What Are Currently the Best Decision Markers for Biopsy and Re-Biopsy of the Prostate?

Author: E. David Crawford, MD

Categories: Biomarkers, Prostate Cancer

Tagged as: Future Directions in Urology Symposium 2015

Date: September, 2015

Dr. E. David Crawford spoke at the 16th Future Directions in Urology Symposium on Monday, August 10, 2015 on “What Are Currently the Best Decision Markers for Biopsy and Re-Biopsy of the Prostate?”.

E. David Crawford is Professor of Surgery, Urology, and Radiation Oncology, and Head of the Section of Urologic Oncology at the University of Colorado Denver (UCD) in Denver, Colorado. He is also the E. David Crawford Endowed Chair in Urologic Oncology at UCD.

Dr. Crawford received his medical degree from the University of Cincinnati. His postgraduate training included an internship and residency in Urology at the Good Samaritan Hospital in Cincinnati. He was subsequently awarded a Genitourinary Cancer fellowship with Dr. Donald G. Skinner at the University of California Medical Center in Los Angeles.

Dr. Crawford is a nationally recognized expert in prostate cancer. The recipient of more than 69 research grants, he has conducted research in the treatment of advanced bladder cancer, metastatic adenocarcinoma of the prostate, hormone-refractory prostate cancer, and other areas of urological infections and malignancies. He has authored or coauthored more than 400 articles, which have been published in such journals as Urology, The New England Journal of Medicine, and the Journal of the...
National Cancer Institute. He has published five textbooks. He is also an editorial reviewer or consultant for a large number of publications, including Urology, Journal of Urology, The New England Journal of Medicine, Cancer, and the Journal of Clinical Oncology. He serves as Medical Editor of Grand Rounds in Urology.

Dr. Crawford is an active member of many national and international organizations, including the American Society of Clinical Oncology, the American Urological Association (AUA), and the American Association for the Advancement of Science. Within the AUA, he is a member of the Committee to Study Urologic Research Funding and the Prostate Cancer Clinical Trials Subcommittee. He currently serves on the board of governors, the GU committee, and the scientific advisory board of the Southwest Oncology Groups, and he chairs the National Prostate Conditions Education Council (PCEC).

What Are Currently the Best Decision Markers for Biopsy and Re-Biopsy of the Prostate?

The title of my talk that I gave that they asked me to give at the EAU was what are currently the best decision markers for biopsy and re-biopsy of the prostate, which really gets into the whole controversy about prostate cancer.

My answer to the question was that markers which help determine which men have a cancer that would benefit from treatment and that’s very similar to what Michael Brawer showed yesterday that we said 20-some years ago about we want somebody to die of something else not prostate cancer.

In the next few minutes I’m going to define the challenge. We’re going to talk about PCMs, prostate cancer markers, and a very important way forward. This is all about a way forward to dig out of this mess, morass of the anti-screening that exists and interacting with family practice doctors and then also implementing change.

The U.S. Services Preventive Task Force gave us this very harsh message a couple of years ago screening gets a D recommendation. The key words they said here is physicians should not order PSA screening unless they are prepared to engage in shared decision making that enables informed choice by patients and that ain’t going to happen. That’s not going to happen with family practice doctors. What do you do?

I think there are a number of things and current needs. One is we need to refine PSA. We need to increase the probability of initial positive biopsy. We need to reduce unnecessary repeat biopsies by better distinguishing benign from malignant tissue. We need to stratify low risk from high risk tumors and the question is will PCMs, prostate
cancer markers, improve and the answer is yes.

We’re in this era of precision medicine, selection medicine, stratifying medicine, genomic medicine and personalize diagnosis and therapy. It this one treatment or one test does not fit all.

PCMs I mentioned this yesterday, a biomarker is a molecule that can be found in blood, tissue or body fluids that is a sign of a normal or abnormal process. Ideally it’s an easily accessible body fluid like urine or blood and tissue is also used as you well know.

There are really three buckets that the prostate cancer marker buckets. Who to biopsy and basically the king here is PSA but we also have PHI, PCA3, and 4Kscore. Then who to re-biopsy. Who to re-biopsy is basically PCA3 and ConfirmMDx and who to offer observational therapy. That is the Prolaris score oncotype Dx we heard about both of those yesterday and also we heard about Decipher and Prolaris yesterday in helping us in that decision.

The way forward I think we have to start with the family doctors. We have to define a PSA level with them that’s little risk and we need to identify who they direct to a urologist. Here’s the problem; we can’t educate family practice guys; they go crazy. We have percent free PSA, total PSA, complex PSA, we have PHI, we have 4K, we have age-specific reference ranges. We have PSA velocity, we have PSA density, and it goes on and on. We have PSA cutoffs of 1.5, 2.5, 4, and older. They go wow. No wonder. It’s also something that’s at the site of a lot of lawsuits.

Then who do they refer to and when do they refer to a urologist. I think the first thing we’ve got to understand is that the bulk of PSAs over 90% in the United States are ordered by family practice doctors, internal medicine, not by urologists. That’s only 6.1% or hematologist/oncologist which is 1.3%. That’s where the PSAs come from. The ways forward they need a simple message. They need something about PSA. We need to improve the performance of the test and find who doesn’t need to be treated and so forth and we’ll talk a little bit about that and we’ll talk about eliminating repeat biopsies.

What did we do? A couple of years ago we went to the Henry Ford database and we combed that database found 350,000 men in the system. We had some data from the PLCO trial about PSAs and we knew that somewhere between 1 and 5 we wanted to look at. We wanted to find a PSA level that was a very little risk within five to ten years of you having a significant prostate cancer. The median age we found 21,000 men eligible that had to have a follow-up of five years and no 5-ARIs and we set an initial PSA between 1 to 5. We have a high percentage of African Americans in there, almost 30%.

This paper was rejected by the Journal of Urology, it was subsequently published in the British Journal of Urology a couple of years ago and it won the best clinical paper of the year in the British Journal of Urology.
What we found was that when your PSA was less than 1.5 your relative risk of being diagnosed with a prostate cancer within 5 years was 0.5% and most of the time those were insignificant cancers. However in this zone of 1.5 to 4 your relative risk went up substantially. It was almost 10½% if you were African Americans and it went up almost 8% if you were Caucasian. If you look at there under the curve with that cutoff right here it’s pretty substantial with that PSA 1.5 as 0.82. A lot of the tests that we’ve been talking about don’t even come close to that 0.82 this was a cutoff. What’s the point here?

The point here this is easy for family practice guys to remember; less than 1.5 come back in 5 years, greater than 1.5 needs some evaluation. I think PSA should be treated like other lab tests lipids, electrolytes, things you do, weight, blood pressure.

Your family practice doctor doesn’t get informed consent to get blood on you for a cholesterol, for lipids, electrolytes. He doesn’t get it for blood pressure, weight. He doesn’t tell you if you have hypertension and I put you on the medication you may get dizzy and wreck your car. They take your blood pressure and then they talk to you about it. The same way with cholesterol drugs. The same way with PSA if its abnormal then talk to the person. What does that mean?

We looked at our prostate cancer awareness week database and we found out with men coming in their first PSAs and so forth in 150,000 men that 70% of men would require no discussion because their PSA was less than 1.5. So 1.5 is actually a surrogate for broader men’s health issues, BPH, prostatitis, prostate cancer, and so forth. I think the way forward is that PSA levels greater than 1.5 evaluate.

How do we improve the performance of the tests and find cancers that need to be treated? There are these new PSA isoforms already mentioned by Mitch Sokoloff. We have PHI, we have PCA3. This is a study that Dr. Shalken didn’t mention that we had done with PCA3. This is one with David Boswick with some 2,000 men where there was a very nice, and these were the first biopsies of men. This was a very nice linear relationship between PCA3 and the positive biopsy. 4Kscore, we heard about that already the value of this test and the 4Kscore is unique in that you find cancers that probably need to be treated, in other words, Gleason 7s and above.

I think that the third thing we want to do is eliminate needless repeat biopsies but don’t miss a threatening cancer. We know biopsies cause anxiety, infections, you miss cancers and then who to re-biopsy we have some help.

That was one of the criticisms of the U.S. Services Preventive Task Force the number of re-biopsies and what happened when you did that. this can be identified by the epigenetic field that both Wim and Chris mentioned earlier, the field effect that’s there that looking at these three genes that are methylated that help determine who is going to have a positive biopsy. As you well know this was dialed in for a negative predictive value to provide actionable information to rule out prostate cancer free men from undergoing unnecessary repeat biopsies.
There are a number of publications this was the latest one the DOCUMENT thing that Alan Parton did that looked at how ConfirmMDx fit there. It fits in previous negative biopsy, ConfirmMDx negative, life goes on. If it’s positive we heard Chris talk a little bit about that.

Here’s how I think we go forward. A man comes in sees family practice doctor. PSA is a routine lab that is done. We can set the guidelines over the age of 50 over the age of 45 maybe up to 75 or so routine PSA. Less than 1.5 a green light; come back in five years. Greater than 1.5 a yellow light; maybe refer to a urologist at this point. That would be about 30% of men. Or know what the next test is.

The next test might be one of these new PSA forums like PHI, PCA3, or certainly 4K and if they come back low risk then you back into the routine follow-up. If they come back higher risk, whichever test you use, then the patient obviously in the hands of a urologist will get a TRUS biopsy or at least an ultrasound because we know that a large prostate also produces PSA from BPH. Then if the biopsy is negative this is where I think ConfirmMDx comes in and if that comes back negative we know that there’s a 94% negative predictive value that there’s no high-grade cancer to 90% negative predictive value that there is not a significant cancer.

If it comes back positive this is where I think multiparametric MRI comes into being where you focus on an area and look for it and do targeted biopsies. If the biopsy is positive, Pattern 4, healthy person treat them. If it’s Pattern 6 or 3/4 that’s where your genomic markers come in. That’s where mapping biopsies come in and if it comes back high risk then you treat the patient. If these markers come back low risk then you follow them in active surveillance.

That’s what I think the way forward. It’s simple. It doesn’t have to be hard. Know there’s not going to be uniform acceptance of this. There are people who say I think cutoff should be 2 or I think the cutoff should be 1 or I think the cutoff should be 2½ and I hear that when I go talk to people. We’ve been saying that for ten years and we haven’t gotten anywhere. All we’ve done is confusion. We need a simple, simple, simple message for family practice and internal medicine so they go forward. I think in their heart of hearts they believe the early detection of prostate cancer helps. I think that will happen in academic centers.

The family practice guys are not seeing men anymore. What drove them in was their wife said go in and get screened for prostate cancer or go in and do this. I think you can argue this all you want I think that we are in a better situation now than we were ten years ago when the U.S. Services Preventive Task Force started studying this to look at who needs to be treated and separating diagnosis from treatment and not over-treating, not over-biopsying, things like that because we all know that if we stop screening or early detection as I prefer that term, we’re going to be back where we were a number of years ago if you completely ignore it.

The PLCO trial there was an arm where people weren’t screened and the result was
that was as good as people that were screened. There were some problems with the trial we overran the sites but when you separated out people that were healthy, and I did this with Anthony D’Amico and his biostatisticians group we found out there was a benefit.

At any rate going forward I think we need to re-look at this. With that I will end. Thank you.


prostate cancer markers (PCMs), decision markers, biopsy, re-biopsy, prostate

N/A