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Redesigning Prostate Cancer Screening Strategies to Reduce Overdiagnosis

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Andrew J. Vickers.
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Guest: Dr. Andrew Vickers is a researcher at the Memorial Sloan Kettering Cancer Center in New York City.

Bob Barrett: This is a podcast from *Clinical Chemistry,* sponsored by the Department of Laboratory Medicine at Boston Children's Hospital. I am Bob Barrett.

The January 2019 issue of *Clinical Chemistry* is devoted to the area of men's health. Aside from non-melanoma skin cancer, prostate cancer is the most common cancer among men in the United States. It is remarkable that even though the introduction of prostate specific antigen, or PSA, into U.S. clinical practice occurred over three decades ago, researchers and clinicians are still debating its value for prostate cancer screening.

In that special issue, Dr. Andrew Vickers published an Opinion article titled, "Redesigning Prostate Cancer Screening Strategies to Reduce Overdiagnosis." Dr. Vickers is a researcher at the Memorial Sloan Kettering Cancer Center in New York City and he's our guest in this podcast. So, Dr. Vickers, randomized trials have shown that PSA screening just doesn't work. Why should we even still consider using it?

Dr. Andrew Vickers: Yeah. What you said is a very common misperception, actually. There's been several randomized trials and as is common in many fields of medicine, some show it works, some show that it doesn't work. And there's a tendency to say, "Well, we don't really know" or "Well, the American trial, the large American trial, the PLCO, showed it didn't work, so we should believe that more." My view is that you have to look a little bit more carefully at the data. So, there have been three large trials that were well done. One in the UK, one throughout Europe, one in the U.S. The U.S. trial was "negative," it did not see a difference between patients in the PSA arm and the control arm. But if you actually dig down, what you find is that most of the men in the control arm got a PSA test because they were just older Americans going about their business and many older Americans going about their business end up at doctors and end up getting PSA tests.

So, if you actually read the paper carefully, the authors of that paper do not say, "This is a trial of screening versus no

screening." They say, "This is a trial of organized screening versus opportunistic screening." So, to say that the PLCO trial, the big U.S. trial, to imply that that says PSA screening does not work, is not true because that was not the question that was addressed by the authors.

So, that leaves the two other trials. The big European trial clearly shows a reduction in mortality from PSA screening. It was modest, but it was there. The UK trial was a little unusual for two reasons. One is that the follow up, how long the trial has been followed, it's relatively immature. So, it's going to be interesting to see what happens as data accrue.

The other important thing about it is that it was a one-off PSA test. So, in the trial you are randomized either not to get a PSA test or just to get one PSA and leave it at that. I don't know anybody who works in the field who says the way we should screen for prostate cancer is to give men somewhere between 50 and 70 one PSA test and leave it at that.

So, many would argue, and I'm very sympathetic to that argument, that the UK trial, which is called the Cap Trial, is testing an intervention that no one would actually want to implement in practice, which is all to say that we should talk about the PSA screening because there has been one large well done trial that did actually address the question of the value of screening compared to no screening, and it did show an effect on prostate cancer mortality.

Bob Barrett: Fair enough. We've been screening men with PSA in the U.S. for over 30 years, has that been good or bad for population health?

Dr. Andrew Vickers: Yeah, that's a great question and people disagree. I personally, probably would -- I'm on the fence. I'm probably leaning over towards the people that say that it's done more harm than good. The key thing to realize about PSA screenings is not one thing, right? We could have a debate. Should we be giving 80 milligrams of aspirin to men and perhaps women also once they hit 65 for heart disease prevention? And we would be talking about 80 milligrams of aspirin daily and you either give 80 milligrams of aspirin or you don't. It's just one thing.

The interesting thing about PSA screening, it's a complex intervention. There's lots of different ways that it can be done and what we've been doing in the U.S. over the past 30 years or so, is a lot of the wrong thing. We've been screening older men but not younger men, so that the age group with the highest incidence at screening are men in their late 70s and we're almost -- we're pretty sure PSA

screening is ineffective for those men. We're also pretty sure it's most effective for men in their 50s which have very low rates of screening.

Something else we've been doing in the U.S. is having very liberal criteria for biopsy. The best evidence suggests, "Oh, you've got a high PSA. Well, that's interesting but we have got to jump through a number of other hoops before we biopsy you, you probably don't have the kind of aggressive cancer, we're interested in identifying" and for many years we would biopsy men at a drop of the hat. I mean, we've often joked that you kind of -- you really need to be a special guy to get out of the urologist's office without having a biopsy because there are so many different criteria to biopsy.

Perhaps the biggest problem is that we were treating the wrong cancers. So, for many years, the low-risk prostate cancers would be treated because we could cure them and we would not treat aggressively the higher risk prostate cancers on the grounds that we felt that those probably couldn't be cured. But the point was that those low-risk cancers were unlikely ever to kill a man and it was the high-risk cancers that were more likely to cause cancer-related mobility and mortality.

So, over the past 30 years we've been screening the wrong men, we've been biopsying the wrong men, we've been treating the wrong men. And there's some ballpark estimates that we've maybe treated a million Americans that didn't need treatment. And remember, these treatments for prostate cancer are not a walk in the park. They cause long term side effects including loss of sexual function, loss of urinary function, and bowel problems.

Bob Barrett: Doctor, what are the key points for making sure that PSA screening does more good than harm for patients?

Dr. Andrew Vickers: I think there's a simple answer to that question, which is to look at everything we've been doing wrong and make sure we don't do it.

Bob Barrett: Okay.

Dr. Andrew Vickers: Make sure that we do what's right instead of what's wrong. So, we've been screening the wrong people with the PSA test. So, lets screen the right people, but the men who have most to benefit from PSA screening are those in the age of -- between about 50 and 70, really very problematic screening men over 70, and certainly men over 75 have little, if anything, to benefit. So, make sure we focus on the younger men, not the older men.

Now the second thing is, only biopsy men who are at an importantly elevated risk of having aggressive prostate cancer. It's often said that the purpose of PSA screening is to identify prostate cancer. That's not a useful way of thinking about PSA screening. It turns out that almost every man will get prostate cancer if he lives long enough. There's been studies of men who had strokes or heart attacks or died in a motor vehicle collision. And if you take the prostate out and look at it under the microscope, you will find cancer very often. So, we can actually do these studies where we can estimate your risk of having prostate cancer given your age.

It's pretty much a ubiquitous disease. We shouldn't be running around trying to find prostate cancers. We should be trying to find only the aggressive prostate cancers. So, it means we have to much more selective about the men we biopsy.

One of the big developments over the past 10 years is now we have both markers, and some imaging approaches, that help us determine that a man who's got mildly elevated PSA -- we often say a PSA above three is worrisome for prostate cancer--so, you have a man with a PSA of about six, it's not explained by a benign disease, should we biopsy him or not? Well, why don't we run one of these markers, do some more imaging, and then make a decision? So, we need to be much more selective about who we biopsy.

Probably the biggest change we can make to the general approach to PSA screening, to make that it does more good than harm, is not to treat the low-risk cancers. About half of the cancers we find with PSA screening are low-risk and would never cause a man any morbidity during the course of his natural life. And those cancers can be managed conservatively using programs, what's called active surveillance.

So, a man has a biopsy. The cancer is found to be low-risk, he's followed every year with a PSA, every few years he gets another biopsy, and he only goes and gets something like surgery or radiation therapy if the cancer is found to progress to a more aggressive phenotype. And finally, we can make sure that when we do have a man with an aggressive cancer that does need treatment, we can make sure that he is treated appropriately, that he gets a good treatment.

Now, there's tons of evidence in the literature, and this isn't just in prostate cancer surgery, it's throughout surgery, that you get better results if you go to an experienced surgeon or a high-volume surgeon.

At MSK, we did some studies showing that you needed at least 250 to 350 radical prostatectomies before your recurrence rate started to plateau, so that you were getting good results in terms of cancer control.

We then did a study to look at a population-based sample of urologists to find out amongst those men doing surgery for prostate cancer, what was the typical number of prostate surgeries they were doing a year? Well, the median was three per year. The mode was one. Twenty-seven percent of urologists who did a radical prostatectomy only did one per year. About 80% did 10 or fewer, which means they would never get up the learning curve during the course of their entire surgical career.

So, we have to make sure that the treatment that is received by patients with prostate cancer is effective and that we lower the chances of long-term side effects such as those I've described, and that means treating them at centers of excellence, regionalizing care to high-volume centers.

Bob Barrett: That gives you something to think about, doesn't it? Finally, doctor, guideline groups have emphasized shared decision making for PSA testing. Now, do you agree or disagree with that approach?

Dr. Andrew Vickers: I both agree and disagree with that. Really, we do need shared decision making. There is something special about PSA screening. That means that we shouldn't do it to men without explaining to them what's going to happen and getting their agreement. This isn't like doing a blood pressure test for a 50-year-old, which is something you do as routine. You really do need to let men take a choice, have a choice in that.

What I disagree with is that these guideline groups are sort of abdicating their responsibility. They're saying, "Well, it's a difficult issue. Let's let the individual man make a choice." And I think what we're going to get, or what we have gotten for years is kind of chaos. There's three things that can happen right now. We can have no PSA screening at all. We can have a systematic and organized program that is specifically designed based on the best medical evidence to reduce the harms of prostate cancer screening and make sure that it has the largest impact on prostate cancer mortality as possible, that would be the second option.

The third option is what we're currently doing right now, which is, well, whoever happens to ask for a PSA test will get one, and then we'll leave it to the doctor to decide who's biopsied and where they're treated, and so on, and so forth.

That's what we're getting right now and it's not good practice and we know that.

There was an example recently in a European country which shall, for the purposes of not wanting to point fingers at the guilty, I won't mention. But this country said "We're not going to have population-based screening, the evidence doesn't meet our criteria, et cetera, et cetera. If the individual man is interested in it, he should consult with his doctor and go through shared decision-making."

Well, some colleagues of mine, and myself and some urologists from that country, we actually did some back-of-the-envelope calculations and we worked out, had that country or were that country to implement population-based PSA screening, they would do fewer PSA tests than they are currently doing. Because what's happening right now is in that country, you're having many men in their 80s getting a PSA test every single year for five or 10 years. And then many of those men are having low-risk cancers discovered and treated. It's not only a waste of time, it's actively harmful to those men. And we worked out that if you actually implement a systematic approach to screening, and many of these screening programs, you need maybe three PSA tests lifetime, you actually do fewer PSA tests. You biopsy fewer men and would treat fewer men if you did it properly rather than the current guideline approach, which is to, "Let the people decide."

So, I do understand why guideline groups say shared decision making, that is important, but I don't think guideline groups can just abdicate their responsibility as to how we should be doing PSA screening, and making sure that the way in which we do PSA screening ensures that it does more good than harm.

Bob Barrett: That was Dr. Andrew Vickers from the Memorial Sloan Kettering Cancer Center in New York City. He's been our guest in this podcast about utilizing prostate specific antigen in screening for prostate cancer. That article appears in the January 2019 issue of *Clinical Chemistry*, a special issue devoted to the area of men's health. I'm Bob Barrett. Thanks for listening!