it is also intriguing that the death rate from prostate cancer in America has fallen since about 2007, and the same can be said for the Netherlands, Austria, Germany, and other countries that screen aggressively. If you look at the UK, where they do not do routine screening, you are not seeing that decline, so we have a gut feeling that explains why are we seeing this decline in prostate cancer mortality here and we are not seeing it in the countries that don't screen.

It is also intriguing that only 6 or 8 years ago the question was raised whether treating prostate cancer mattered at all. At least we now have a reasonable level of evidence that there is a survival advantage in patients who are actually treated. So I think there are legitimate concerns about not screening at all because we are looking for the optimal patients who will benefit from being treated and if we don't look for them we won't find them.

Dr. Oyer: You talked about looking at population profiles in the PSA era versus prior to the PSA era; that is a valid point. Is there any other evidence in the scientific literature that we should be evaluating? Are there other types of trials that look at the impact of screening on survival from prostate cancer?

Dr. Sieber: I don't think we have such studies. All I can basically state is that the disease presentation is dramatically different from what it was in the past, and there are a number of places in the world where we have seen a decline in prostate cancer deaths, which we can't fully explain. I don't think there are any other larger screening studies.

Dr. Lin: A recent publication in the New England Journal of Medicine called "Quality of Life Effects of Prostate-Specific Antigen Screening" argued that the Task Force recommendations were comparing apples to oranges, in that they were comparing deaths to side effects like erectile dysfunction, incontinence, quality of life, but there is no common metric to make that comparison. This paper took the ERSPC data and attempted to assign quality-adjusted life years to both outcomes to help men figure out if they really wanted to be screened or not, based on how much they valued function versus life.

I think it is an admirable attempt, but the problem is: #1, they based everything on the ERSPC study and they ignored the PLCO. That is a problem if you feel the true result of prostate screening is somewhere in between.

And #2, it is very difficult for a man who doesn't have prostate cancer to understand what it would feel like to be diagnosed with prostate cancer as compared to a hypothetical question. So the estimates of quality of life that they got in this paper may not truly represent what a man might feel when actually diagnosed. I don't know if there is a way around that, and this may be the best attempt. The conclusion that I took away from this paper was that certainly for some men, and probably for many men, the side effects of prostate cancer treatment might not be worth any life gained from prostate cancer screening. Is there enough data to make a firm recommendation? Probably not from this study alone.

Dr. Oyer: Now I would like to make time for the point/counterpoint part of this discussion. Dr. Lin you mentioned earlier that you pretty much agreed with Dr. Sieber about the important issues of contamination and the interpretation of the PLCO. Are there differences that you want to emphasize?

Dr. Lin: The observation that the practice of urologists has changed is obviously not something we can experience as primary care physicians, but their experience of seeing more men with treatable cancers can be misleading in that overall we are diagnosing more men with prostate cancer than we did before. Many of these are men who never would have found out they had prostate cancer. It is estimated that up to 50% of men in the ERSPC study were over-diagnosed in that their prostate cancer probably would not have presented in their lifetime. So it dilutes the groups because you are adding a lot of men who thought they were healthy, but as a result of the screening they have been diagnosed with prostate cancer. We treat the prostate cancer and feel good about it because these men do well, but maybe they would have done well anyway. So, it is an issue of epidemiology versus the gut feeling of the treating physician, and it is very difficult to adjust for that. I don't disagree that prostate cancer treatment has likely improved the prognosis, but I don't know how much of the improved survival really can be attributed to screening rather than to better treatment over the last 20 years or so.

Dr. Sieber: If the explanation is better treatment in general, we would have expected survival of all cancer patients to have improved dramatically over the last 20 years, because they all have the same improved care of their medical condition. So if we don't attribute the improved survival in prostate cancer to screening, we would have to single out prostate cancer and say that improvement in medical care has uniquely extended the quality of life more for prostate than for any other cancer.

Dr. Lin: There have been similar kinds of critiques with breast cancer, as to how much of it was due to screening. With thyroid cancer, we pretty much know that screening doesn't work, but nonetheless the number of thyroid cancers has skyrocketed. If you were a thyroid specialist, I guess you would see lots of people with early disease detected by screening, but we know that the death rate hasn't changed at all. So no, when we say that screening may not be helpful I don't think prostate cancer is alone. It is just the most prominent one, and that is why the issue comes up, but I think it does apply to other cancers as well.

Dr. Oyer: In 1980, I think the overall 5-year survival for cancer was 46%. Now, it is around 67%. You are talking about the same sort of spread in prostate cancer over time, so it has been experienced in other cancers as well. There is an enormous contribution by prostate cancer to the overall survival number because it is so common, but we can certainly show that in subsets like colon cancer, colonoscopy has affected survival.

The U.S. Preventive Services Task Force weighted the negative consequences of PSA screening heavily, including over-diagnosis, overtreatment, and treatment complications, which we have touched on. Still, there has been a 44% reduction in prostate cancer mortality between 1993 and 2009, a period of time when PSA testing was the only major change in prostate cancer care. So, given the current state of knowledge, Dr. Sieber, and understanding the limits inherent in a PSA test, what are the advantages of PSA screening?

Dr. Sieber: We've covered them. Basically, the advantage is earlier detection at an earlier stage, and the advantage of operating at an early stage is true for all cancers. Though we stated that the prostate cancer rate could have fallen just from improved medical care, we could also argue just the opposite, that half of the improvement in death rate is attributable to earlier detection. So the issue that comes up is, what price do we pay for improved outcomes. The interesting thing with the Task Force report is that although they talk about the harms of treatment, no one ever seems to talk about how to measure the detriment to quality of life of a painful, difficult prostate cancer death, because that is not really in the formula.

There is also very little discussion about the cost of death from prostate cancer because it is relatively costly. It is probably the most common cause of bone metastasis of all the cancers, and bone metastases are exceedingly costly in terms of treatments, hospitalizations, and detriment to quality of life.

Dr. Oyer: You have added something that should be called out as a headline here - morbidity due to prostate cancer, which is not addressed in the screening studies which are all about mortality. Dr. Lin, if we do not have a replacement test for the PSA, can we quantify the dangers of not doing prostate cancer screening? Dr. Sieber has already talked to us about morbidity rather than mortality.

Dr. Lin: I agree with Dr. Sieber that morbidity is important but it is very, very hard to measure in an unbiased way in a screening trial. We actually looked for that information in 2008; we discussed a center in the ERSPC that tried to measure cancer metastases as an outcome and, in fact, showed that men in the control group were more likely to have metastatic prostate cancer than men in the screening group. The problem is that it is hard to avoid bias when you are measuring that, because although for some men metastasis would present as bone pain, and then you would do appropriate diagnostic studies to confirm the diagnosis, for others the reason they had a metastasis discovered was because their physician knew they had prostate cancer and then ordered a bone scan and found it, though the patient didn't have any symptoms. That would be more likely to occur in the screening group because they are the ones who are getting PSA tests, whereas in the control group you could have men walking around for some time who wouldn't know that they had metastatic prostate cancer or were dismissing their back pain as just getting old or something like that. So, I agree that if we could measure the morbidity it would be an important outcome, but it is very challenging to do that and be assured that we are not overweighting it on one side or the other.

Dr. Oyer: Dr. Sieber, what are the risks of overtreatment of prostate cancer? Can you give us a little bit of data on the side effects, and possibly also the psychological impact?

Dr. Sieber: Whatever the treatment modalities, whether surgery or radiation, they have side effects, and they are particularly troublesome in the urinary tract, whether it is sexual dysfunction or urinary dysfunction. Then, when you add in radiation treatments, you have a lot of rectal dysfunction. In quality of life surveys there are well established measurements of the detriment in function that people suffer when you treat them for their prostate cancer; it is not a small issue. The tougher thing to measure is the harm of hormonal therapy, which—in later disease—is the result of not being aggressive in the early stage of disease. That is a harder side effect to measure because it adds psychological issues that are even more challenging to surgery, and the data are certainly more difficult to acquire.

Dr. Oyer: Can you give us a picture of the hormonal side effects?

Dr. Sieber: Weight gain, depression, hot flashes, long-term potential worsening of cardiovascular risk factors, whether it is hypertension, diabetes, or hypercholesterolemia. Osteoporosis is probably the easiest thing to measure as an absolute number.

Dr. Oyer: Do these affect the majority of patients on hormonal therapy?

Dr. Sieber: For osteoporosis, yes, but the clinically significant cardiovascular effects are difficult to quantify. There is a warning about that on all of our androgen deprivation products from the FDA, yet the clinical trial data—particularly from the radiation therapy sector—suggests that the cardiovascular risks are no greater among people treated with hormonal therapy and radiation than among those who got radiation therapy alone.

I can tell you the average weight gain is about 10 to 15 pounds. The psychological effects such as depression are difficult to quantify.

Dr. Oyer: Dr. Lin, are there subsets of men who more clearly benefit from PSA screening? Would you also specifically comment on younger men, how does life expectancy factor into the decision to screen? Finally, how reliable are the currently available systems to distinguish a life-threatening prostate cancer from one that is unlikely to cause morbidity or mortality?

Dr. Lin: The answer to the first question is complicated. There probably are subsets that would benefit from PSA screening but we don't know which they are. To use an analogy from primary care, if we give

antibiotics to all people with sinus infections, there probably are some people who benefit, but we just don't know who they are, so we give antibiotics to either everybody or nobody. Similarly, you would want to screen only those you think would benefit from PSA screening. From what we know about the biology of prostate cancer, most groups use a criterion of at least a 10-year life expectancy. The problem is that I have yet to find a decision tool that allows me to predict with 90% certainty whether someone is going to live 10 years. These tools work very well in large populations, but for an individual they are almost useless. Even if I could predict life expectancy, I think it is really hard for physicians to tell patients "you are only going to live 9 years, so it is not worth doing this for you." So that leads to a lot of the aggressive screening we see, even in men who are 75, 80, 85 years old, who are very unlikely to benefit.

Young men have longer life expectancies, and theoretically would be more likely to benefit, but I don't think we know enough about the differences between the tumors that young men get versus the tumors that older men get. There was an intriguing finding in the ERSPC that men between 50 and 54 actually did not experience a decrease in mortality from prostate screening. Though that may have been an artifact of statistical power related to how many men were in that group, it does suggest that it may not be correct to automatically think that the younger the men are, the more likely they are to benefit. We often tell African-American men and men with a family history, "you are at high risk and you should get screened." The problem is that although they are indeed at higher risk, that we are not certain that we can benefit them more by screening, that even though it sounds intuitive to say "well they are at higher risk, they should be targeted for screening, none of the trials have shown more benefit from screening in those patients than in the general population.

As to your second question, I think the currently available systems to distinguish life-threatening prostate cancer from indolent prostate cancers are still very crude. There is active surveillance which is based on the theory that if you have a low PSA and your tumor is not that aggressive on biopsy, you can just sort of follow it with repeated testing. Most of those men do very well, but those criteria are very restrictive. There are a lot of men who don't meet the criteria for active surveillance but who nonetheless will have prostate cancer that will be very indolent. Since we just can't figure out who those men are, they end up being treated as aggressively as men who need to be treated aggressively.

Dr. Oyer: Dr. Sieber, any counterpoint to Dr. Lin's comments?

Dr. Sieber: There are actually a lot of people who are candidates for active surveillance in our practice —somewhere in the neighborhood of about 35% to 40% of those with prostate cancer. Our dilemma is , as Ken suggested, that it is hard to know whether they are going to progress. I tell people who choose that route that we are going to probably find—either with repeat biopsies or time—that probably at least a third of them will progress to need treatment. I think the number of people like this that we are seeing here is increasing, but I am not sure that we are necessarily representative of the whole United States. Certainly in a community setting we have a lot of people that are in that active surveillance program and are not progressing.

I think our numbers are changing and it is a work in progress. When you look at some of the original work that was done, particularly from the group up in Toronto, we had talked about a 70% progression rate. Now we are down to saying that about a third of the people who are selected for surveillance will ultimately progress and require treatment. I wish we had better tools but I wouldn't say I am holding my breath for anything better than the relatively crude tools we have right now.

When it comes to the issue of screening ordinary patients, our dilemma without screening is how to detect prostate cancer if there are no symptoms, because if someone comes in with symptoms, they basically have incurable disease. So it is a difficult discussion to have with the patient when we say we are not going to screen. If the argument is that no one in between has ever benefitted, that is kind of a tough pill to swallow. So our dilemma is how not to over-screen, but not to do no screening at all, because waiting until they have symptoms has historically led to definitely bad outcomes.

Dr. Lin: I think that the answer to the dilemma is that we just need to develop a better test.

Dr. Oyer: Okay, I agree. Alright, so if we accept the following 5 points:

1. The PSA test is not cancer-specific.
2. Prostate cancers aggressiveness varies widely.
3. The U.S. PSTF analysis of the available data is accurate.
4. There are issues of clinical relevance for which there are no data and you gentleman have raised three

morbidities, especially bone metastases. Risk prediction models are poor for prostate cancer itself, and life expectancy is difficult to predict.
5. Men are still dying of prostate cancer despite progress to date.

So, what should we be doing today? The American Cancer Society has recommended that physicians provide patients with a brief written handout on prostate cancer that summarizes the Task Force recommendations, including potential benefits and harms of PSA screening. What advice are you giving your patients and your physician colleagues, and are you providing these written materials for your patients?

Dr. Lin: Yes, I usually provide them with a handout. There are various websites that have handouts where they show the average benefits and risks for, say, 1,000 men who are screened. (Here's a good example created by family physicians at Virginia Commonwealth University: http://www.familymedicine.vcu.edu/research/misc/psa/index.html) But I also say that I generally recommend against screening, and if the patient wants to know more about that, I go into the history of where the pendulum has swung from screening everybody to maybe screening fewer people to some groups, like the Task Force, recommending against screening.

From a primary care perspective, the time that I spend on something that is either not effective or very minimally effective versus something that is very important is an opportunity cost. A few years ago a study asked physicians how much time they spent on various preventive services, and for men over 50 physicians were spending up to 5 minutes having a prostate cancer discussion, less than a minute on diet, and 30 seconds on smoking cessation. One of the consideration of the Task Force, although it is not explicit in their report, is that in the limited 10 to 15-minute visit with primary care physicians, the prostate cancer screening discussion was taking time away from things that were much more likely to harm health. Cardiovascular disease causes 10 times as much mortality as prostate cancer does, yet we are spending almost the reverse amount of time on things that could reduce cardiovascular disease than we spend talking about prostate cancer. So our approach should be to spend less time on prostate cancer. If a man understands the risks and benefits and still wants to get tested, I will do the test, but my practice has changed considerably over the last few years as the evidence has come out. Now, I no longer portray it as "here is the information, you decide." Instead, I will actively say that my recommendation is not to do this, unless there are extenuating circumstances that I don't know about.

Dr. Oyer: Dr. Sieber, is it possible to maximize the benefits of PSA testing and minimize its harm? We heard that there may be significant benefit to screening men between the ages of 45 to 50. In a way that is not surprising because the CDC tells us that the risk of prostate cancer in somebody under the age of 45 is 1 in 2500, and by age 50, it is up to about 1 in 450. That is an enormous change over a 5-year period. Additionally, we are used to the idea that the most aggressive prostate cancers may be the ones that occur in younger men, and that is something that we see with other types of cancers as well.

Some have proposed stopping PSA screening in men who have a PSA of less than or equal to 1. Others have indicated that PSA screening should not be done in men 71 years of age or older, or in anyone with a life expectancy of less than 10 years. So are there some parameters that could recommend PSA screening for some men but save others from screening? What are your current practices, what are you telling your patients, and are you using some of the same education materials?

Dr. Sieber: Not being in primary care, I don't have the same kind of question raised, because everyone who comes to me has already seen their primary care physician and probably had their PSA done, and they are in my office. So I really don't have any means of intervening before the PSA is done, because they either have an abnormal exam or abnormal PSA or I examine the patient with voiding symptoms, and there is something abnormal before I see the patient.

I think you are referring to the data from Sweden, and that Sloan-Kettering has done a lot of work with, that the PSA between 45 and 50 is particularly predictive of risks logarithmically over the next 30 years of your life. I am aggressively changing my practice so that if I have a younger man who says I had a screening PSA at age 50 and my PSA is 0.3, I will tell them that yearly testing is overkill, and the probability of them getting cancer is minute compared to someone whose PSA is 1.8. I think the problem is that as I see it, primary care doesn't understand the data or is very unaware of those data. I think that is something that is incredibly robust, and I think that is the thing I knock the Task Force report about—that people suddenly turn a

blind eye to PSA. So that is what I am incorporating in my patients who are at risk. I think the other dilemma is, when do we stop screening people? At age 70? The average age of death for prostate cancer is age 80, so although it is great to stop screening at age 71, with the improvement in lifespan, what are we going to do with these older guys?

Dr. Oyer: Could you expand on that? You are right, it is that decade from 70 to 80 where most of the prostate cancer deaths happen, but it is felt that by then those men had prostate cancer for more than a decade, maybe 2 decades. So, is screening past 70 actually going to pick that up? Those men already have prostate cancer, they have elevated PSAs, they have had treatment, and they have bone metastases. As you know, people with bone metastases live years, so they don't just get prostate cancer at 75 and die at 80. Just help us with a little perspective on that.

Dr. Sieber: My concern is the man at age 70 who says his PSA was 2.1 when he was 50, and he fell through the cracks. When you start to see him later, his PSA has actually been telling you for a long time he has a problem. You could identify many of these people before they hit 70, so I think the notion of saying we are going to stop screening at 70 is like saying we will stop looking for all disease at age 70 and wait until they just come in the door with a back problem. So although I think you are right, a guy who has had a low PSA probably doesn't need any more screening at age 70, a significant percentage of the high risk patients can be identified long before they get to there. I think the Task Force has to be so incredibly careful when they make broad statements, because people get the impression that everybody can be ignored starting at age 70. But while I agree that the vast majority of people can be ignored, the bad players shouldn't be, yet they may be, because of this age restriction that basically says no one is going to have problems after age 70.

Dr. Oyer: Dr. Lin, it is very clear in screening for breast cancer and colon cancer, that we have a risk-based strategy that calculates risk and tailors screening strategies based upon that risk. You have spoken to the fact that it is difficult to construct that risk for prostate cancer, so I want to ask you: within our current scope of knowledge, is it possible to identify men who benefit from PSA screening or at least men in whom we should not yet abandon PSA screening?

Dr. Lin: The breast cancer risk assessment tool isn't even that good, but it is much better than what we have in prostate cancer. At least, you can get somebody a ballpark percentage of what their risk is. Someone asked me, if you had to keep PSA, what would you do? I think this probably will never be implemented in practice, but I said I would set a much higher cutoff level than we have now, because prostate cancer prevention trials show that you can have prostate cancer if your PSA is 1, you can have no prostate cancer if your PSA is 4, it varies, and it is, at best, a weak predictor of whether you have prostate cancer. A PSA cutoff level of 10 was actually the level in the most recent PIVOT study of radical prostatectomy versus watchful waiting in the PSA era (Wilt TJ et al., NEJM 2012;367;203-13). It showed that those men seemed to benefit from treatment, whereas for the ones with PSA levels lower than 10, it was inconclusive. That approach would greatly reduce the harms of over-treatment. Of course it would cause you to miss more men, and you will always have this tradeoff whenever you talk about a screening test where you have a level that you have to set, but it might be more acceptable when that would guarantee that whoever has either a positive PSA at that level would be somebody you would need to address versus somebody with a PSA of 3.5 that is creeping up, and you are thinking about the PSA velocity. Actually, I don't think all those steps really have panned out to be very accurate in showing who is at greater risk.

Dr. Oyer: Just to clarify, and I am not at all suggesting that I disagree, but you are saying that we don't have similar predictive instruments for prostate cancer that we have for breast and colon where there are a lot of clinical radiographic criteria, breast density, age, family history, etc., colon polyps, all that. Are you dismissing the value of a PSA level between age 45 and 50 as a potential instrument? I am not even sure that is an official part of the Task Force recommendations, but it is just a question you can answer from where you sit.

Dr. Lin: I think there may be some value in that testing, but we are building this scaffolding on top of a test that inherently is bad, and you do all these modifications that may make the test less bad, but it still doesn't make it better from my perspective. I have seen the data that if you are age 70, your PSA is below a certain value, you never get prostate cancer, they have followed men for enough years to show that, but that is only a small percentage of men. Most men will have values that are

a tiny bit higher and then you can't tell them that they need to stop and so you continue to test but then trying to reduce over-treatment is really not adequate in the long run, there are still going to be a lot of men who will get over-treated, no matter how you manipulate PSA to try and reduce its adverse effects.

Dr. Sieber: Again, it goes to how we look at the same information but we interpret it differently. So when I look at a prostate cancer prevention trial and the comment is "yes you can see prostate cancer with a PSA of 1, but at a PSA of 10 you will certainly see a significantly greater number of men with high grade tumors, the argument somewhat hinges on whether we are going to treat every single man with prostate cancer, which, unfortunately, some urologists do.

An early stage prostate cancer with a Gleason sum 6 score is not really one that deserves treatment. Our dilemma is the guy whose PSA we have waited to test until it is actually a 10 or certainly when it is 20, and we know that in general, our results with treatment at that point are not so hot. Our recurrence rates are exceptionally high, so we thought the cat was out of the bag when we waited that long, and we are basing our impression not just on the PSA alone but on a constellation of other findings besides just the PSA, and particularly, on the Gleason score as a predictor of progression.

Dr. Oyer: Ken, last comment for you. What do you think is next for us in the prostate cancer arena? What are we going to be doing to reduce the risk of dying of prostate cancer?

Dr. Lin: I know we have been saying this probably for the last 10 to 15 years, but I hope that, at a minimum, even if people don't follow the Task Force recommendations and completely discontinue prostate screening, we will have improved the quality of discussions the patients are supposed to be having with their physicians about what their risk is, what outcomes they value, and what they are willing to endure to make sure that they don't develop late stage prostate cancer. The most important take home point is that better information is there from the PLCO and ERSPC trials; it is not perfect, but at least we now have some idea of what the potential benefits are of screening, whereas before we were just guessing.

Dr. Sieber: I think, in the short term, the best instrument we are going to have will come from the genomic predictor, from men who are diagnosed to look at their cancer and give us more information besides the current algorithm. I think a better blood test is not forthcoming in the next decade, so I think the likelihood of seeing any significant change is highly unlikely, and I think that unfortunately, we are going to be stuck with a lot of men diagnosed. We need to try to pinpoint who to treat and who not to treat, and that is the more likely scenario versus saying we will stop looking because I think if we stop looking, we will go back to only finding late disease when our ability to help is limited.

Dr. Oyer: I think those are both very important interim strategies when we don't have the data that we all want. Thank you both for taking the time to prepare and talk with us.

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