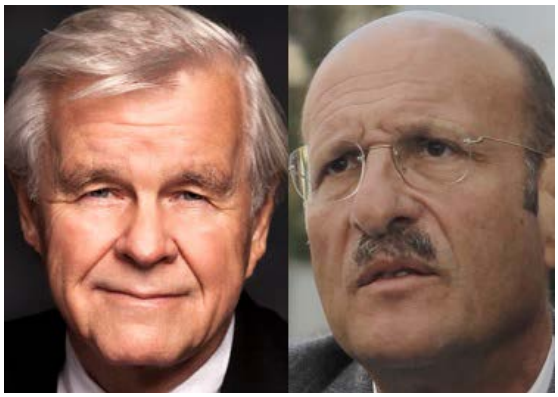
Clinical Chemistry

Chromosomal Instability in Cell-Free DNA Is a Serum Biomarker for Prostate Cancer



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Guests:
Dr. William Mitchell is a Professor in the Department of Pathology, Microbiology, and Immunology at Vanderbilt University in Nashville, TN; and Dr. Howard Urnovitz is the Founder and CEO of Chronix Biomedical in Göttingen, Germany.

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.

Prostate cancer is the most common cancer in men, with nearly a quarter million new cases diagnosed each year in the United States, and leading to approximately 28,000 deaths yearly. Typically, screening for the disease relies on digital rectal exam and measurement of prostate specific antigen, PSA, in blood. Limitations of the PSA test include its relatively low diagnostic sensitivity and specificity.

In the January 2015 issue of *Clinical Chemistry*, a Special Issue devoted to Molecular Diagnostics, a group of researchers in a multi-center study described chromosomal instability in cell-free DNA as a promising serum biomarker for prostate cancer.

In this podcast, we are joined by two of the authors of that paper: Dr. William Mitchell is a Professor in the Department of Pathology, Microbiology, and Immunology at Vanderbilt University in Nashville, Tennessee; and Dr. Howard Urnovitz is the Founder and CEO of Chronix Biomedical in Göttingen, Germany.

And Dr. Urnovitz, we will start with you. How does this study advance the field of molecular diagnostics; what is unique about the findings?

Dr. Howard Urnovitz: In this study we look at four big points, so first of all is the size of the study. Often in the field of cell-free DNA and cancer genomics, we are looking at as low as one patient and perhaps a couple dozen, so the sheer size of 400 samples, 200 cancer, 200 normals, gets us into that area of having a statistically valid conclusion.

The next thing is that a lot of the attention focused these days is on the genes that code proteins, and more

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specifically the genes that are related in the cancer and carcinogenic process. What we did was we looked at the whole genome, so by including the non-coding regions, instead of looking at 1% of the genome, you are looking at 100%; so that's a very significant advancement in the field.

And when you look at the genes that code for proteins, often you are looking at single-nucleotide polymorphisms of single mutations and that leads to prognostic tests that are getting better, are not quite there, but what we looked at was the imbalance of the chromosomes. In other words were there any consistencies in gains and losses in prostate cancer? So another advancement in the field.

And lastly is, we were comparing these samples to a normal database, moving away from a lot of studies that look at the same patient with time, this one were snapshots that we looked at a normal database. Those were the four things that we think advance the field of molecular diagnostics.

Bob Barrett: Okay, Dr. Mitchell, I would like to ask you about your approach in prostate cancer diagnosis. What's the advantage of your approach over PSA assay?

Dr. William Mitchell: The PSA has been around for decades and it is the subject of a lot of controversy about its value. The major problem with the PSA is that non-cancer events can increase the PSA levels, leading to high false positive rates. With the cell-free tumor DNA, one is only looking at what's coming from the cancer.

In comparing performance, the standard in the field is to use something called a Receiver Operator Characteristics, or ROC curves, and this statistic is used to compare a test by comparing deviations from zero specificity and zero sensitivity, which would be 0.5, and is referred to as the area under the curve.

So most clinical tests today have area under the curves that are greater than 0.7; and in fact, in one large gigantic PSA study with over 5,000 men reported in 2005, the area under the curve of prostate cancer versus no prostate cancer was 0.68. We show in this study that using cell-free DNA, the area under the curve is 0.92, directly comparable.

So if you set the specificity at 95% in the PSA, sensitivity would be around 20% versus the 73% sensitivity at 95% specificity; 73% you would see with cell-free DNA.

So the bottom line is that cell-free DNA is superior to widely used PSA tests for detecting prostate cancer, it's that simple.

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Bob Barrett: Were there any surprises revealed in this study?

Dr. William Mitchell: Yes, and that was the lack of correlation with a Gleason score. The Gleason score is a histopathological grading, it can only be done really by experienced anatomic pathologists who do this everyday. And there are deviations between the way that people compare them, but nevertheless, it is the standard for grading. The grading is Gleason score of 2 to 10, 2 being very low grade, 10 being very high grade or assuming with a high grade is aggressive.

And we saw no correlation in cell-free DNA and the prostate cancer patients, regardless of the stage of the disease.

Bob Barrett: Doctor, what are chromosomal hotspots in prostate cancer and do they provide any insight into the origin of prostate cancer?

Dr. William Mitchell: Well, we have demonstrated chromosomal regions of greatest instability that comprise less than a half a percent of the total genome, and in the top 20 regions were found in 12 chromosomes and these include both coding and non-coding elements.

Within the coding regions, we found 49 coding genes that are directly relevant to malignant neoplasia, but we also found non-coding elements. And in fact one hotspot contained no coding genes that suggest, at least to me, that this may be the origin of regulatory controlled processes in prostate cancer.

Bob Barrett: Okay, now Dr. Urnovitz, can cell-free DNA in blood be used to follow the efficacy of treatment?

Dr. Howard Urnovitz: The answer is yes. We actually showed at the 2013 ASCO cancer meetings that we were able to follow the efficacy in a low risk breast cancer cohort where patients only received surgery. And we showed that in 13 of the 16 patients that there was no cell-free DNA detected several weeks after the surgery, that's good, and that's what you would expect.

What was unexpected was that in 3 of the 16 breast cancer patients a few weeks later, we were able to see the continued presence of cell-free tumor DNA, which suggested to us that they had minimal residual disease. We will be showing more data next month that this also can be used in pancreatic cancer and it’s widely believed that it will be used on all cancers.

Bob Barrett: Finally, the focus of your study is chromosomal instability. Can chromosomal instability be used to predict response to specific cancer treatment modalities?

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Dr. Howard Urnovitz: The answer is yes. And it's exciting because this is really a great application of the human genome project, all these new machines in next-generation sequencing. Earlier this year, 2014 in June, again at the ASCO meetings, we presented data for both head and neck cancers, and colorectal cancers. the data strongly indicate that the patient responses to DNA targeting therapy including radiation, 5-fluorouracil (5FU), cis-platinum, were dependent on certain hotspots in certain chromosome instabilities. And more recently, again, we will show in pancreatic cancer that we were able to predict the treatment outcome.

So the upside of this, the opportunity, is the fact that we'll be able to now apply this kind of molecular diagnostic capability to no longer treat patients that won't respond, over treat or mistreat patients, and in doing so relieve them of the toxicity that it won't work. And secondly, reduce the cost of healthcare because you're no longer giving drugs and radiation when you know in fact it won't work. So this is a very important outcome of this type of approach.

Bob Barrett: That was Dr. Howard Urnovitz, the Founder and CEO of Chronix Biomedical in Göttingen, Germany. We also heard from Dr. William Mitchell, a Professor in the Department of Pathology, Microbiology, and Immunology at Vanderbilt University in Nashville, Tennessee. They have been our guests in this podcast from *Clinical Chemistry* on cell-free DNA technologies to detect prostate cancer. Their paper appeared in the January 2015 issue of *Clinical Chemistry,* a Special Issue devoted to Molecular Diagnostics.

I am Bob Barrett. Thanks for listening!

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