

Host: This is the podcast from *Clinical Chemistry*. I am Bob Barrett. Prostate cancer is a leading cause of morbidity and mortality among middle-aged and older men. The discovery of PSA, or prostate-specific antigen, and the demonstration of its utility for early diagnosis and monitoring of prostatic carcinoma initially raised hopes that this laboratory test could be valuable in the screening of asymptomatic individuals for early prostate cancer diagnosis.

Recently, the results of two major randomized clinical trials from the United States and Europe on the effectiveness of PSA as a screening tool have been published. These results are not clear cut, and for this reason the controversy surrounding prostate cancer screening will likely continue for years.

The March issue of *Clinical Chemistry* published a panel interview that discussed the results with four authorities in the field. Our guest in this podcast, Dr Carsten Stephan from the Department of Urology, University Hospital Charité, in Berlin, Germany, continues this discussion.

Dr. Stephan, what do you think is driving the widespread PSA testing for prostate cancer screening during the past decade despite the absence of evidence for its benefit?

Dr. Carsten Stephan: Yeah. So far one of the most important things for me is the clear correlation of PSA to tumor stage, and increasing risk of prostate cancer with increasing PSA. And another big point is that we have now a clear reduction of primary metastatic carcinomas, from 20 to less than 5%, so this reduction is about 80%.

But what you have to consider if you measure the PSA, there are many possible errors which can occur. For instance, with different assays, you can have several conditions before testing. For instance, prostate inflammation, prostate manipulations, and this is one thing you should also consider.

Host: Well, what do you recommend patients do to minimize possible errors when testing PSA?

Dr. Carsten Stephan: Yeah. There is a big issue, because I know a lot of doctors, they don't know about this and they don't recommend something. So there are somethings you

should always know. You should tell the patients that you should stop cycling for at least two or three days. You should have no sexual activity the last day, because the PSA concentration and the semen is about one million fold higher than in the serum.

And also, if you have one elevated PSA, you should definitely undergo repeat test before you make any consequences out of this. And if you have a PSA value, you should -- in some questions, you should also add the free PSA to increase the specificity and you should also know about the prostate volume, because high PSA value and the large prostate glands doesn't affect me that much, but if the PSA is half of this and the prostate gland is very small, I would of course think about a biopsy then.

And one issue is also important, I think, that the PSA change over time, calling PSA velocity, is possible of course, but also always rely on this and ask the patient about his PSA history.

Host:

Well, you mentioned PSA velocity seems to be useful, but there have been some contradictory study results recently. Could you comment on that?

Dr. Carsten Stephan:

Yeah, they are in general two opinions from important urologist. So one big group is the group of Catalonia. He did very well-designed studies in large cohorts, with more that 1,000 patients, and he was the one who was changing the PSA velocity cutoff from 0.75 per year to 0.4. And if you see the studies, it's really convincing. You should follow this one.

But there is another lot of big urologists, they say, well, PSA alone is already very strong, so that PSA velocity does not really help you. They are the urologist, Dr. Thompson from the big Screening Study and another one is from European Study, Professor Schröder. They have the opinion that PSA alone is already very strong, so that PSA velocity is not really helpful.

So, my opinion is clear. I understand of course both groups, but I see different kind of patients. If you have a patient with a clear increasing and steadily increasing PSA, of course velocity is definitely useful, but we also see a lot of patients with fluctuating PSA, and in these patients, velocity of course does not really help you, and of course this is something you definitely have to consider.

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Host: Well, what do you think of the two large randomized trials on prostate cancer screening that seem to reach contradictory results?

Dr. Carsten Stephan: Yeah. So, I got news on the last year's European Conference, my first reaction was, wow, one study for and one study against this. But then I checked it more clearly, and I saw there were several flaws in the smaller U.S. study.

In general, I am convinced with a lot of other clinicians that this was unfortunately a disappointing design in the PLOC study, and because of the big contamination and the data also somewhat premature, I had the feeling that this study was only published, because the other study was just published. This was my first reaction on both studies.

Host: Well, both studies of course in *The New England Journal of Medicine*. What are the concrete differences between the two studies, and in your opinion, what are the consequences of these studies?

Dr. Carsten Stephan: Yeah, yeah. Of courses, differences, if I would first come to the study in Europe. If you see there—if you also consider the participation and contamination, there is not only a 20% reduction in mortality, there is already a 31% reduction in mortality. So this is really impressive, and these are the data I used to tell, and I would wonder if this study would have been published alone, what would have been the reaction? I think everybody would talk about PSA and its main impact.

But if I come to some weakness of the U.S. study, I think more than 50% contamination of PSA testing, the non-screening arm, is really a significant weak point. And if you see, if you compare this to the screening arm, where they have about 85% PSA test, this is not really a comparison between screening or not screening, this is a comparison between two different screening arms.

And also of course duration, the follow up, and also the behavior, what happens in the U.S. study, with an increased PSA, is really not that favorable for patient, because they didn't biopsy all patients with an elevated PSA and also the agreement of patients. If they had to increase PSA for biopsy, was much lower than in the European study, and therefore we don't know what really happens.

I think many cancers worse than this, which didn't undergo biopsy in the United States, but problem is now, that the consequence for everybody in the world, for not specialist, they see, well, there were two studies; one is for screening, one is against, so you can interpret the results as you want yourself.

And really, I think, that's a shame for the well designed European study, and not only for these workers there, but also for, I think, most of the others, not only Europe, that this is a problem that everybody can make interpretation now as he wants. Because he can always say, well, one study didn't show us that PSA really reduced mortality, and this is, I think, a big problem. And you can make your interpretation yourself.

Host: Well, based on your statements, I would expect that you do recommend PSA testing to your patients. If so, how do you justify that decision?

Dr. Carsten Stephan: Yeah, yeah. I think that's clear. I definitely recommend screening, but you have to be informed. So I recommend this only to inform patient and they must know about all consequences about elevated PSA, about biopsy, and side effects. And if the biopsy is positive, about treatment effects and all options of therapy, including watchful waiting, you have to tell this before you undergo even the PSA test.

Then of course I can argue with the better European study, that you have a 31% reduction in mortality, because this is a bigger study and I can—if they ask again, I can tell them the weakness of the U.S. study, and I also argue it with a clear correlation of PSA to develop prostate cancer and the correlation to stage, and of course the big fact that you have now—with PSA you have a 80% reduction of primarily metastatic prostate cancer.

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But of course I also mention that, the correct reputation of PSA is definitely also important to avoid possible errors before drawing any decision based on one single PSA value.

Host: What is your opinion for the future diagnosis of prostate cancer with new markers or better imagining?

Dr. Carsten Stephan:

I think that's quite interesting and good situation right now. The current screening situation showed that there were some blood and also urine markers with extraordinary good results. But so far only those markers can be used which are on a commercial basis.

And there are two tests I would highlight. First, the PCA3 test in urine and -2 pro-PSA. And these tests, they have chance to improve screening, especially for aggressive cancer of course, beside the well-known serum PSA and also free PSA. And I have my opinion from other markers, like the gene fusions, they are promising, but the specificity is too low and they are so far unfortunately not commercially available.

But I see more and more patients who want to use all options before even go to biopsy, and they want to use PSA free test, they want to use multivariate models, including artificial neural networks or nomograms. And they understand if I tell them, well, you should not only draw your decision on one PSA, but you should also include the patient's age, prostate volume, and percent free PSA.

And we offer this in a program which we have in our clinic since 2003, and which we have for definitely a more PSA test since 2008, and of course I also consider PSA velocity, if it's available for the patients, but you should not use a strict cutoff of 0.4 or something, it helps you to get the right biopsy decision.

And also for the biopsy itself, you have also further improvements. We use now a contrast-enhanced prostate biopsy or of course also MRI-based prostate biopsy, and with these special diagnostic tools, you can again increase the cancer detection rate.

But I think the main problem is still, so far that we need to detect aggressive cancer and only aggressive cancer. We don't need to detect the cancers who should not be treated. But so far the problem is, of course you have the overdiagnosis, but you can lower the overdiagnosis, but of course first the careful selection of the patients for biopsy and of course for selection of screening at all. You don't have to screen a 80-year-old man.

And I think these ways to careful counseling of patients, with also new markers and new diagnosis, these can also take part, so that you can definitely

reduce the over treatment and that you will find those patients that really need the treatment.

Host:

Dr. Carsten Stephan is from the Department of Urology, University Hospital Charité, in Berlin, Germany, and has been our guest in this podcast from *Clinical Chemistry*.

I am Bob Barrett. Thanks for listening.

Total Duration: 14 Minutes