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**SCOTT EGGENER:** Hello, thanks for joining and your interest in this topic. I'm Scott Eggener from the University of Chicago Medicine. I'm an associate professor of surgery. My special expertise is in urologic oncology and also in prostate cancer.

What I wanted to talk to you about today are really three main topics, screening for prostate cancer and then the most commonly used item to screen for prostate cancers, PSA-- and what I title the good, the bad, and the ugly of PSA screening for prostate cancer-- and then also talk to you about over detection of prostate cancer. We certainly have a large volume of men diagnosed with prostate cancer. And there are strategies to identify the men with certain cancers that we can diagnose and cure, while minimizing the impact that we have on men quote unquote "never needed to know" about their prostate cancer.

So first let's dive into PSA, the good, the bad, and the ugly. So first the good, undeniably based on the data that's available, smart rational PSA screening can save lives. And fewer men are dying of prostate cancer because of PSA screening. And we have randomized studies that show that to be true.

Now the bad is that PSA can also diagnosed men with cancers that were never destined to cause them any problems. And we need to be smarter about the ways we screen men and whether we treatment for their cancer or not. And then the ugly of PSA screening is what the US Preventive Services Task Force recently did in 2012-- that in my opinion was short sighted and not good for public health-- was discouraging all men from undergoing a PSA test.

And admittedly, the way PSA was being used in the United States wasn't very sensible. And we need to rethink the way that we use PSA and which man should get a PSA, what we do with that information. And hopefully, I'll give you some practical tips on how to use a PSA sensibly in your practice.

So first the good news, PSA can save lives. If you look here at this figure, starting in the early 1990s, the death rate from prostate cancer in the United States has gone down incrementally each and every year for about 20 years straight. And on an age adjusted level 40% fewer men to 50% fewer men are dying of prostate cancer in the United States.

There are all sorts of models and reasons why. But every article that has looked at it suggests that the single biggest reason is PSA screening. So it's a big public health success story. And fewer men are presenting or being diagnosed with metastatic disease.

Here's some ancillary evidence that also suggests it to be true. This is data from the World Health Organization from a whole bunch of countries on their death rates from prostate cancer. And quite simply, here's a list of countries with decreasing rates of prostate cancer death. And these are countries that adopted PSA screening in the late '80s, early 1990s. And here are a whole bunch of countries were PSA screening was not used on a regular basis, hence rates of death are increasing.

Now this was a paper that came out just this year, which is really interesting. And it's looking at the median survival rate for men diagnosed with metastatic prostate cancer. Because one of the hypotheses why mortality rates are going down is that we have newer medications that extend life. And that's the reason we're pushing the curve to the right and men are living longer.

However, what this data suggests is even with all these new medications that are available the median survival for men with metastatic prostate cancer has not changed much over the past 20 years. Therefore, leading even more evidence to suggest that PSA screening is the single biggest reason why we've seen such a dramatic decrease in the rates of death from prostate cancer.

So let's dive into the data. This really is the backbone of what PSA can do. And the good news is in Europe and in the United States there were randomized trials for PSA screening. We're going to get into all the specifics of these three trials in more detail. This is basically a summary slide of a US study, a big European study, and then a Swedish study, which was a subset of the European study.

So in the United States, there was something called the PLCO study. And it was a very ambitious trial, taking men aged 55 to 74. 76,000 men, and they were randomized, where half the men were intended to get a PSA every year for six years coupled with a digital rectal examination. And the control arm was not supposed to get a PSA test.

Now, before any data from this trial came out, we knew it was a fatally flawed study. And you can look back in the literature, and there were people writing about all the time. Unfortunately, in the United States, even if you were assigned to the arm where you shouldn't get a PSA test, half of them ended up getting a PSA test. So that completely counteracts the intent of the study.

Additionally, about half of the men, 45% of the men, had a PSA test before even being randomized in the trial, suggesting that men with a high PSA with meaningful cancers were excluded from the study because they had already been pre-screened. So nevertheless, with these fatal flaws, it basically studied intensive screening versus moderate screening, because the control arm had about 50% of their grouping screened. Not surprisingly, incidence rates of prostate cancer were higher in the intervention arm. And not surprisingly, there was no difference in mortality rate largely, because of the flaws that I mentioned too earlier.

Now, interestingly-- and this is a subset analysis, hypothesis generating, and is not something to hang your hat on, but if you took men in the study that were the healthiest men by really few comorbidities, measured by zero or one comorbidities, and you looked at them, PSA screening did save lives. And the acronyms up there, NNS is number needed to screen at 10 years to save a life. So that was 736 men. And then the number of men that needed to be treated at 10 years to save a life was only five. So that's very encouraging data, but not the primary objective of the study.

The European study was done much better for a variety of reasons. There were 182,000 men, a little bit looser screening criteria. They were screened primarily every four years. But they had good follow up that went from 11 to 13 years.

And the bottom line is, as you can see from the curves there, if you've got a PSA test, you had a lower likelihood of prostate cancer. And the initial analysis suggested a 21% decreased risk of death. There have been some other future analyses of that with longer follow up and looking at the men who actually showed up. And it goes up to about 30% to 35% decreased risk of dying of death a prostate cancer.

And the most likely reason it showed in the European study and not the US study is that in Europe, if you were randomized to the arm where you were asked not to get a PSA test, the patients and their physicians actually didn't order a PSA test. So the good news is it save lives. The daunting element of it is you need to screen about 1,000 men to have one life saved. And the men that were diagnosed with prostate cancer you had to treat 37 of them to save one life.

Now that's at 10 years. We do know that prostate cancer is such a slow growing disease that with longer follow up those numbers will come down with the number needed to screen and treat. And you can see from the curves there, the impact of a PSA test was not seen until at least seven, eight years after randomization. Emphasis that you should only consider getting a PSA test for well informed men, if they have a life expectancy of at least eight to 10 years.

But that primary objective was death from prostate cancer. There's more to life than death in that it also dramatically decreased metastases. Metastasis cause pain. They cause limitations. They lead to hormone therapy, which is basically medical castration of a male. So you can see widely divergent curves when it comes to preventing metastasis. And not surprisingly, that divergence took place much earlier at about five years.

So here are some other analysis if you want to go through the slides. The Rotterdam section was one of the larger sections. And when you corrected for contamination-- contamination where basically people in the control arm that weren't supposed to get a PSA test, but they did-- and you controlled for people that actually showed up for their screening, the rate of death from prostate cancer dropped 50% if you've got a PSA test-- very dramatic.

And then probably the best elements of the European study was the Swedes did it best. And that was one country that contributed to the European study. And let me just spend some time going over this data.

It was 20,000 Swedish men that were randomized to getting a PSA test every two years. That's a little bit more rigorous screening than the Europeans elsewhere that we're getting about every four. And the control arm was not getting a PSA test.

They had a lower PSA threshold for recommending a biopsy. And their follow-up was longer. Their median follow-up was 14 years.

So for the reasons I mentioned there this is a higher quality study. And what did it show? This showed a 44% lower risk of death from prostate cancer if you were in the arm that was recommended to get a PSA test.

And again, those curves diverge about seven, eight years. And as you get to 10, 12, 14 years, those curves diverge even more, suggesting the highly powerful potential for PSA to save lives. Now, the number needed to screen to save a life was 293, much better than our previous trials. And the number of men that you needed to treat to save a life was 12. So now we're talking numbers that are a lot more palatable when you think about screening on a population level.

My favorite part of this study, though, is not every man diagnosed with prostate cancer needed treatment right away with surgery or radiation therapy. The philosophy in Sweden-- and the results support this-- is that screen intelligently, diagnosed men with prostate cancer. But at the time of diagnosis, if a man has a cancer that is unlikely to cause him problems in the future, you can keep a close eye on it with something called active surveillance. But if the cancer had elements that look dangerous, surgery or radiation are highly effective forms of treatment.

So comparing PSA screening a lot of other things that we do in medicine, how does it benchmark? And here's a list of other things that are commonly accepted, like mammography, colorectal cancer screening with colonoscopy, screening for high blood pressure or high cholesterol. And if you look at the number needed to screen and the number needed to diagnose or number needed to treat, PSA is on par with virtually all of these other screening strategies.

So the much maligned PSA test, in my mind based on the data, can absolutely save lives. It just needs to be used intelligently. And we have not been doing a great job of it in the United States.

Now, many of you are probably familiar that the US Preventive Services Task Force came out in 2012 with a blanket recommendation discouraging men from getting a PSA test. This was a well intentioned group. I think they had-- I know they had their biases going in, and they had alluded to that before hand. But they were very concerned about the rate of over detection, meaning men being diagnosed with prostate cancer, who would have lived a long, full life, died of something else and never needed to know about their prostate cancer. And that's certainly a real issue.

So they recommended against PSA screening. The disturbing part is there were 16 members of this government panel. You can see the composition of them there, health policy, internists, pediatricians, geriatricians, OB/GYN. It makes no sense to me. And I've yet to hear a good explanation why that panel didn't have anybody that actually sees patients with prostate cancer, like urologists, medical oncologists, or radiation oncologists.

So the ugly, and I admit this and we need to shine a light on ourselves as primary care physicians and even urologists on how we use the PSA test. When it first came out in the late '80s and early '90s, it made a lot of intuitive sense that every man over the age of 50 should get a PSA test every year. If you diagnose a prostate cancer, you should treat the cancer as soon as you can.

That does not necessarily have to be the case nowadays. I won't get into all of those details in this talk. We'll save them for a talk in the future.

This is a paper that we did looking at how PSA is used in the United States. And if you look at that figure there, the x-axis is the age of men. And the y-axis is the chance of them having a PSA screening test in the year prior.

And what you can see, somewhat disturbingly, is that as men got older, they were more likely to get a PSA test. And we're looking a guys in their '70s and '80s that have dramatically higher rates of PSA screening compared to men in their '50s and early '60s. Now, remember based on the data that I showed you, that PSA is a sensible test for men that have a life expectancy of at least eight to 10 years.

So as a man gets older and sicker, you'd think the rates of PSA screening should go down. And that's the exact opposite of what we saw. So we need to do a better job of this. And I'd like to see the curve higher for younger men and then fade off as men get older.

Now, admittedly some of the problem is men in their '50s are also men that are feeling well, no symptoms from anything. They don't show up to their doctor. And that certainly contributes to why they might not be getting PSA tests.

This is a figure that simply shows you for the men that are the sickest men and the oldest men in the study, anywhere from 25% to 45% of those men are still getting tested for PSA. That is not appropriate. And unfortunately, even though it's a simple blood test, the blood test can lead to biopsies. Biopsies can lead to treatments. Both biopsies and treatments have risks of side effects.

I'm going to skip over this or just spend a very little time on it. This Preventive Services Task Force back in 2008 discouraged men from undergoing screening if there were over the age of 75. What we were interested in and published in a journal is what happened afterwards. Did practitioners change the way that they took care of these men? And the short answer is no.

So even though this generated a lot of press and was printed widely, it didn't really change how doctors practice. And the reason I mention this is this 2012 recommendation of discouraging prostate cancer. We need to see how that plays out over subsequent years.

So the guidelines released by the American Urological Association were recently revised. And I'm very proud of the organization, because they are data based and sensible, as opposed to what there used to be, which was just sort of blanket every year at a certain age, every man with a reasonable life expectancy should be screen. So what the data suggests is less than age 40, no one should be routinely screened. Aged 40 to 54, no routine screening if a man is an average risk. But from age 55 to 69, a man should at least be informed of the pros and cons of PSA screening. And as long as he has a reasonable life expectancy, measured by eight to 10 years, and understands the pros and cons, should be offered screening.

The routine interval used to be annually. Now based on data, it's sensible to do it every other year. Now, certainly if a PSA is slightly higher than it should be, but doesn't want a biopsy, maybe you should monitor annually. If a man has a family history or is in a high risk group like African Americans, starting to screen earlier or annually makes more sense. But age greater than 70 or estimated life expectancy less than 10 years, no routine screening is recommended.

So hopefully, I've explained to you with the data that you agree with that prostate cancer screening can absolutely positively save lives. But the big elephant in the room is we certainly do have a problem with over detection and over treatment. And over detection and over treatment is diagnosing and treating men for a cancer that was never going to cause them any problems during their natural lifespan.

So what I want to share with you today are ways, really tangible ways, that you can take back to your practice on how to minimize the rate of over detection while still maintaining the upside of PSI a screening, which is identifying meaningful cancers, treating them effectively, and still curing men of their cancer if needed. This is at the heart of the problem why we have an over detection problem. The adage is true that if you're a man and you live to be old enough, you're going to develop microscopic prostate cancer within your prostate.

And this is a famous study done in an inner city hospital in Detroit of men who died of other causes. They came in for traumas or died of heart attacks. And they looked at their prostates. And as you can see from the figure, your risk of having prostate cancer in your prostate basically paralleled your age as far as a percentage goes. So if you look at 60-year-old men, there's about a 60% chance that's somewhere in their prostate there's prostate cancer.

Our job as urologist is to find which of those cancers are meaningful and may one day cause problems, so we can diagnose them early and treat them effectively. And all the men that have prostate cancer hanging out in their prostate it's never going to cause any problems, we need to figure out ways to never know about it. Or even if we do find out about it, not necessarily recommend treatment.

So here's some numbers for you on the over detection and over treatment. Since the PSA era this is somewhat older data that was published a few years ago. But it's estimated about 56,000 men have had their lives directly saved because of the a test. But unfortunately, there's over 1 million men that have been diagnosed with prostate cancer who quote unquote "never needed to know" about it.

So the models that I showed you earlier is for every man diagnosed with prostate cancer that we treat, anywhere from five to 37 men need to be diagnosed in order for one of those men to have their life saved. So how do we take care of this problem of over detection and do our best to minimize over detection? One strategy put forth by the Preventive Services Task Force is just stop PSA screening. That way the only way you're ever going to diagnose a man with cancer is once it has spread or it's causing major symptoms.

I believe that's cutting off your nose to spite your face, or the adage, throwing out the baby with the bath water. I think this is not a good strategy. But it has been recommended.

Another strategy, which takes a little bit more effort, but I think is far better for public health, is just use our PSA test more intelligently. So here are some examples. And I'm going to get into the details.

Consider a screening PSA test if a man has a life expectancy greater than eight to 10 years, also if he understands the pros and cons of PSA screening and wishes to get a PSA test. Number two, don't give empiric antibiotics for an elevated PSA. And I'll show you some data to support that.

Number three, discontinue screening if a man is older, sicker or wants to stop being screened. And I'll give you some tangible, quantitative data to go by on that. Number four, always repeat to the newly elevated PSA. Number five, don't biopsy based on PSA velocity, which is the rate of rise of PSA. And then I'll also touch on some novel screening strategies that are trying to be studied, have been studied and that are being studied that we hope do a better job than PSA. But currently, as of now, PSA is the best screening test we have.

So understand age and life expectancy, just because a man's 50 years old, doesn't mean he needs a PSA. These are examples of 50-year-old men, who you would never think about checking a PSA, because they're highly unlikely to live another 10 years. Alternatively, it is very reasonable for some men in their '70s and even early '80s to screen them, because in the United States, the average life expectancy for 75-year-old men is about 10 years.

So if you have a 75-year-old man, and he's healthier than the average 75-year-old man, I think it is reasonable to talk about a PSA test. Now, the only reason you're checking a PSA test is to make sure he doesn't have a large or aggressive prostate cancer that might one day cause problems.

This is some data on average life expectancy based on age in the United States. If you have made age 70 in the United States as a male, take all 70-year-old men from the sickest to the healthiest, the average life expectancy is about 14 to 15 years. And like I alluded to earlier, 75-year-old men, the average life expectancy is about 10 years.

Here's some data on empiric antibiotics for an elevated PSA. It was a widespread use, certainly throughout my training and early afterwards, that if a man had an elevated PSA, let's give him some antibiotics, because PSA is often elevated from inflammation or infection. And if the PSA decreased after a course of antibiotics, well then he will avoid a biopsy. This was never data based. It was all empiric.

We did a randomized trial to study this. We had 77 men with an elevated PSA having a biopsy. Half of them got antibiotics. Half of them didn't. We rechecked their PSAs. And the take home message and the bottom line is, whether you've got antibiotics or whether you didn't, your PSA change was not any different.

So not only does empiric antibiotics for an elevated PSA not change the PSA compared to doing nothing, but antibiotics can also be dangerous. It changes the bacterial flora in the rectum. Rates of infection and sepsis with prostate biopsies go up if you've recently had any antibiotic. And then there are also very rare, but pretty severe side effects with any antibiotics.

When do you stop checking the PSA? There's some data to go on. There was a big study in Baltimore where they had over 800 men.

And the bottom line is if the man was age 75 or greater and their PSA was three or less, no man died of prostate cancer. Stop checking for it. There's absolutely no reason to keep checking a PSA.

In a Swedish study, there's been a couple publications that have supported data that at the age of 60 if your PSA is less than the average PSA for a man your age, which is about 1.0, your risk of dying of prostate cancer is 0.2% over the next 25 years. So you can use that data to say, wow, if it's less than 1 at age 60, let's just stop checking. At the very least, I would encourage you that if you have a man aged 60 with the PSA of 1 or less, at least screen less frequently, every two years, every five years, because it doesn't appear that it's going to be helpful.

This is more data to suggest that the utility of a PSA at age 60 can help predict or sort of risk stratify how frequently a man should have a PSA if at all. Very similar to men who have colonoscopies that you get a colonoscopy at a certain age. And based on what they find, they tell you to come back in one year, two years, five years.

Always, always, always repeat a newly elevated PSA. If a man comes in with the newly elevated PSA, I always ask them to come back in a couple months and recheck it. This is some data from about 10 years ago that was published in JAMA that showed that basically 40% to 50% of all men with an elevated PSA, if you checked it in this study a year or two later, 40% to 50% of the time it returned back to a baseline level. PSAs vary a lot, fluctuate. Always recheck it.

PSA velocity is the rate of rise of a PSA over many years. There's a lot of people who are firm believers in PSA velocity as an indication for a biopsy for men with prostate cancer. I would point you to this article, which was published in a highly impactful journal, elegance analyses, and probably the single best article on PSA velocity. All I would tell you is PSA velocity does not add predictive value on whether a man has prostate cancer or high grade prostate cancer once you already know their baseline PSA, how they're prostate feels, and their family history.

So PSA velocity is often used to do more biopsies and try to identify cancers. And it's well intentioned. The data does not support.

This is a list of novel strategies that you may have already heard about or you will be hearing about. And this is trying to get a better PSA. Many of these are combined with PSA testing.

PSA is the best test we have. It's not perfect. But the goal is to augment it or even replace it with a better screening test that just identifies the men with meaningful cancers and limits the number of men that undergo biopsies where they don't find any cancer or biopsies that find cancers that we never needed to know about.

And one is called the Prostate Health Index, which is using a lot of isoforms of PSA into a novel calculation. One is called the 4K panel, which is a kallikrein panel. There's something called the T2 ERG, which can be a urine or blood test.

And those are all very early in testing. PHI is available and can be obtained, as well as the T2 ERG. But we await further data on whether they should be used on a widespread basis.

MRIs are very useful for men-- for certain men with prostate cancer. And there are trials ongoing to use MRIs as a screening tool, very similar to how they're used for some women, instead of mammography, and also as a tool to help guide biopsies. And lastly there's some genetic analyses that suggest we can tailor the screening strategies for men with prostate cancer.

So in conclusion, hopefully, I showed you based on data that screening, diagnosing, and treatment of certain men with prostate cancer can save lives. There certainly is an epidemic of over detection and over treatment. We as a medical community need to be doing a better job of combating that.

I focused in this talk on how to limit over diagnosis of prostate cancer. Hopefully, at some point we'll have available another talk on how we can minimize the rates of over treatment of prostate cancer. Surgery and radiation, highly effective forms of treatment, they do have risks of side effects in expert hands. Those are relatively low. But they're also our strategies, such as active surveillance, where we keep a close eye on certain cancers.

So screen wisely based on a man's age, their health, their life expectancy, and what their PSA level is. And you can benchmark that and come up with a strategy on how often you should be checking it.