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Toward Improved Prostate Cancer Screening: Insights from the Göteborg-2 Trial

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Guest: Dr. Hans Lilja is an emeritus professor in the Department of Translational Medicine at Lund University, Malmö, Sweden.

Bob Barrett: This is a podcast from *Clinical Chemistry*, a production of the Association for Diagnostics & Laboratory Medicine. I'm Bob Barrett. Prostate cancer is the most common cancer in men, with an estimated one in eight men developing the disease at some point in their lifetime. The good news is that prostate cancers often grow very slowly and most men with prostate cancer usually die of some other cause. PSA-based [prostate-specific antigen-based] screening is a sensitive tool to identify prostate cancer at an early stage, but it requires follow-up biopsy to differentiate between low- and high-grade disease.

Critics of widespread PSA screening point out that it mainly identifies men with clinically insignificant disease, causing them to undergo unnecessary biopsies and aggressive treatment that led to a diminished quality of life. But what about the minority of aggressive cancers with a high likelihood of progression? How do we identify and treat those at an early stage while simultaneously reducing overtreatment of low-grade cancers?

A new perspective article, appearing in the August 2025 issue of *Clinical Chemistry*, highlights the recent findings of the Göteborg-2 trial, a population-based study evaluating whether MRI can reduce biopsy rates and overdiagnosis in men with an elevated PSA during initial screening. In this podcast we welcome the article's senior author. Dr. Hans Lilja is a clinical chemist with Memorial Sloan Kettering Cancer Center and an emeritus professor in the Department of Translational Medicine at Lund University, Malmö, Sweden.

His research focuses on blood biomarkers associated with risk phenotype and outcomes of prostate cancer. So, doctor, what is the main outcome of the large, randomized population-based prostate cancer screening trials both in Europe (the ERSPC [European Randomized study of Screening for Prostate Cancer]), and in the US (the PLCO [Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial]), over 15 plus years of follow-up?

Hans Lilja: The most important thing to remember about these trials is that they actually show the same effect, that prostate cancer screening with PSA testing reduces cancer-specific mortality.

So this has been quite controversial in the past, in terms of discussing this effect, because the trials and the environments these trials were performed in, and the setup of the trials, were so different. But with long-term follow-up of these trials we now know very well that a key outcome of these trials is reduction in mortality from prostate cancer, which is significant. The effect size is most likely wrongly underestimated in the trials.

And why is that so? That is because of contamination. And what is contamination? That is in the control groups in the trials, there's been various amounts of PSA testing. So for example, in the US PLCO trial almost every man randomized to the control group had PSA testing. When the European trial started at about the same time as the US PLCO trial, which was in the mid-90s, very little opportunistic PSA testing was going on. Certainly, less than 10% and perhaps only 5% of those randomized to the control group in the European trial had a PSA test.

However, during the long-term follow-up on these trials, those numbers have changed. So nowadays in the control group, many more men have had PSA testing, which explains also why the relative reduction in prostate cancer mortality in the European trial has somewhat been reduced. So that is what I meant with an underestimate of the effect size.

Another aspect is at which age the testing starts. Both PLCO and the main part of the European trial invited men starting at age 55, and up to 70 or 75 years of age. Now, the Swedish arm of the trial, performed in the city of Göteborg, started to invite men already at age 50. And now in the recent publication two years ago, actually we could show that the effect when you start inviting men at younger age, meaning not later than age 55, the effect is much stronger.

So that means that prostate cancer mortality reduction could possibly be reduced by about half. A second main outcome is not a beneficial outcome. It's the harms associated with this testing. And that refers to many men are being diagnosed with prostate cancer and that the majority of those cancers detected with the design set up in the mid-90s for the screening programs, that half or more of the cancers detected are so-called insignificant. Meaning they pose little risk to cause harms or shorten the lifetime of the man who has these cancers.

So, this is big and important harms that is associated with that the design of these trials was: you take the PSA and if the PSA is elevated, in this case in the European trial being 3 nanogram per mL or higher, then you go directly for a biopsy, and the compliance rate in the European trial was 90% for that. And that showed then very clearly that this modality in

terms of prostate cancer screening causes important harms. And then if those diagnosed with these kind of low-risk cancers, if they are being treated, for example with surgery or radiation, then you have a risk of incontinence associated with this treatment or loss of sexual function associated with radical treatment.

And it's important to understand that this scenario, where the design of the screening studies was something that was contemporary in the early- to mid-90s when the study started, based on the limited knowledge that you have, and then that we have advanced the knowledge very heavily and now know that if you start PSA testing as such, you reduce mortality by the prostate cancer, but you also cause harms by the over detection, the overdiagnosis, that nowadays is mostly managed by active surveillance that then have risen as a common management option.

But of course, many men walking around with those cancers do not feel comfortable for it. So therefore, it's important to address this drawback of PSA testing as a screening approach. And this is also reason as to why there is no overall endorsement to do and implement PSA-based screening for prostate cancer. So this is the background as to why some newer screening designs have been set up and started on.

Bob Barrett: Doctor, can you explain the role of digital rectal examination in prostate cancer screening?

Hans Lilja: Yes, and the answer to this is that there is no role for digital rectal examination as a screening tool for prostate cancer. It has been clearly shown in the European screening trial, which in one early part evaluated and compared a program that included the digital rectal examination and the PSA testing versus doing only PSA testing, and could then clearly show that the rectal examination contributed no benefits at all in terms of detecting other cancers. And that has then more recently been replicated in other studies and shown as a screening tool. The digital rectal examination has no role.

Bob Barrett: What are the key findings that were recently reported in *The New England Journal of Medicine* from the G2-RCT in Göteborg, Sweden that might help shift the balance between the benefits versus harms of prostate cancer screening?

Hans Lilja: Well, the team in Göteborg, led by Professor Jonas Hugosson, they sat down and reflected on the results of the first trial and given then that the magnetic resonance imaging has been refined, has been suggested to provide an important means to help to screen for prostate cancer. They designed the G2 randomized screening trial in Göteborg, randomizing up to 39,000 men age 50 to 60. So they invited the men to take a PSA test. But then instead of men with the elevated PSA

being referred directly to biopsy, now they instead ask the man to instead be subjected to a magnetic resonance imaging examination, a so-called MRI imaging.

And then only those that were positive on the MRI with the suspected lesion would then be subjected to biopsy, directed only at the suspected lesion or lesions. The trial was a randomized trial in terms of that one arm was set up to examine men with both the old algorithm, meaning you have a PSA elevation, you're being referred to biopsy, and you take the biopsy as a systematic. So you examine all different parts of the prostate gland. Typically, you have 10 to 12 needles pushed into different parts of the prostate to examine whether any of those parts of the prostate holds prostate cancer.

In parallel, they were having an MRI. And if then MRI showed findings that were suspected of being prostate cancer lesions, they also added extra cores to those lesions targeted to those cores. In a separate arm of the trial, they only did the MRI for those men with elevated PSA and only biopsy in then the men with the suspected lesion on the MRI, directed at the suspected lesion.

They first reported results in 2022 in *The New England Journal of Medicine,* with the initial data. And now in late September of last year, in 2024 they reported about four-year follow-up of those data. That then includes both the initial findings and then finding when men are being reinvited. If they had a PSA above 1.8, they were reinvited two years after and if they had a lower PSA, they were invited four years after their initial PSA level. Typically, as a cut point to be referred either directly for a biopsy or for an MRI was, in this case, 3 nanogram per milliliter. And what this study then shows is very interesting because it shows that by having the referral after a PSA elevation to men being subjected to an MRI and only biopsying men with the positive MRI and targeting the suspected lesion with the biopsy core does that first in terms of those cancers that are being considered significant.

There was no difference to the prior standard approach with the systematic biopsy. So both arms were equal in terms of finding those cancers that are being considered dangerous. However, in terms of those cancers that are being considered overdiagnosis and insignificant, the approach with the MRI after the PSA elevation and only doing biopsies to the targeted lesion reduced detection of insignificant cancers by about half or more.

So there was a very significant drop in the detection of insignificant cancers by this approach. This is an important advance. Although it should be noted this is a preliminary report on the biopsy findings. But in terms of prostate cancer,

we need typically minimum of 10 but typically 15 years or more of follow-up to know whether to which extent this translates into cancer-specific mortality reduction.

Bob Barrett: Are there additional approaches to minimize harm from overdiagnosis of clinically insignificant prostate cancer while still detecting clinically significant cancers and at an early stage?

Hans Lilja: Yes, there are. And those approaches are some of the approaches that we, as well as another group, have worked on in terms of blood biomarkers. Several groups including ours have then worked on developing blood marker panels. We, for example, have used the PSA biology to develop test against not only the commonly measured PSA, which we call total PSA, but also the free non-complex form of PSA, and then sub fraction of that which is a single chain form of free PSA, which is called intact PSA. And then the fourth marker which is closely related to PSA, which is called human kallikrein-related peptidase 2.

Based on these four markers, we have worked throughout a large series of clinical studies and developed a statistical model where my collaborator at Memorial Sloan Kettering Cancer Center, Dr. Andrew Vickers, have been the key individual of designing a statistical model, which is then pre-specified, and which have shown promise in terms of reducing the number of biopsies needed to detect cancer and also possibly reducing the overdiagnosis of low-risk cancers. This is a test which has also been commercialized in the US as the 4Kscore test.

And I should also point out that as an inventor and as an individual who receives royalty on the basis of this test, I should disclose these kinds of arrangements that run to me. In terms of this 4Kscore test approach that we have developed, there are a study published in April of 24 online, and then later published in *European Urology,* which is a sub-study of the G2 trial, where individuals referred with the elevated PSA, they were asked to submit the recent blood sample that was shipped to my laboratory.

We measured the markers, calculated the 4Kscore, and then looked at whether or not there was a benefit of using this test in the context of the G2 trial that I just discussed in those results. And that showed then that using a tentative cut point of 7.5 of the 4Kscore test detected almost all of the insignificant cancers. So there were only two out of the cancer that were not detected, so less than 10% were missed. And those cancers could be debated in terms of their character because they were favorable in terms of the nature of those cancers when they were detected.

But that showed then that you could actually reduce the number of men referred to MRI by about 40%, which then would have meant that you would have reduced the biopsies are those who underwent the biopsies in the G2 trial under the MRI algorithm and that that reduction would have been 28% which would have led to that you would have detected even less of those low risk cancers that are being considered insignificant with the reduction of more than 20% of that.

And what is interesting then is that in Finland, there has been started another prospective randomized screening trial by Professor Auvinen in Helsinki and in Tampere. They overall randomized close to 120,000 men. And in the first report based on 60,000 men randomized for the trial, which published in *JAMA* in April of last year [2024], they showed data that is very similar to what I just discussed from Göteborg, based on the trial design, which then starts with that men age 50 to 63 are invited for PSA testing. And similar to Göteborg, around 50, 52, 53% participated. Men with a PSA above 3 are being referred to 4Kscore measurement and men with a 4Kscore test result above 7.5 are being referred to MRI.

And when MRI shows suspicious lesions, then they take biopsies on those suspicious lesions. And the results of that trial, which are preliminary again just like the G2 trial in Göteborg, shows data that are highly compatible with those from Göteborg. So that shows that then about 2/3 of the men referred to biopsy by this schedule have evidence of cancer at biopsy. So more than 60% of the individuals referred to biopsy have evidence of cancer at the biopsy, which is very different from the earlier studies, where only one out of three or one out of four had a cancer detected at the biopsy.

Even more importantly, out of those men who had evidence of cancer at the biopsy, four out of five had the signature of a cancer that is being considered significant. So only 20% of the cancers are those low-risk cancers that are being considered overdiagnosis. So, these two trial data from Finland and Sweden are highly compatible and suggests that an approach with PSA elevation and referral to MRI reduces the harms from the previous trials of prostate cancer screening with PSA alone followed by a biopsy. But then that this strategy can further be improved, do these the more recent studies suggest, by further reducing the need for using MRI by 34 to 40%, and then further reducing the number of men having a negative biopsy and having a low-risk cancer detected at the biopsy.

So these are promising signs, but far too early to declare a definitive outcome of these strategies. And I mean, of note is of course also that nowadays many men are having their

PSA taken. So that means that the control arms of these trials are contaminated to some extent. As we have advanced our knowledge, it has also made it more difficult for these trials to show significant effects in terms of reduction in prostate cancer mortality, because across the Western countries, prostate cancer mortality have trended downwards to a large extent due to increases in PSA testing.

Bob Barrett: That was Dr. Hans Lilja from Memorial Sloan Kettering Cancer Center and Lund University in Malmö, Sweden. He wrote a Perspective article in the August 2025 issue of *Clinical Chemistry*, describing ongoing efforts to improve prostate cancer screening and he's been our guest in this podcast on that topic. I'm Bob Barrett. Thanks for listening.