

**Article:**

Andrew J Vickers and Hans Lilja.

Eight Misconceptions about Prostate-Specific Antigen.

Clin Chem 2024; 70(1): 13–16. <https://doi.org/10.1093/clinchem/hvad138>

Guest: Dr. Andrew Vickers from the Department of Epidemiology and Biostatistics at Memorial Sloan Kettering Cancer Center in New York, NY.

Bob Barrett:

This is a podcast from *Clinical Chemistry*, a production of the Association for Diagnostics & Laboratory Medicine. I'm Bob Barrett.

Prostate-specific antigen, or PSA as it is commonly known, has been available as a diagnostic test since 1986 and plays a central role in the screening and monitoring of prostate cancer. In the early years of prostate cancer screening, an elevated PSA was a guaranteed ticket to prostate biopsy and the vast majority of detected prostate cancers were treated. As a result, more than a million American men have experienced complications related to treatment of a cancer that would not cause symptoms before the patient died of some other cause. With this in mind, PSA has been viewed negatively by many, but proponents argue that PSA remains a remarkably useful diagnostic test when used correctly.

A reflection article appearing in the January 2024 issue of *Clinical Chemistry* describes 8 common misconceptions about PSA and proposes strategies to harness its benefits while minimizing harm. In this podcast we are excited to chat with the reflection article's lead author. Dr. Andrew Vickers is an Attending Research Methodologist in the Department of Epidemiology & Biostatistics at Memorial Sloan Kettering Cancer Center. He works in prediction modeling and clinical trials and has a special interest in the early detection of localized prostate cancer.

Dr. Vickers, PSA was introduced into clinical practice more than 35 years ago. Why do you think it's still so controversial?

Andrew Vickers:

That's a great question. I think it's that a lot of people don't keep up with the literature and, you know, why should they? I mean it's a highly specialist area, you know, the latest findings are coming out all the time, and people's knowledge gets out of date. That's perfectly understandable.

I think that the key thing is that there's two controversies here and we have to be clear on which controversy is justified and which one is not. So, one controversy is, "Does PSA screening save lives?" and the second one is, "Does any

benefits in terms of reduced prostate cancer mortality outweigh any harms in terms of overdiagnosis and overtreatment?"

The first controversy, that's the one that's out of date and I complain about people being -- not keeping up with the literature and not really understanding that. I really don't think there's a serious debate among academics about whether PSA screening reduces prostate cancer mortality or not. The data were in from the higher-quality randomized trials that have been followed sufficiently and the epidemiologic data is in. Give or take, prostate cancer mortality in the U.S. has fallen by about 50% since the introducing of PSA screening, and it's just really hard to say, "Oh, we've better hormonal therapies now. Maybe that--," you know, you just can't -- it doesn't add up to 50%. So, it's quite clear that PSA screening does have a role.

Now there are some people that say, "Yeah, but it hasn't been shown to reduce overall mortality," which is just a straight misunderstanding of public health interventions, because it's almost impossible to show that any public health intervention directed at a specific problem or disease, seatbelts for example, is going to affect overall mortality because motor vehicle collisions are only a small part of overall mortality, so you can get rid of them tomorrow and it will be very difficult to see any impact on overall survival. So, I don't think there's any serious debate anymore about whether prostate cancer screening saves lives. The issue, and this is a genuine controversy and people are absolutely right to debate this, is whether the benefits in terms of reduced mortality outweigh the harms, and that's in terms of overdiagnosis.

I mean, men will tell us that the worst day of their life is when they heard they have prostate cancer, and then the treatments for prostate cancer, as is well known, have a lot of persistent side effects. Urinary dysfunction, erectile dysfunction, and bowel dysfunction, these are not things that anyone really wants to deal with, especially not in the last decades of their life.

Bob Barrett: So, is the controversy then that the screening isn't the problem but the treatments are the problem?

Andrew Vickers: I think it's a little bit of both, but I actually want to move the controversy a little bit away from this balance of harms and benefits, do the harms outweigh the benefits or whatever it is, and think more about how can we move the ratio of benefits to harms? How can we do screening better? Screening isn't just one thing just done in one way. You can do PSA screening in all sorts of different ways. One of the things that interest me for example is that screening older

men, you know men aged 70 or over, has very little benefit if any, and a lot of harm.

I mean, these are the individuals that are most prone to overdiagnosis, and we've done some research showing that close to half of all the overdiagnosis in the U.S. occurred in men aged 70 and over. So, we could dramatically reduce overdiagnosis and all those downstream harms of overtreatment if we restricted screening in older men, and that's where I think the debate has got to go. And then, the analogy I use is, just think about drinking, all right? The drinking controversy, is the benefits of drinking in terms of pleasure and social interaction and so forth, do they outweigh the harms in terms of disease, of liver cirrhosis, and drunk driving? We don't talk like that. We say, "How can we get people to drink responsibly?" And we say to people "If you do drink, drink in moderation," and that's what I'd say about PSA screening. If you are going to do PSA screening, do it in moderation, and then we have less of a question about whether the benefits outweigh the harms.

Bob Barrett: And is there an education problem with the patients themselves? They hear the word they've got prostate cancer and they say, "Do something. Get it out of me," where a lot of these cancers, they're just going to sit there until they die of something else?

Andrew Vickers: Right, yeah. Well, there's actually a group of people interested in that--urologists, pathologists, researchers like me, who've actually argued that there's a whole category of prostate cancer called Gleason 6 prostate cancer, that shouldn't even be given the label cancer. We think actually removing the label cancer from this subtype of disease, which has been shown it cannot cause metastasis, I think the ordinary meaning of the term *cancer* is that it can harm you and so if we just took the word cancer out of from what's called prostate -- Gleason 6 disease, that would that would have an enormous benefit. I mean we can go into education, and so on and so forth, but we know that's slow and there's a lot of incentives for doctors to treat, and relatives get involved. I really actually think there's not much of a way around it if we still call things cancer, which is such an emotive term.

Bob Barrett: Well, getting back into the lab, lab reports indicate that PSA is either in range, which is typically less than 4 nanograms per milliliter, or out of range. Why do you think that that's problematic?

Andrew Vickers: I think there's two problems, is one is where that cut point came from and Hans Lilja, who's the co-author on the original paper with me, we spent quite a long time tracking it down. It turns out that this was an internal Beckman Coulter report

saying that the upper 97.5 centile of PSA in older men was 4. Now, I don't understand why that's a rational cut point, all right, that are we going to define two and a half percent of the men being at risk of prostate cancer. So, that's one problem. And secondly, there is an extremely strong gradient of risk below 4. So, if you have a PSA of 3.5, you are at a dramatically higher risk of prostate cancer mortality and morbidity than you are if you have a PSA of 0.5, and most of the current recommendations from the major academic groups and societies, and so on, say that once you know your PSA, you should then risk stratify so that if your PSA is low, if it's less than 1, you need screening maybe every five to eight years and maybe even stop once you hit 60, and if it's 1 to 3 then you get screening more regularly, you know, in every two to four years.

I actually have some friends who say to me, "You know, hey, you're a prostate cancer guy. I had my PSA test and it was negative." That's what they get told by their doctor. It was negative, you know, as if it was -2 nanograms per milliliter or whatever. Of course I say, "Well, what was their actual numbers?" Someone came back to me and said it was 3.8 and he was like, "Oh, I'm great!" I'm like, "You know what, you really need to follow that very carefully because you're at much higher risk than average."

Bob Barrett: Now patient guides for prostate cancer screening say sometimes that you might still have prostate cancer even if your PSA is low. You seem to be agreeing with that but you say that's not a problem. How could that be the case?

Andrew Vickers: Because prostate cancer isn't the problem, right? Prostate cancer morbidity and mortality is the problem. That's the disease, is when prostate cancer is causing you symptoms and it's shortening your life. Prostate cancer is a ubiquitous feature of aging in the older man. You know, I'm in my mid to late 50s. If I was to die tomorrow of some other cause, there'd be a 30% to 40% chance that you would find prostate cancer cells in my prostate. Pretty much every man will get prostate cancer if he lives long enough.

People say, "well, PSA is a terrible test for prostate cancer." I'm like, "yeah, you're probably right, but who cares?" That's not what we're trying to detect. What we're trying to detect is the prostate cancers that lead to morbidity and mortality. With my co-author, Hans Lilja, and other co-authors from Sweden, we've done a series of studies that show that PSA is incredibly sensitive to the long-term risk of metastasis and death, with areas under the curve of 0.85 and above.

Bob Barrett: Finally, in the U.S. and most other high-income countries, current policy is a PSA screening is an individual choice based

on shared decision making. Do you agree that that's the best approach?

Andrew Vickers: Absolutely not. And, in fact, multiple colleagues throughout Europe and the U.S., we've just written a paper in the *British Medical Journal* criticizing this policy. This policy of individual choice has led to the worst possible outcomes of very high rates of PSA testing, very high rates of overdiagnosis and overtreatment, a minimal benefit, because we know that the way that people are getting screens in general practice is just not that effective, and massive inequity. I mean, I just was talking with some colleagues.

In the U.K. You can pretty much predict the PSA incidence in a region of the U.K. by the average income in that region, because income is associated with education and access to care and so on and so forth and seeing your doctor. And those are the people that are going and asking for the PSA test.

Our view that we expressed in the paper was, "do prostate cancer screening well or not at all." And doing it well means a limited number of PSA tests, a very high barrier before you undergo a biopsy, and treatment for only the most aggressive prostate cancers. And we actually show in this paper that for many countries, if you implemented that program, compared to the current status quo, the number of PSA tests, the number of diagnoses, and the number of treatments would likely go down. So, we're told we can't possibly, don't introduce population-based PSA screening. Of course, all these people will get tested and there'll be a massive increase in the number of incidents and the number of treatments we do, and the health system just couldn't handle it.

And I actually think in many cases that's wrong. We would actually get fewer diagnoses, fewer tests, and less treatment if we implemented a well-designed systematic program of PSA testing. And there's actually some evidence. There's one country that's done that, which is Lithuania. And Lithuania saw something like a 90% decrease in screening in men aged over 70 once the population-based program was brought in. And, of course, that's the group with the most over diagnosis.

Bob Barrett: How hard are scientists or researchers trying to find the replacement to the PSA test?

Andrew Vickers: Hans Lilja, with whom I wrote this *Clinical Chemistry* piece on PSA, and we got so frustrated by people calling for a better test than PSA, is.... We actually had this editorial in one of the urological journals that said, I think the title was, "We need a better test for prostate cancer. How about renaming PSA?" Because everyone says, "we need a better test than

PSA.” And it’s going to be really hard to find one that PSA has such remarkable properties.

I’ll be at a meeting at the National Cancer Institute and some researcher will be teasing me about PSA. And I say, “wait a minute, you do breast cancer.” So, tell me what the marker you have in breast cancer that PSA in prostate cancer we should be jealous of. PSA is a completely remarkable marker. It is incredibly sensitive to a man’s long-term risk of prostate cancer, morbidity, and mortality.

Now that said, while it’s very sensitive, it’s not very specific. And so, a lot of research on how to make PSA more specific. And so, the idea is you do a PSA test. If it’s low, you’re fine, and if it’s high, instead of rushing off and getting a biopsy, there are other things you can do first. One of them is to get an MRI. And if you don’t see anything on the MRI, perhaps you don’t need a biopsy.

There are other markers. The one that I’ve been involved in and to declare conflict of interest, I received royalties from, is called the 4K Score. If your PSA is high and your 4K Score is low, then you don’t need a biopsy. So, the question isn’t how to replace PSA, but how to develop markers that are more specific than PSA. Because PSA is incredibly sensitive, but a high PSA does not mean you will get an aggressive prostate cancer.

Bob Barrett: So, we’ll change the name to PVSA, prostate very specific antigen.

Andrew Vickers: Very specific. Yes. No, I think we thought of renaming PSA as the EPCM established prostate cancer marker. Yeah, I don’t think PSA is going away soon. I mean, certainly it’s well known to be very good for monitoring advanced disease. But even as a screening test, I just don’t see that we’re going to get anything better anytime soon. I really don’t think it will be replaced. The question is, once you’ve had your PSA test, and it’s high, what do you do then? And there’s a lot of research on how to refine workup. So we’re only biopsying the very highest risk patients.

Bob Barrett: That was Dr. Andrew Vickers from Memorial Sloan Kettering Cancer Center in New York City. He served as lead author for a reflection article describing eight misconceptions about prostate-specific antigen in the January 2024 special issue of *Clinical Chemistry*. And he’s been our guest in this podcast on that topic. I’m Bob Barrett. Thanks for listening.