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**16th Annual Future Directions in Urology
Symposium**

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Welcome and Overview of the FDUS - E. David Crawford, MD

[START RECORDING]

E. DAVID CRAWFORD, MD: We'll go ahead and get started. I want to extend my warm welcome to the Broadmoor and this, our 16th Annual Future Directions in Urology Symposia.

This thing is often called the urology think-tank because it's an intent not only to discuss the state-of-the-art and various topics within urology and genitourinary diseases but also to follow up and discuss future avenues for research and so forth, and best practices along with us and the experts in industry.

This meeting actually started out in Colorado at Cordillera some 16 years ago. It was a prostate think-tank then. My good friend Frans Debruyne, who I'll introduce in a minute, was one of the people that have been through just about every one of these with us and many more of you have been to many of these also. We'll have everybody introduce themselves in a minute.

The idea was at that time to talk about where we are and where we should be or could be or ought to be in five and ten years. There was a lot in prostate so we did that for prostate probably for eight years all over the place and it really grew as a unique meeting where we would have interaction between physicians, scientists, and industry and have collaboration. At first there was a lot of concern about Company X and Company Y being together and talking about things and synergism. It turned out to be very productive, a lot of good friends developed over the years, concepts and some of the changing things that have happened on prostate really emerged from that. We go back everybody's all excited about the CHARTED trial and STAMPEDE and everything right now in prostate. That started with a lot of discussion we had way back some 15 years ago about the concepts.

Then we go into renal cell and the TKIs and all the excitement about that and bladder cancer and the excitement in bladder cancer has been up and down, mostly down, but we had some ideas about neoadjuvant chemo and other things like that, and bladder-sparing, and markers and so forth.

We incorporated that.

Also there was an interest in some other nonmalignant urological conditions such as BPH and things like that that were hot for awhile and did that and interstitial cystitis and fun things like that. It continued to evolve and we go with the flow of what's exciting now and what the tempo is and where we should be and that's one of the things that we really do want to talk about as we end each session; here we are, where can we be.

We've gotten a lot of advice from Mitch Steiner [phonetic] last year a couple years ago told us about the idea, very focused presentations to various companies and we did a little bit of an amalgamation of that and that's worked out.

The financial support for this is basically by the sponsors, who are listed, and we'll go through those. None of the faculty here are being paid anything. None of them got their travel paid. They get their rooms paid and that's it, which looking at the faculty here it really does reflect on quality of the people, their interest in what we're doing and those that have been here the rewards that have come from this. We do this along with a lot of camaraderie and cocktail receptions and sitting around talking and having lunches and so forth and it really is an extremely valuable thing I think and one that we are very proud of.

This is not a CME program. That creates some problems with some companies; it's got to be CME if we're going to talk off-label and things like that. It is an intimate setting we try to talk about, as I said, where we should be and opportunities and so forth. We have an Array system and we'll get to you in a minute. Brandon from Educational Measures will describe this in a second. It's a chance for you to interact, ask questions, take notes on slides. You'll get this all back and you can do it either with the iPads here or with your own device that you brought, your iPads, your computers and things like that.

All the sessions will be held here and we will announce where we're having the various social events starting with cocktail reception tonight. I think it's out by the golf course.

We also introduce state-of-the-art presentations from industry. We limit it to ten minutes. Bela, as you well know, and yes sir or you get cut off, and we are going to have discussion afterwards. That always turns into some I didn't know they were doing this or I didn't know this was in their pipelines or one thing after another. It is a lot of fun and I'll make some other announcements as we go along.

We have our bibliography with all our faculty listed here. As you can see there is extremely expressive along with all the participants are listed. We're sorry for the folks that we didn't get in at the last minute or changes or things like that.

There are two people that, as far as we know are not going to make it because of personal things that happened. Gerry Andriole is having family issues and called the other day and begged that he could not come. He's been a great contributor to this whole venue and sorry that's he's not going to be here but we've got plenty of people to fill in. Many times what we've done with people is have them call in.

The other person we're sorry about who, as far as we know, is not going to make it unless something changes, is Elaine Jeter. The reason that she can't make it is that she got called into federal court or something with what she is doing and she's going to get back with us here tonight or tomorrow to let us know where that is and may call in. We're very sorry to hear that.

One of the hottest areas in prostate cancer right now without a doubt is the thing we've seen emerge over the past couple of years has been biomarkers, genomic markers, PCMs as we call them, and prostate cancer markers. That's reflected in the numbers of presentations and the interest that we have. Dr. Lucia, we're very fortunate, Scott Lucia from the University of Colorado, who has been here many times, is going to be the moderator of this session.

Brandon if you want to come up and just come up and say a few words about Array we'll get going. After we do that we'll just have everybody go around the table and say who they are and we'll get started.

BRANDON: Good afternoon everyone. My name's Brandon, I'm with

Educational Measures and we're helping out with the iPad technology for the whole week. If you have any questions feel free to come back and poke my shoulder and then I'll help you out with that.

If you turn past the participant list in the catalog you'll see some access instructions if you want to use your own device and we also have some extra iPads if you don't want to use the technology through your own device come back and grab me; I'll get you your own iPad.

The key here is, it's an interactive technology. You're able to follow along with the presentation. You will also see there's some resource buttons over on the side giving you some information about participants and the faculty. In addition to that, some cool things that you can do with the technology. You can ask a question directly to the presenters and those questions will come directly to an iPad right up here. Don't feel hesitant to ask a question through the technology.

DR. CRAWFORD: We don't identify people unless they say who they are, we don't - - .

BRANDON: Those questions come in anonymous.

The other thing is if you want to take a note on a slide if you see a slide that you want to save and have emailed to yourself you can take a note function. I'll give it back to you guys, but like I said, if you have any questions feel free to come back and ask.

DR. CRAWFORD: Alright. Hear ye, hear ye let's begin by having everyone introduce themselves starting with Dr. Petrylak at the end of this table and just go around and go through the audience quickly. I know we've got a bunch of people still coming. Dan?

DANIEL PETRYLAK, MD: I'm Dan Petrylak Head of the GU translational program at Yale, I'm also co-director of the signal transduction program, and this is the 16th meeting I've been to.

THOMAS KEANE, MD: I'm Tom Keene, I'm from Charleston. I'm the head of urology at medical university South Carolina and I feel like I've been to all 16 - - .

FERNANDO KIM, MD: I'm Fernando Kim from Denver Health Medical

center. Been there for 15 years Professor of Urology. In defense of David Crawford for that time that's a lot of years.

TY HIGUCHI, MD: I'm Ty Higuchi from the University of Colorado also. My area of interest is genitourinary reconstruction and male urethral penile cancer so the unusual thing.

DR. CRAWFORD: We're rotating some of the older folks off so that's why we've got two of our younger—Kim's intermediate, he's the head of Denver health. He's done a lot with the AUA, Portuguese Urological Society. Ty, the same way, is an unbelievable clinician and researcher and we're glad to have him here.

WIM VAN CRIEKINGE, MD: Wim Van Criekinge Professor Bioinformatics and Epigenetics in Belgium and also - - . I will be presenting and show you some of our work.

DR. CRAWFORD: Wim and the person opposite, Jack Shalken are probably two of the most brilliant people I've ever met in my life and you'll get a taste of that. Scott Lucia is okay too. Go ahead Concepcion.

RONALD CONCEPCION, MD: Ronald Concepcion Urologist Nashville, Tennessee.

JACK SHALKEN, MD: I am Jack Shalken the Research Director Urology - - University of Nijmegen.

L. SCOTT LUCIA, MD: Scott Lucia, Professor of Pathology University of Colorado. I'm glad I haven't gotten old enough to rotate off yet.

STEVEN FINKELSTEIN, MD: Steven Finkelstein. I know many of you. It's nice to be here. It's my first meeting. I'm Chief Science Officer for 21st Century Oncology. Many of you know my background. I did surgical oncology at the National Cancer Institute doing fellowship in immunotherapy. I went back to school, picked up radiation oncology skills and now I do radiation oncology and run research worldwide for 21C.

DR. CRAWFORD: I don't know how many of you know that 21C, is how many radiation oncologists are in there?

DR. FINKELSTEIN: We have 700 physicians.

DR. CRAWFORD: Seven hundred physicians in their group. That

would qualify as a real LUGPA.

MITCHELL SOKOLOFF, MD: Mitchell Sokoloff Professor and Chair the Department of Urology at UMass, first time here.

MARC GARNICK, MD: Marc Garnick Medical Oncologist, Professor of Medicine at Harvard Medical School and Beth Israel Deaconess and Editor-in-Chief of the Harvard Medical School Annual Report on Prostate Diseases, which David has contributed very nicely in the past.

DR. CRAWFORD: Marc does this Harvard newsletter that does prostate diseases every year and it's really good. It's first-class. Marc is also the guy that we owe the LHRH agonist to. He was the guy that did the pivotal trial back in 1984 was it published? That's sad. There are people here that weren't even born then. That was the pivotal trial that got leuprolide started. We have another new person; Stacy.

STACY LOEB, MD: Hi, I'm Stacey Loeb. I'm a urologist at NYU. I specialize in prostate cancer but I'm actually speaking about social media so my other hat. I'm on the committees for social media for the AUA and the EAU so maybe I can inspire some of you to tweet at the meeting.

DR. CRAWFORD: Are you going to tweet about this meeting?

DR. LOEB: Thanks for the invitation it's an honor to be here. Yes, I already tweeted it about this morning actually.

[Crosstalk]

DR. CRAWFORD: Maybe I'll learn this whole thing about social media and that but other than that if you just look at the literature Stacy's already made a lot of contributions already.

[Crosstalk]

DR. CRAWFORD: Stacy has done a lot of work. She's on every journal now and she's done a lot of work with PHI which and the whole thing and many, many other things, screening and that. Dr. Gomella.

LEONARD G. GOMELLA, MD: Thank you. Leonard Gomella from Thomas Jefferson University in Philadelphia. I have a couple of unpaid jobs including being the Urology Chair for RTOG which is now NRG and also trying to keep Dr. Crawford

honest, which is a fulltime job.

FRANS DEBRUYNE, MD, PHD: I'm the most senior participant of all here; Frans Debruyne. You can ask all the details on my career directly to David but don't believe it because he's not going to tell you the truth. Thank you.

DR. CRAWFORD: A lot of you know Frans. Frans is being a little modest. Frans started European Urology the EAU and is attic I think, or basement, I can't remember which one, wherever the beer was, I forgot. The EAU quite honestly I've been to their last few meetings and I've seen it grow over the last 25 years as well beyond the AUA. The quality of the meeting, what they do. The European Urology Frans has been responsible for so many things that have happened in the world of urology. We're fortunate to have him here. The next person is-

J. CLIFTON VESTAL, MD: [Interposing] Your worst fellow.

DR. CRAWFORD: Oh okay. Thank you for saying that.

DR. VESTAL: You don't have to say it now. Cliff Vestal I'm in Dallas/Ft. Worth doing urologic oncology at USMD.

DR. CRAWFORD: Cliff, kidding aside, was one of my best fellows. He's moved around a little bit, academics and then down to Texas and he's in that very large group. I send patients to him; he's actually reeducated me in cryotherapy and a bunch of other stuff and so forth. The last person is Alan Cordell.

ALAN S. CORDELL: Hi, Cincinnati Ohio, general urology with a urology group. I'm a FOD, a friend of Dave's, from high school it seems like but way back in Cincinnati when Dave was there. Thanks again. This is my 15th year. I'm one of the old guys moving out I think maybe.

DR. CRAWFORD: We're still going to have you. We had George Drach talk about people aging and Alzheimer's. We'll find something for you to talk about.

Let's just go around the room quick. Everybody introduce themselves. Susanne Rodriguez.

MS. SUSAN RODRIGUEZ: Thank you Dr. Crawford for the invitation. My name is Susan Rodriguez, I'm the CEO of - - .

MR. STUART ATKINSON: I'm Stuart Atkinson the Head of Medical

Affairs at Tolmar Pharmaceuticals.

DR. BELA DENES: I'm Bela Denes from Genomic Health.

DR. CRAWFORD: Is that where you're working now?

DR. DENES: Still.

DR. CRAWFORD: I pull up Bela Denes in my phone there's a whole list of things. Gosh you've been there since the beginning; a long time. Congratulations. I kid Bela a lot. We have a lot of fun.

Congratulations Mitch on your new position.

MR. MITCHELL STEINER: [Off mic]

DR. CRAWFORD: Mitch has been to this meeting a bunch of times and had a lot of good suggestions. He ran GTX for a long time. Congratulations on your new appointment.

PENELOPE: Hi everyone I'm Penelope - - I'm the vice president product - - strategy at GMGX Biosciences. It's nice to be here.

MR. ROBERT DEN: Hi my name's Bobby Den. I'm Assistant Professor of Radiation Oncology and Cancer Biology at Thomas Jefferson University. It's a pleasure of working with Lenny.

DR. PHILLIP GINSBERG: Phillip Ginsberg newly appointed Chief Medical officer at MDxHealth. I've been there all of three weeks and this is our first FDUS meeting and I wanted to be - - .

MR. MICHAEL IMEOKPARIA: Michael Imeokparia, Senior Medical Director for - - at Ferring Pharmaceuticals and I've been with them about - - .

DR. PETER KNAPP: I'm Peter Knapp from - - practicing urologist and also cofounder of Strand Diagnostics - - security system.

MR. SCOTT MCGAFFIN: I'm Scott McGaffin, I'm President of Churchill pharmaceuticals first time attendee. - - .

MS. MICHELLE NOYES: Hi, I'm Michelle Noyes from Bayer Healthcare - - .

DR. MICHAEL BRAWER: Michael Brawer VP Medical Affairs, Myriad

and David Crawford.

MS. LAURIE CABA: I'm Laurie Caba, MDxHealth Director of Medical Affairs.

MS. ANGELA SPAIN: Angela Spain - - liaison for the mountain states.

MS. JODI CRAWFORD: Jodi Crawford. I'm the Director of - - for OPKO Lab.

MR. GREGG BERNIER: Gregg Bernier with Medivation Marketing.

MS. LISA SHAMES: Lisa Shames with Medical Affairs at Ferring.

DR. CRAWFORD: Let me just stop. Gregg you've been here way in the beginning long time ago, 10 years ago, right?

MR. BERNIER: Probably 12.

DR. CRAWFORD: This meeting was integral in a way for a job that he got too.

MR. BERNIER: It was.

DR. CRAWFORD: That launched his career to where it is right now.

MR. BERNIER: Thank you.

DR. CRAWFORD: I remembered that, don't worry.

MR. STEVE GALL: Steve Gall, Director of Sales for MDxHealth.

DR. CRAWFORD: Steve is an internationally known fly fisherman, ski instructor. He did that his whole life until he got a job with MDxHealth. Who else do we have?

CHRISTOPHER J. KANE, MD: Chris Kane, Chair of Urology UCSD.

DR. CRAWFORD: You belong up here.

[Crosstalk]

MS. TRACY MCGOWAN: Tracy McGowan, Janssen Pharmaceuticals.

DR. CRAWFORD: Walking in is one of our outstanding residents, Mike Masini [phonetic]. Did I get everybody else? Mark and Joe?

MARK: Mark - - President Educational - - .

MR. JOE GIGLIO: Joe Giglio [phonetic] - - .

MR. DAVID ERN: I'm David Ern I'm CEO of Carden Jennings Publishing and I think David this is our ninth year working together on - - .

DR. CRAWFORD: It is.

MR. ERN: We're the ones responsible for pulling all this together. Thanks for being here and thanks for your support.

DR. CRAWFORD: I'm going to turn it over to Scott right now to get started a half an hour late and it's my fault. But it won't be tolerated from now on.

Session 1: Biomarkers in Genitourinary Cancers - M. Scott Lucia, MD - Moderator

DR. LUCIA: It's my pleasure and honor actually to be a moderator for this biomarker session here. I remember the time when biomarkers was a single talk of about ten minutes snuck in somewhere during a meeting and quickly ignored. Now we've got a whole session and really it probably isn't even enough time for the biomarker work that's been done.

The first speaker today is Jack Shalken who comes by way of the Netherlands. He travels a long way to be here and share his expertise here. He was instrumental in understanding biomarkers long before the word biomarkers became a buzzword in medicine. With no further ado.

Featured Lecture: Basic Science and the History of Biomarkers - Jack A. Schalken, PhD

DR. SHALKEN: Thank you Scott and David. It's really a pleasure to be here for the so many-ith time. I've taken the liberty to make my talk as concise as possible because the goal is that from the lessons that I have learned with my team and with many other teams we can be smarter and swifter in bringing these biomarkers into your clinical practice. The subtitle that I have is biomarkers running the gauntlet because indeed if you're going to work in this field it can be a big pile of hurdles before you get to

where you want to be. Probably the first issue that we have is what I have always called the biomarker identity crisis and I "Freeley" adapted this from Descartes.

Many of us only start to think about the application of the biomarker halfway through. The best way so I mean for which indication are you going to do use this. The best way I can do that is to very quickly take you through the entire PCA3 case very quickly and then again show you how I think we can be much more efficient in the coming year.

This is the slide that we always have to give from David. This is where we are at this moment. Serum PSA with some clinical parameters, clear strengths of serum PSA, we all know them, but also clear limitations that will guide you to a rather suboptimal way to find the cancer, ultrasound guided biopsy, and then still with a rather suboptimal way of addressing the prognosis of that patient from whom the tissue was taken. I think we are halfway to where we should be in five years and the thing of course is that we are working with this golden standard, which at best I would call argentum, which is Latin for silver.

This I think is where we are going. New tools directly derived from serum PSA are available now. Wherever I put the thing in yellow I think they are going to be discussed at this meeting and I'm going to talk about the urinary biomarkers, the urinary molecular diagnostics.

Maybe a little bit more enthusiastic Europeans for multiparametric MRI but I think we all agree that in five or ten years we have to be much smarter in finding that cancer be it only MRI, be it molecular imaging. Then of course we need the optimal way to identify the most aggressive clones and determine the aggressiveness of that lesion. I think only then we will have the new golden standard.

You already see automatically the dilemma the tests that we are evaluating and making at the moment are being valuated against a suboptimal golden standard. In time we will learn whether these tests that I'm talking about today are in fact better or worse because the new golden standard should be there relatively soon I would hope.

That clinical unmet need that we need to solve has to be affordable and has to be desirable to let's look for that

clinical unmet need. I summarized that and I think for any biomarker project that you are going to run you have sit with your team at least an hour or two or three to clearly define this. This may be a truism at the moment but the risk for PCA3 we never started in this way. We need something that can be obtained with minimal invasiveness, preferably noninvasive, and it should ideally be suitable early in the diagnostic triage because I think the most great presentation from David at the EAU this year in fact the gray zone for serum PSA is not really 3, 4 to 10. It starts at 1.5. We will discuss this. Therefore in that particular area where we know that PSA needs aid I think that's where we have to focus. If each and every biomarker with this indication would have been developed that way I think we would have saved quite a lot of time and money.

PCA3 I cannot believe in all my modesty that people are not aware about PCA3. In fact it's almost 20 years ago that the project started. More than 300 publications and I still think at the moment the positioning of PCA3 is not even mildly wrong; it's completely wrong.

It was cloned with old-fashioned technology. Old-fashioned technology does not mean that it's poor technology. Its long known coding RNA that took Bill Isaacs, myself, and Marion Bussemakers three years to get this published because genes from this side cannot encode just an RNA, another protein. Arule Genian [phonetic] this year did a full genome mapping of non coding RNA in the human genome. There are 63,000. Almost three times as many as protein encoding genes. This is what I would call the bias hurdle amongst reviewers which is quite common.

In 2002 I wrote my inaugural lecture for Nijmegen when I was appointed as professor in Frans' department. We put forth this concept of detecting cancer cells in urine, we called it molecular uroscopy, and within the year we had proof of principle. The license was taken by Genprobe and the tests came on the market in 2006 in Europe, probably around the same time as LDT in the U.S. and finally the completely wrong indication for the use for repeat biopsy was obtained here.

This is pretty much the situation that you're all very well aware of. A man of 50 gets a PSA, the dilemma what do you do, send him through the hospital, give him a biopsy and

only when you find no cancer you go back to do the repeat biopsy and this is exactly where the urine test PCA3 was positioned. Already from 2005/6 onward there were studies doing it before the first biopsy. Nobody even attempted do to a study with GPs with low PSA values and there is, amongst the 350 papers only 1 paper that systemically looked at the urine tests in the low PSA range and then again in a very strange population of men that got their fourth round of screening in their SPC. I think this is exactly what we should change with the new biomarker panel.

PCA3 was not developed as a prognostic biomarker. Five patients without cancer were compared with five patients with cancer and PCA3 came out as a very strongly upregulated gene. The axis that you see here is a logarithmic axis so in fact what you see those values are on average 60 times higher in the cancer when compared to the normal tissue.

The thing that you see here from left to right is a normal prostate BPH, low-grade cancer, high-grade cancer, CRPC and metastases. There is an adverse - - it's in PCA3 that the more aggressive the lesion gets you find a number of dropouts. If you would look for an ideal profile you would not directly take PCA3 and with that marker we have used for many, many years now.

We said taken all these lessons in 2008 or so we interested a company in Nijmegen called - - to do everything again in the right sequence with the right design and this is in fact what we did.

Profiling with at that time state-of-the-art technology the Affymetrix array an independent validation of the hits so a selection of the hits on P value and full [phonetic] change, an independent validation in another tissue set and from there we took eight candidates to a clinical trial. With very little threat of over fitting the dataset we thought this was an optimal design and this where we came up with three new biomarkers. This is the way of finding those progression markers again, from left to right, low malignant potential to high malignant potential these were the type of biomarkers that you were looking for. This is more or less how they were selected.

This paper is published just a couple of months ago so you

can read everything. We have eight new markers. Initially we do the urinary sediment as a substrate, PCA3 obviously is a comparator, and as the endpoint we boldly took not cancer, but clinically significant cancer, and that's how we calculated our diagnostic accuracy.

Here you see a complex dataset but you see that the algorithm that we have and the way we do this is very efficient. You see almost all of the eight candidates that we selected through the second round of validation had a good diagnostic potential but we were not interested then. We were more interested in the prognostic potential and then you have to look at the left slide here and look at this lane over there. How well are they in separating Gleason 6 from Gleason 7 and higher? This is pretty much what we knew that PCA3 would fall through.

In a cartoon this is in the area under the curve that was we derived from there that is the one but last a figure from that table. I will show you the validation data in a minute. You see that the three gene test we gave it a project name QUATTRO because they're all normalized for messenger RNA for KLK3 so it's just a project name. You see that it's superior to PCA3 and if you combine it with serum PSA you find in that its value.

We always have chosen so far to really purely at the one test before we are going to combine everything to take advantage of the other parameters at the right time in our development process.

This is the one slide that you may need to take some time to look at it. The black bar is the area under the curve for the QUATTRO test and then look at it per PSA category. Obviously we know that the lower the PSA value the lower the accuracy of serum PSA as a prognostic marker for identifying patients with high-grade cancer. You go close to 0.5.

The unique thing about the urine test and the way of selecting the biomarkers is that in the low PSA ranges the diagnostic accuracy of the four gene test sustains and that gives us the confident feeling that in the low PSA ranges the added value of the test probably lies.

There is only one proper way to test that. A couple of things had to be done. From here it's hard work and little

science. You have to go from a research test to a LDT test that can be run in the CLIA lab, and in fact for Europe the company went through the procedure to get a CE-IVD registered and that happened just last week. This is not a research test that one person can do at the right day at the right time in my lab. This is a routine test that can be run in any molecular diagnostics lab with the right equipment.

Very simple, just like with PCA3 - - and after DRE once the - - isolation of nucleic acid and straightforward come PCR.

You can do many, many statistical tricks on your initial study and we did them all. Of course the logistic regression analysis, the bootstrapping but the most convincing step is always an independent validation study. We're going to submit the manuscript this week and I can just give you a very brief preview at the validation.

It's a fully independent validation study within validation study preset values for the QUATTRO score assay. This is probably the only way how you should do it. 901 is the study I presented first. Let's - - the test cohort at the given lower risk threshold with the highest NPV we evaluated 1201 and it is virtually identical as you can read from those figures. The 92% sensitivity have a similar specificity in a totally independent cohort.

We all know that the dependent on the clinical question you have and where you are in your decision triage you say also want to go with certain patients for a high PPV so we took a high PPV level at 15.5 at the specificity of 90% you see also pretty much similar sensitivity so there is a value at which you can predict with more than 50% accuracy that there will be high-grade cancer. This is the validation study the ROC where again you could confirm that it was superior to PCA3.

Here you see by Gleason score the QUATTRO score if you compared no prostate cancer to Gleason 6 to Gleason you see significant P values between the groups. If you do this for PCA3 in this cohort it will only be significant between normal and the remainder of the group and you see that also in the independent validation study. Once again, test cohort and fully independent validation study.

The clinical utility would be that if you take that low

threshold value with an NPV for clinically significant prostate cancer at more than 90% you could save 35% of your biopsies.

The conclusion is that I think in a very well-designed way we've come up with an improved urine test to predict biopsy outcome particularly significant cancer. I think we need to carefully evaluate this also with the new golden standard. We are quite proud to have the tests included in a big study from Yela Baron's [phonetic] multicenter prospective study where multiparametric MRI and ultrasound guided biopsy will be taken.

The thing that we need to discuss here is what type of a risk do you accept when you are going to use a test in the PSA range of 2.5 to 10. There's no doubt if you are going to take that population of 2.5 to 10 if you are going to say 35% of those patients are not getting a biopsy you are going to miss a small group of significant cancers and the question in terms of acceptance is to discuss this openly what you would accept as what I would call a state-of-the-art risk profile. My starting point would be that the state-of-the-art risk profile that you have at the moment serum PSA you could derive that from PCPT. If you meet that you would say that would be one step further.

I think it's important for the design of studies where you're going to use even lower PSA values as inclusion criteria.

Thank you.

DR. LUCIA: Thank you Dr. Shalken.

We will have time for discussion and questions after the next speaker. I'd like to move on to the next speaker right now, Wim Van Criekinge comes to us from Belgium. I think you will find that his viewpoint to be particularly refreshing.

Featured Lecture: The Future of Biomarkers in Prostate and Bladder Cancer - Wim Van Criekinge, PhD

DR. CRIEKINGE: The future of biomarkers in prostate and bladder

cancer, again my background is single transaction professor in bioinformatics and epigenetics so it's a little bit coming from a different angle but I hope to get you excited about what epigenetics can do and I'll provide from my perspective what I think is going to be future avenues for biomarkers in general and then apply them to prostate and bladder cancer.

A little bit on epigenetics because I think it's interesting to open your perspective a little bit on what I can do, why we apply it in oncology, and why it's so heavily used and it's only limited to that field but I'll hope to give you some insight in that then again some future perspectives.

Epigenetics as a textbook definition, pretty sure you are aware is you want to be able to activate certain functions in a genome and that you do without changing the primary sequences. I think the way I usually explain is it allows you to do multiple things with one genome. All the cells in our body have the same genome yet they do very different things. Most of that is driven through epigenetic decisions. It also allows to us integrate environmental signals which is another very important aspect of studying epigenetics.

This is the molecular biology behind it very quick, histones small protein complexes are winding DNA around it. People initially thought it was a passive process to fit the long stretch of DNA into the nucleus. It turns out that the decision to wind it or to be able to unwind it is defining what is active or non-active. It's a very important decision to make for a cell.

It's very complicated. This is a recent picture showing that the histone code is more than what's happening on the DNA level so you see the various stretches of histones here with all their modifications. I typically call it a molecular foreplay. This is what happening before you decide whether a gene is active or not. Once the DNA gets methylated at very specific sites it is decided and irreversibly committed. This is what it usually does in a normal functioning body it results in defining the different tissue. Actually when you think about it the tissues are defined by all this epigenetic decisions and it's maybe one of the underlying features why we treat all

the different types differently. If it would be only genetic in nature you would expect that different solid tumors would have a similar treatment regimen. They are very different because the underlying epigenetic landscape is extremely various. Another thing is that you can define pluripotency by reprogramming a few epigenetic factors actually four genes give you pluripotent cells. I also want to point out is that people are now working and we are also active in the area in terms of differentiation so trying to differentiate cells in different states without going over pluripotency so that's a very active area of research.

This is the one which I want to get your mind on is monozygotic twins are an ideal model the check what is genetic and what is not genetic. These are diseases which are shared between identical twins which are the white bars. The gray bars are fraternal twins. What you see on the left-hand side are all CNS type disease which have a very big genetic component. On the right-hand side you see diseases which are not shared between identical twins so which are by definition less genetically defined and you find diseases as RA, stroke, Crohn's, and there is cancer. Cancer very early on when you look at these concordant monozygotic twins was identified as a disease with a genetic component which we know with a very big epigenetic component.

Cancer, again, this is which everybody has so I had to have the Weinberg there with all the essential functions that are known to be inherent in different types of cancer was known to be impaired by genetics. We studied ten years ago the relative importance of genetic and epigenetics. That's what seen on this graph. We did this together with John Hopkins and - - did exome sequencing before it was called exome sequencing and they looked for cancer genes. Cancer genes are actually very infrequent. If you look at the frequency of mutation it's 10% roughly across all these cancer genes. For some of those genes you see that they are impaired by methylation, by epigenetic regulation. What this tells us is that if you need to knockdown essential functions, essential pathways the best way to do that is to use the endogenous mechanisms of methylation in the promoter and making sure the transcription is not occurring any more. That's what primary cancers are doing

a lot.

This is how we can use it as well. If something is very prevalent it's potentially a good diagnostic marker. If something is less prevalent it might make it as a companion but that's a whole different story which I will not go into today.

Next generation epigenetic biomarkers I want to give you a flavor of what we do and then apply it to the two fields and what the field has been doing and what we've been doing in many different settings.

I'm going to go a little bit faster over this because I'm sure you're familiar. There is a compound called bisulfite which you can use to treat DNA and depending on the methylation status it's going to be conserved as you see, the red ones, or it's going to be converted by deamination reaction into a uracil. By being clever in the design of primers you can exploit that being a primer design is going to hybridize after the bisulfite treatment, you're going to see a PCR product that is going to be inferred indirectly that it was methylated or not methylated. That has a lot of advantages which I'm not going to go over. I'm sure we can ask if people have questions on that.

The last five to six years we know that sequencing is everywhere so we and others have published a lot on employing next generation sequencing methods to do exactly this. Can we look at epigenetic signals in a genome-wide context? We've been looking at different enrichment strategies and as pointed out before, 60,000 long non coding RNAs we see roughly 3 to 4 million regulated sites in the genome so there is a lot more happening than purely the 25,000 protein coding genes. We have also panel strategies; we have deep sequencing strategies which are all based on next or third generation sequencing.

If you put it a little bit in perspective, and then I'll come to the practice in prostate and bladder, is you can look at a full genome or you can look at a single base pair on the right-hand side. There is methods in genetics, there is PCR, there is whole genome sequencing and they're all equivalent from an epigenetic point of view. Epigenetics we also can do whole genome sequencing, we can also do PCR, we also have different vendors of panels,

enrichment panels, and different types of technology.

There are two things we see happening. First is that the research is moving into the clinical space and secondly, we see a lot of people that are starting to combine epigenetics and genetics. From a biomarker what we can expect in the coming years to come out is people looking at panels from different angles. Wide span foundation one, I don't know 500 genes or 600 genes. It's a significant amount of money and some of those genes are wild type but regulated by epigenetics. A lot of that panel is prone to epigenetic methylation so doing both sides of the coin is something we see happening a lot.

Now I want to switch to the applications in urology and prostate. I'll be quick and confirming the X probably people are familiar with that. It's been a story that's been building up with medical studies, with a key clinical study, the MATLOCK study which was published in 2013, a document study. This was all geared towards negative predictive value so this is all using leftover biopsy material and excluding that there is going to be cancer found upon repeat biopsy.

This has been a significant amount of work and approached from different angles. There's also a clinical utility study and some economic studies as well.

This is basically what it comes down to. If this is the prostate you take core samples and you might miss the cancer. But there is this, what we call, halo or field effect where if you take this core you might be able to detect an epigenetic change while there is no cancer there to be detected through a microscope. The field effect is something we're leveraging here with a test.

This is the basic layout; negative biopsy but reasons to suspect there is something you can do the test. If it's negative you can avoid repeat biopsies.

What we've been doing is digging a little deeper into the data because everything was geared toward negative predictive value. One of the things we've been doing is can we also look in that residual tissue and that assay data we have to see if we can discriminate as pointed out before, between clinically significant cancer and indolent cancer.

The basic strategy we took there is we said more genes that are methylated is probably bad news and more cores that are positive is probably even more bad news. We tried to make a way to score it by informatics approach where we measure the methylation intensity and see if that can be a risk calculator for the presence of clinically significant disease.

This is exactly what we see. Negative repeat biopsies have lower methylation intensity scores and if you have clinical significant cancer as defined by the current gold standard which might not be gold, but fine, that's what we have, we see that the scores are higher. It's intuitive but I's leveraging more from the data what we generated before.

We can do a little bit more. We can define also or include in our model classical factors, PSA, in this case as a continuous variable but a logarithmic version of it, DRE, histopath, we can take all that into a score and come up with a better classifier. In this case there are other risk scores. There is the NCCN, there is the PCPTRC2, and you see they take into account different types of information, demographics, clinical and molecular scores.

We've been doing this and we've been comparing ourselves to the other risk factors and that's what I have.

The next slide we will see if we do the multivariate analysis that the classical ones like PSA is predictive for clinically significant cancer but with a similar odds ratio than a TPR but way less than the odds ratios we see if we integrate this methylation intensity signals.

This is an example, just to sharpen the minds a little, this is on the first biopsy which is negative, all the different contributing factors give you a very high epigenetic health index and indeed that patient came back months later and had a Gleason score 8 - - so we gained a little bit of time there on being able to detect it on the first biopsy.

That's summarizing where we are. In prostate you do the test. If it's negative you can avoid repeat biopsies. If it's positive you can apply a risk scoring algorithm which we compared then and you see the different area under the curves.

I hope I have a few minutes left for the last one which is bladder epigenetics just to show that this epigenetic mechanism is something we've been doing in other solid tumors but I will only share here where we are in bladder. That's why I spent a little time on the epigenetics that it's not confined to prostates.

We published, in 2010 a study where we found two markers TWIST and NID which were found to be bladder cancer specific. I'm not going to go into the details on how we found them. It came out of a very different discovery approach than what people are doing these days. It's using inhibitors of methyltransferases and measuring differential expression. They came out. Many people since then have used these markers in other studies so they've been published on by other groups and they've been shown indeed to have very high odds ratios to be associated with bladder cancer.

Nevertheless since 2015 if we look TWIST and NID as detection markers from an epigenetic point of view there is a lot of other stuff happening. It took here the liberty of looking at all markers that are published from an epigenetic point of view, genetic point of view, interesting there is overlap, some genes are regulated by both mechanisms. There is a lot happening. What we set out by ourselves is given this complexity and landscape of molecular markers is for a clinical application following hematuria who has bladder cancer what's the optimal panel.

The study we did we looked at a subset of markers which we knew had a very high chance of making it, set up a case control study in 160 patients and set out what is the best possible marker. In that case we are leveraging a lot of research and papers and data that is out there and we combine also genetics and epigenetics. This is the model that came out of it. The model is very small; only a limited number of molecular markers. It has a very high negative predictive value and you don't miss clinically significant bladder cancers which are the higher stages or grades. Very sensitive model. That's basically where we are. We have submitted this. We are currently in debating and reviewing and it going to come out very soon.

In summary a very limited set of markers and that's a big difference with for instance expression. Two or three

markers we can get away. It's a - - , that's how we've been doing our clinical study here and it's something we are exploring in other backgrounds like the potential in recurrence monitoring setting. That's what I have.

Discussion

DR. LUCIA: Thank you. This is a time for a discussion. In the discussion we can also have question directed to the speakers but also a general discussion of what you've heard so far. We've limited what we saw today so far into the diagnostic world but there are other means of biomarkers that we should be thinking of prognostically and even predictive markers that might come up in conversation. Do we have a traveling mic for the back? Great. We've got one right here. Dr. Kim.

DR. KIM: - - precedent for us clinicians but one thing that I've never understood very well is that there are more than probably two decades of markers in terms of blood markers, urine markers, tissue markers and particularly you Jack, you have such long history of research in all this. If you had an aptamer a sequence that you can—and that's not considering tertiary or quaternary design, but you had not an RNA driven aptamer, a ligand that you can target an aggressive cancer what would that be? DD3? PSMA? Let's say you have the ability of getting a sequencing of - - target prostate cancer cells, - - because RNA protein will be probably metabolized after the first pass so a DNA makes more sense in going there. What would be that target? Knowing all that you know about the biomarkers and while thinking, I'm just trying to understand myself what's the relationship between apoptosis and methylation?

DR. SHALKEN: The first one is a tough cookie because it's a methodology that you describe by itself which still the effectiveness of the methodology is still suboptimal.

DR. KIM: I just asking because I'm going to present something that - - in our lab. I'm trying to learn.

DR. SHALKEN: Certainly the studies I have presented were not designed to even come to a conclusion on that aspect. The one thing that we learned on using urine is that probably the most important effect is that at a certain volume or at

a certain aggressiveness cells start to coming to the prostatic ducts and shed into the urine. We never could understand why PCA3 would be a progression marker because it's pretty much the same level and the ones I mentioned were more selected as being a progression marker. I find that relatively difficult to answer at this moment. I'll -
- with your discussion tomorrow.

DR. KIM: I was just thinking about PSMA. Is there anything you can comment about that because you used to focus so much on that?

DR. SHALKEN: If you do the profiling PSMA will always come up as again, a good cancer marker. The thing is that it's remarkable if you go look at Gleason 6, 7, 8, 9, 10, they go mildly up and it's a very heterogeneous disease. I think if you, because you're talking a little bit more also about the molecular imaging I think we may need different approaches there.

Wim is the expert on methylation apoptosis.

DR. VAN CRIEKINGE: Apoptosis is one of these pathways that you need to knock down because otherwise the cells will eliminate themselves and wouldn't sustain themselves. Quite a few of the key enzymes for instance in the BCL2 family from the intrinsic apoptotic pathway are very heavily methylated. I think one of the first things we assume is that the DNA repair gets methylated so the repair enzymes are off and then you start accumulating genetic changes.

DR. KIM: When you do Fox [phonetic] or anansin P [phonetic] or Tono [phonetic] how do you describe it? We see an array of new technology coming out and how can you define a very good apoptotic reaction and then define methylation? If you want to describe a good way of getting primers so you can get - - .

DR. VAN CRIEKING: Probably - - or all the other functional apoptotic readouts are superior but they're just going to be linked pretty heavily to the BCL2 members that are methylated. Probably one of the things you could do is use a methyltransferase inhibitor to see if your functional apoptotic readout is going to give you a differential signal. That's one of the things you could do.

DR. LUCIA: For you that have the pads in front of you there is a possibility to ask questions through the pad and if you look down at the lower left hand it says ask a question. Please encourage you to do that if you'd rather do that than raise your hand. I've gotten a couple of questions here. One of them is almost verbatim from a question I was going to pose and that is what is the future do you think of tissue-based tests versus a blood or urine-based test. Do you think we will still need tissue-based tests? Where are you with those concepts. To our two speakers.

DR. SHALKEN: I think that's why I put this triage in there. The noninvasive tests should be useful earlier in the disease and you should take that in your design I think it will be pretty optimistic to hope that all the information that you have will be in that urine because it's a mixture— if you what ask me what percentage of the cells in the urine are cancer cells I could not really answer that question. Most of the RNA is not in the cells but in the exosomes and the proteins so it's really a big mixture of cells. For me, in my way of thinking it may be a very simplistic, pragmatic approach. Blood and urine in the cascade and once you have tissue add to what you already give the Gleason grading and then get the - - information because you could even say I want to have that information from this area of the tumor. I think it's like increasing complexity. The price will increase and increasing information so for me they are perfectly complimentary.

DR. VAN CRIEKINGE: Yes, I totally agree so blood and urine earlier for sure because it doesn't make sense that you need tissue for a detection test because then you have the tissue already you know there is an issue. That doesn't make any sense.

For prediction prognosis probably the best material is at that point the tissue.

DR. LUCIA: I think of the array of limiting steps that is probably a big lion in the room that no one's really addressed is how things are handled. When we were coming around to really understand how tissue is handled affects the way biomarkers behave. There was a very unfortunate thing that happened at the NIH that made the news about ten years ago where there was an ovarian test and they looked at a prognostic factor in the tissue that looked at

prognosis of ovarian cancer and they published on it. It turns out, to make a long story short, that it was the way the tissue was handled that they were able to get a marker for it. They actually showed a marker for having that tissue sit on the table for an hour rather than really be a cancer marker because the cancerous tissue was handled completely differently than the benign tissue that they used for that. We have to understand that we've got to get to some kind of regulation on how we handle these things. Pathologists, me included, need to be sat down and said there is a way tissue has to be handled if we're going to take tissue biomarkers seriously. I'd prefer anyone else to chime in on that that would like to.

DR. DEBRUYNE: Maybe I can comment quickly on that Scott because I think it's crucial and when I talked about the last year and a half - - that LDT to a CE-IVD I mean 80% of the times its designing the fixative, doing what I call the cabinet of pathetic experiments you take the urine, you let it stand for one hour, two hours, three hours, four you see how the pre-analytical handling influences the test result. In fact, for making a test that is one of the essential things so you're absolutely right. The example you're referring to is also a typical example of over fitting dataset.

DR. LUCIA: Right. We're guilty of doing it because we want to write papers and make a big splash but we've got to be careful with what we're handling and what we're reporting on. It's not just a numbers game. It's also really handling the methodology as well.

PCA3 where does it fit today?

DR. SHALKEN: It's very quiet. Most of the things that happen on PCA3 are even beyond my view and I think they're not a scientific nature.

If I may bounce back one question because we were going to talk about phi, we're going to talk about OPKO 4K, I talked about PCA3, and I talked about the QUATTRO score. All of the four say that in a population that you, the urologist, must use to do a biopsy, you recommend that you do not have to do a biopsy so you get this risk question. You take a risk. Can anyone give me an idea what kind of a risk would be acceptable to you or to your patients because if you say

we don't accept any risk—

MALE VOICE: A hundred percent.

DR. GARNICK: The problem is from the medical/legal circumstance and you're got a low QUATTRO score and you've got a PSA of 8.8 and you decide not to do a biopsy and the patient turns out not to be in that category that doesn't have cancer, you've got major medical/legal issues from the primary care physician and the urologists that interprets that data as such. That's the issue so—

DR. SHALKEN: Why would PCA3 with roughly, I would guess, 700,000 tests that treat that you're posing has never resulted in a case like that? I mean 700,000 tests have done, many biopsies have not been taken also so is this a kind of a ghost that we are putting forward or is this—

DR. GARNICK: No. The issue is having an abnormal PSA for which you don't act on that then turns out to be positive.

DR. SHALKEN: That's a good point Marc/k but the thing if you look at PCPT Ian Thompson [phonetic], Scott's data on the pathology; we also know that PSA of 3 has a risk of significant cancer. If you go between 2 to 3 it's even 5 to 6% so there you also have the same thing even though you say 3 is the threshold you know that's 6% risk of significant cancer you also don't do a biopsy. I think this is a very difficult issue that we have to get around.

DR. GARNICK: It's very difficult.

DR. CRAWFORD: When you talk about an elevated PSA last week I spent five hours on the stand in Omaha defending a urologist who had followed PSAs over six years on this 67-year-old guy who wasn't in great health that went from 1 to 1.9 to 2 down to 1.6 up to 2.7 down, it was a saw tooth thing, and then it went from 3 to 9 in one year and he had Gleason 9 metastatic disease. I'm talking about normal PSAs, NCCN guidelines said that if PSA goes up greater than 0.35 per year, not 0.75, 0.35 per year that it's a harbinger of high risk for aggressive metastatic disease in 10 to 15 years. This whole case was based on this. If you ask a hundred urologists would you biopsy somebody like that? The whole medical/legal thing is a joke. The other thing is we have to be extremely careful about what guidelines are and what people say are important things

because they get in court that way.

DR. GARNICK: I can tell you that within the Harvard medical institutions 35% of medical malpractice is based upon cancer and within the cancer domain failure to act upon a PSA velocity is now becoming the single most reason for Harvard physicians getting sued by patients. Even though the PSAs - - normal.

DR. SHALKEN: I think there you both have a very good point because that means that—it's varying philosophies where you would come in with a need for a new test because you have this dilemma there.

DR. KEANE: PSA velocity that has been shown not to be particularly useful in numerous publications.

DR. CRAWFORD: Correct. You tell that to the plaintiff's lawyers.

DR. KEANE: You're stuck in a situation where people don't get one PSA. It's basically the overall performance as you look at it, is it steadily going up or as you said, is it a saw tooth pattern, do you look back if the guy's had a biopsy, has he had prostatitis, does he have BPH. They're also compounding factors. People look at this and they grab this one thing out of the literature and say this is malpractice. You need somebody like David or the rest of us here to defend that stuff and we need to be very vigorous about defending it because we're the authors of our own destruction by putting down things like PSA density, it's irreparable. Definitely. Hang your hat on that. You can't and you can't hang your hat on nearly everything that's out there.

[Crosstalk]

DR. CRAWFORD: - - question about the ConfirmMDx. How often has an abnormal epigenetic profile led to the diagnosis of an anterior tumor in a patient that's had a negative biopsy before?

DR. SHALKEN: I cannot answer that off the top of my head because I don't have the location of the tumor. The original one is more MPV so it's not about—

DR. CRAWFORD: [Interposing] Does anyone from the company have that information?

DR. KEANE: Are you asking how far away from a biopsy - - is the area that you can see the abnormality? Anybody know that?

DR. LUCIA: I think there are two parts to that question. It's not only whether the tests can locate and pick up an anterior tumor it's whether or not the urologist does something different when they go into biopsy the second time after having that abnormal tumor. If you do the same thing over and over and expect a different result-

DR. KEANE: If you did get that and want the positive test you would then do a focus biopsy.

DR. LUCIA: We would hope.

[Crosstalk]

DR. CRAWFORD: The problem with that is how many times do you see when you do biopsies and then you do a radical and the cancers on the other side that has a nodule and you do a biopsy and the nodule is negative but the biopsy on the other side is negative. How many times have you, as a urologist, fallen asleep at the switch when you're doing biopsies and talking and forget where you did it and which side. It happens all the time. That's the problem with the targeted biopsies I think.

DR. LUCIA: How do you get excited for ordering these tests with the current trends in prostate cancer screening especially when you're dealing with primary care physicians?

DR. CRAWFORD: I don't think we have time to answer that one.

DR. VESTAL: Scott, just one comment at a clinician. One is you've got to assume that the PSA never ordered for any of this to be germane. That's the big problem we're coming into right now is we're seeing advanced mets disease. One of the premises of the meeting is what's going to happen to clinical urology in the future and what I hear from you two guys is that these tests are almost ready for primetime not only in prostate but in bladder as well. For the urologists that actually practice out in the community and at the universities how do you see these tests changing the way you do things? With the urinary test I can see a time when we don't do cystoscopies because the urinary tests are negative. Is that something that we're looking forward to in the future? As practicing urologists will this change

what we do ten years from now?

DR. CONCEPCION: Cliff, all that would be blasphemous to say I'm going to order a test where we're not going to do cystoscopy I tin if you're living in the world where you're going to continue to believe it's going to be fee for service then you're right that would be a blasphemous statement. I think we all know that that's not the way the government wants us to go. They want us to go to disease management, the want us to go to episodic care. They're looking for bundling and I would say that as the field of urologists we have to position ourselves to better manage these patients whatever these payment reform models look like. To have a test that actually can be more predictive and yes, it may be less cystoscopy, it may be less biopsy but we need to be positioned to be able to take on that risk.

DR. LUCIA: Fernando you have the pleasure of a health system taking care of the patients in Denver. How do you see these tests affecting how you?

DR. KIM: I'm not optimistic. I'm part of the AOA quality assurance and just writing the patient safety issues in surgery there's just a note that is under ethics and the reason why I'm saying all this is because there's meaningful use. I think Raoul is so right. It doesn't matter what we find in science. It's going to really take a big deal of political, what Tom said is a lot of leadership, number one, about how we deal first of all with all the issues with screening; number one. Second, fee for service just basically the most vocal advocate of the ACA was insurance companies to really put the landscape in a very low budget. The third most important thing that I see is how that market place in the federal and the state government really will translate. Your practice will be different than mine I'd bet you.

We're just publishing a study in a healthcare magazine journal. We saw all the states that were pre-ACA and who was red, who was blue and also the socioeconomics. I'll tell you it wasn't about being blue or red it was about having money in the state or not. Colorado, Hickenlooper put a lot of money and put a state marketplace so we had the infrastructure to do that. All these great things we're talking about it may help in the long future. I hope

not, but unfortunately in our country I think we're going backwards. Science is progressing but the socioeconomics and politics are just basically tamponading our practice.

DR. KEANE: It's even more basic than that. It's teaching the GPs that if a man presents with gross hematuria you shouldn't give him an antibiotic and tap him on the head, which is what happens with most of the men who present with hematuria for the first time.

DR. LUCIA: Cliff and I were talking about this slide that Wim showed that showed 99% negative predictive value, 97% sensitivity and that's as good as cystoscopy isn't it?

MALE VOICE: That's actually better than - - . A narrow band imaging has shown that and - - has shown that as well.

DR. LUCIA: The discussion is great and that's the point of this meeting. I don't want us to get too far behind in this. I'd like to have Mitch give his question since he's been given the microphone.

DR. SOKOLOFF: I want to make a comment and get us back to the original question that Jack asked of the group. It really starts out with why are where we are now and it's because PSA is great. It's highly sensitive but not specific. The government came back to us and told us through the United States Preventive Services Task Force it doesn't work harming four men to find that aggressive disease in one man does not work. The world has changed over three years. PSAs are down, biopsies are down a third and today 945 of the PSAs that are done out there are not done by urologists. They're done by primary care physicians. Urologists only do 6%. The question is what tools are we going to use and how are we going to talk about it.

The terminology that's coming along to help us address this issue is something called informed decision making process. It makes the patient and the physician together talk about what is going on moving forward. If the PSA is abnormal however you define or suspicious the next step should be a discussion with the patient about what should we do? The answer could be imaging with MRI, it could be some of these blood-based markers, and if we're going to develop these blood-based markers we need to start talking about them a little differently. For example I think we should start talking about them like they're therapeutics. For example

in therapeutics we have efficacy and we have safety. Efficacy means what is the risk. Does your test give you— what the patient does with that risk is up to the patient based on their circumstances. A 90-year-old man versus a 40-year-old man is going to look at live very, very differently and that discussion will go very differently.

If your test is for high-grade disease does it pick up high-grade disease and what is the risk for that individual patient. Safety, it gets back to Marc's point, safety means you're going to miss some. If you're going to miss some what does that mean? For example if you believe that that PSA of 8 in that patient was missed and if that was a drug almost all of our drugs kill people. We should not give a single drug because if you go look at death in most of these drugs its 2% to 5%.

Our decision-making with a diagnostic is not that high. It's lower than that. At some point you have to say that's good enough because we're giving drugs including aspirin that's killing patients about 7%. I come back to yes, there is a risk level and the risk level is if you can start with clinical validity meaning if you're looking for high-grade disease how well does your test find high-grade disease that's your number. Then what happens after that is out of your hands. We should be encouraged to develop biomarkers and the bar for biomarkers is exactly what the biomarkers trying to do; detect cancer.

We use detection for prognosis and prediction interchangeably. I'd like to say that detection means that you're detecting something at biopsy and perhaps you're detecting something at radical prostatectomy which are both surrogate markers of what's going to happen to the patient going forward. A biopsy Gleason 7 doesn't kill the patient. Having cancer outside the capsule is not going to kill the patient. Painful metastatic disease will kill the patient. When we talk about prognosis especially with tissue base we're really looking into the future about what's going to happen to that patient. Most of the blood-based tests can do both but I think we have to be very sensitive are we detecting cancer. If we're detecting cancer it's a different legal argument. If we're trying to pick out a prognosis, still yet, a different argument. I think we just need to put some discipline around our biomarkers area and we'll go pretty far.

DR. LUCIA: That may be the last word. Thank you.

State-of-the-Art 10-minute presentations from Industry

DR. LUCIA: Now, we have an hour to have industry pipe in and give their presentations and we've got a packed session. Six different talks in this hour so I'm going to try to keep it to ten minutes.

Our first talk is Michael Brawer from Myriad Genetics. Michael began at this meeting before he was in industry and now he's seen the world from both sides. Mike?

MR. MICHAEL BRAWER: Thank you Scott. It's an honor, David as always, and Frans.

I'll start this talk with this slide not to illustrate my wife but to illustrate that she stood between me and Tom Stamey as we would battle about prostate cancer over the years. I started it because more than 30 years ago Tom Stamey started his metamorphosis to study prostate cancer as his swan song in urology. He wrote a monograph and this is how he started the front piece. I submit that 33 years later this question is even more difficult to answer.

David Crawford and I were asked at a meeting that Frans was at in Belgium, Louie Deni Reid [phonetic] to come back the next morning and answer the question what is the goal of treatment of prostate cancer David and I retired to the bar and came up with this; to allow the man to die of something else and subsequently we added, without the morbidity of prostate cancer.

These two slides I think illustrate where we are and fundamentally in the United States today we have two problems. We have an overtreatment problem due to finding lots of cancers that we would be better off not knowing about and we have an under-treatment problem, we treat with monotherapy advanced prostate cancer or high-grade prostate cancer and we lose 30,000 American men each year.

This was a very smart pathologist, as smart as Scott Lucia, who taught me how to do the Gleason grading system. This was an unbelievably effective way of prognosticating prostate cancer for a long time. Certainly when he

developed the test in the sixties Dr. Gleason showed it to be the dominant predictor of prognosis in the VA cooperative trials but subsequently it's lost its power.

Wim made some reference to this. The quintessential hallmark of cancer is mitosis or unregulated cell proliferation. At Myriad Steve Stone used genes that are cell cycle specific 31 of these genes to develop a prognostic test for prostate cancer and he set the genes and the algorithm that everything else before he had any actual patient outcome data. It's been locked and never changed. The test is validated and available most in biopsy in radical prostatectomy specimens and it provides personalized risk assessment with real oncologic endpoints biochemical recurrence, the development of metastasis, and disease-specific mortality.

We've published now nine validation studies across a whole gamut of patient types, treatment modalities, et cetera, all of these showed Prolaris was the dominant predictor in outcome with real oncologic outcomes as the endpoint.

The hazard ratios aggregate, as you see here, around two. That is for every one unit increase of the Prolaris test you double the risk of disease-specific mortality mets or BCR here in one of our three conservatively managed cohorts or initially conservatively managed cohorts with a median of ten year follow up. This is the most recent publication of earlier this year and it shows for every one unit increase of Prolaris as you march up this upside down European style over KM curve you double the risk of dying of prostate cancer.

In this study by Cuzick Prolaris as you see provided more information than PSA and Gleason combined; although they stay in our model as being useful additions to Prolaris.

We're talking about markers this afternoon and this was truly the most unbelievable slide I've ever seen. This is two conservatively managed cohorts from the U.K. accrued a decade apart. These are two of our biopsy-based studies. You can see the risk curves are superimposable. Very different biopsy penetration of PSA, et cetera, but they chose the robustness of this test.

I want to bring to you something that's brand new from Prolaris and eventually will be part of the report. We

said can we establish a cutoff? Clinician like cutoffs and urologists in particularly like their life simplified by having cutoffs. We said what is the amalgamation of CAPRA, the most validated clinical pathologic amalgamation of risk factors along with the CCP or Prolaris test in men who might be candidates for active surveillance. We used men with Gleason 3, 4 or less. I'm still - - different. Twenty-five or less positive core, PSA less than 10 and T2A or less. To add safety we said we defined a threshold of combined Capra plus Prolaris at the 90th percentile of about 500 men that were tested this way.

We tested in two of our validation series where men were initiated on watchful waiting and then followed for a decade at least, we can see there were no deaths in these men that had a CCR below 0.8, and as you see as the CCR goes up there was a dramatic increase in the likelihood of disease-specific mortality. This provided a useful cutoff that I think will again be available to clinicians in the very near future.

These are data from about 5,000 men. The orange would be men that fit those criteria for active surveillance and you can see about 80% actually had a CCR using standard pathologic parameters to predict men for active surveillance that exceeded that, that fell into the area where there were observed deaths in our two validation studies.

In contrast you would increase all the blues that didn't meet the clinical pathologic criteria for active surveillance actually all of these, so you take the number up to about 55% of a series of contemporary men tested with Prolaris, about 55% of men would actually have a disease-specific mortality less than the Point A where we observe no deaths in the two validation studies.

The conclusions for patients considering deferred or management with active surveillance CCR combining CAPRA plus Prolaris less than 0.8 does provide a cutoff where there were not observed deaths.

Prolaris has now been mentioned in the NCCN guidelines. We anticipate there will be more clarity in guidelines in the near future and has been approved now for reimbursement for low risk men by Medicare.

With that I will buy wine for anyone that can tell me where it took that picture. Who doesn't know? I always find someone that's smart enough to know it.

Questions or after?

DR. LUCIA: You've got two minutes maybe two plus.

DR. CRAWFORD: Why is everybody—I'm just so fixated on—there's all kind of different guidelines. I asked urologists how many use NCCN guidelines and most of them don't even know what they are yet everybody's pushing them.

Why is everybody so fixated on NCCN guidelines? It's not level one evidence. There are a lot of other political things that go into much of this stuff.

MR. BRAWER: Good question. It actually dovetails a little bit with what Dr. Steiner was saying. First of all having co-chaired Pivot there never will be level one evidence for early stage prostate cancer in my belief, again in the U.S., so we're not going to see it. We're not going to see those studies done.

What's happened is Mitch raised the issue of safety and efficacy. If most of these companies doing these tests were under FDA guidance that's all you would have to do. The payers require two other milestones; clinical validity that changes practice and economic wherewithal and Raoul made a very good point about that. When you dovetail all that the payers are looking at guidelines because they don't have the bandwidth or the wherewithal to really develop this on their own. I think it comes from them. But you're right, most urologists don't use NCCN.

[Crosstalk]

MALE VOICE: I think the patients like it. Its visual, it's linear. It's easy. You don't have to sit there and read an entire paper by the AUA or ACS or whatever and it's just a very easy thing for the patients to grasp onto personally.

DR. LUCIA: Next we're going to hear from Genomic Health. Bela Denes who has spoken here on several occasions. Bela?

DR. DENES: Dave, good to be here. I think this is actually about my tenth year here and I'm grateful that you didn't

go back to Charleston in August.

I'm going to talk to you a little bit about the Genomic Approach to Active Surveillance, A Step Toward Precision Medicine. This is a future directions conference and I think that part of the goal in terms of the future direction for medicine as a whole is precision medicine and the tenet of precision medicine is to deliver the right treatment to the right patient at the right time.

Just a word on Genomic Health. Genomic Health is a world leader in tissue-based molecular diagnostics with products in the invasive breast cancer, the ductile carcinoma in situ colon and most recently in the prostate cancer space. Each of these tests answers a critical question for that patient along that journey with their cancer diagnosis and treatment and for prostate the specific question is do I need treatment or the converse of it can I be managed by active surveillance.

Here's where we are today and we've all alluded to this in the prior talks as this is a current treatment shift that we're experiencing in prostate cancer. We came from the early PSA era where the mandate was to screen, screen, screen and treat, treat, treat. I was just mentioning to Mitch during one of the previous discussions that I recall in the early nineties operating on a man whose surgical pathology showed Gleason 4 prostate cancer under the old Gleason scoring system and walking in and telling him that he was cured. He was probably cured before I actually ever saw him.

The shift today is to not so screen and not to treat. Of course, as we just heard all of this has to be balanced. Everything is a balance between risk and benefit and the biggest risk that we're accountable for as treating physicians is the risk of having aggressive prostate cancer and missing that disease.

Active surveillance sounds like a great way to go. You've got a cancer that you assume is indolent and you're going to monitor it closely. There are hurdles; there are barriers to adopting surveillance. We've touched upon some of these and part of it is the uncertainty using the current tools in the actual diagnosis of what we're creating. Our current tools are not adequate to address

the true biologic potential at the time of diagnosis or to predict the biologic behavior of that disease; in other words when to pull the trigger of surveillance. This adds to the anxiety and there are economic burdens as Raoul mentioned before. I think we will see change here. The economics will be taken care of for us because there is certainly the movement away from fee-for-service where you're going to be paid not to operate rather than to operate and we'll be managing lower risk prostate cancer probably as a chronic disease.

We also alluded to the legal problems but I foresee the day when the liability will not be the failure to diagnose or the failure to operate but the failure to survey because we're over-treating a fair number of patients.

When you're considering a patient for active surveillance I think there are two critical questions that you have to ask. One is if we agree, and I think almost everybody in this room would agree that - - Gleason pattern 4 or higher grade tumor and disease outside of the prostates are bad things to have at prostatectomy. Wouldn't we want to identify these in patients before we recommend it to place them on surveillance? I think that most people would agree to that.

Second is how well can we predict things things based on our current biopsy techniques and I think that answer to that is not very well. The literature will support that. If you look at this series published, and these are fairly recent publication, of the concordance or the agreement with Gleason 6 at biopsy with Gleason at prostatectomy overall there's about a 70% concordance. But we're wrong. The biopsy does not capture the biology of the prostate at least 30% of the time. If you're at Hopkins you're a little bit better. You're wrong one out of five times. If you're at the Lahey Clinic it's a flip of the coin because it's 50/50, and if you're at Stony Brook it's a little bit worse than that; you're right one out of three times. This is Gleason 6 which can only be upgraded.

Look what happens with Gleason 3 plus 4 which can move in both directions. Overall biopsy is reflective of the pathology within the prostate essentially 50% of the time. It's no better than a coin toss. Why is that? Is it simply because its represented on this cartoon random

biopsies are random by nature so you've got a guy here who's got small volume, organ confined 3 plus 4 disease and this is the potential outcome of his random biopsies, anywhere from negative all the way up to 4 plus 4 disease or high risk disease. I look at this slide and I always ask myself how radiation oncologists sleep at night because this is what's guiding their treatment recommendations.

You've got a patient here whose got a low risk lesion that you've biopsied but he's got high risk disease elsewhere within the prostate and the question is how can—as good as Scott Lucia is looking at that area, area of low risk cancer in the prostate he doesn't have access, there's no window for him to see the high risk disease that's hiding within the prostate.

Following up on that your biopsy is low risk and you know that there's a likelihood that there's high risk cancer elsewhere within the prostate what are your options to try and get to that answer. You can do what Dave Crawford does on some patients and instead of taking 12 or 14 cores you can do a 60, 80 or a hundred core biopsy, the more biopsies you get the more information but that comes at a cost as well. You can perhaps talk to your radiology colleagues and perhaps and MPMRI scan will show up with an index lesion someplace that you can biopsy but again that comes at an added cost.

The real question that Genomic Health set out to do was can we look at the molecular profile with that low risk tumor and detect a signal since it's a field-based disease that there's high-grade cancer hiding within that prostate.

DR. CRAWFORD: I've said that for a long time. You were right on with radiation. With surgery we know what we've got after we've taken out but 30% of the time you're going to miss something and that's why I think these are - - for people that are considering an XRT.

MALE VOICE: The radiation docs never bought into it though.

DR. DENES: If you look at the graph on the Y axis is the likelihood of favorable pathology and on the X axis is the GPS score. The GPS is a continuous variable that reflects the biology of the disease from a score of zero, which is most favorable, to a hundred which is the least favorable.

When you look at a group of patients like in this cohort that are stratified by NCCN it does a little better than just stratifying by Gleason score. What you can see is that for patients who are NCCN very low risk their likelihood of being upgraded or upstaged at radical prostatectomy is around 15%. It jumps to about 25% for men who are by NCCN considered low risk but it jumps up to about 45% for men who are intermediate risk.

In this representative graph what you see is in that yellow dot which is the NCCN low risk there's 200 men in there. Twenty-five percent is the point estimate for the mean average for the likelihood of upgrading or upstaging but when you're faced with the individual patients it's very hard based on any of these predictive nomograms to identify who is the guy that's going to be likely upgraded or upstaged at surgery. This is where the biologic information comes in and whether you look at NCCN very low risk, low risk or intermediate risk what you see here is the individual GPS scores below here. Each one of these dots represents a patient from a 400 patient cohort at UCSF. What you see is that there are patients who come in with a clinical diagnosis or a clinical risk assessment of very low risk who have very high GPS scores. These are the patients who are likely going to be upgraded or upstaged. I think it would be important to know this before you have a long discussion about active surveillance with these patients. Then you ask well these are intermediate risks. Who are these guys down here with the low GPSs and these are the patients that are likely to be downgraded or downstaged at radical prostatectomy as we saw in that earlier meta-analysis.

These studies have been published in *European Urology*. This is the report that the physician gets. What you see is that this is a particular report for an NCCN low risk patient, a patient with very low risk will get an individualized report, low and intermediate likewise.

In this report you see this patient comes in with low risk features, his GPS is 8 which predicts his likelihood of favorable pathology is on this scale is right at about 16% which is what we saw was the favorable pathology for the NCCN very low risk. He is moved from low risk down to the very low risk category and we report out the individual likelihood of high-grade disease as well as non-organ-

confined disease individually.

How does this work in practice, active surveillance a genomic approach to active surveillance. Here's a patient who comes in, he's 69-years old, his PSA is 9.7, he has two cores positive. His PSA density is 0.22 and his urologist is a little bit nervous about talking about active surveillance because he's got a relatively high PSA and a relatively high PSA density. They ordered the GPS. The GPS comes back at 25, confirms that he within the low risk group, and remember he has that—remember the mean point estimate for low risk? It was 25%. He comes in right along that mean. This patient goes on active surveillance. This is in 2012.

Three years later the patient's PSA has now jumped to 12. On biopsy he no longer has two cores positive he has six cores positive. Now the discussion is the urologist is very nervous and so is the patient because the PSA is up and appears to have higher volume disease within the prostate. The discussion now is about radiation therapy and I think that's a reasonable discussion but the patient said why don't we repeat that Genomic assay that we had two years ago. This is what it comes back. His GPS is 25; it's identical to what it was. They have a discussion and based on this GPS the patient stays on active surveillance and has a follow-up PSA of 8.7 again highlighting the inaccuracy of PSA which Tom alluded to.

The final case is just to show you here's a patient who comes in with very favorable features, looks like he's a great candidate for active surveillance but remember the question that I posed before; wouldn't you want to know what the patient's risk is of harboring high-grade disease at the time that you discuss the recommendation about active surveillance?

This patient's GPS moves him out of the very low risk up here. He's got a relative high GPS and based on this the recommendation was to proceed with radical prostatectomy. His surgical pathology was Gleason 8 pathologic T2C disease. As Mike Brawer pointed out the NCCN now includes a discussion about tissue-based diagnostics and risk assessment and then the next frontier, because this is a futures course, is non-muscle invasive bladder cancer. We heard a little bit about this. This is the current

treatment paradigm. You come in; either you have a cytology or a cystoscopy that's negative. You go back to the surveillance. If it's positive you go onto a cystoscopy under anesthesia, a resection. This is the current paradigm. What we're looking to do is to change this where you come in; you have a liquid-based biopsy test which has better than a 98% likelihood of negative predictive value. If that test is negative you go back into the surveillance route, avoid that routine cystoscopy. If it's positive then you follow the normal treatment paradigm.

Thank you.

DR. LUCIA: Thanks Bela.

DR. CRAWFORD: I would comment that I don't think PSA let you down there Bela. A lot these people, and I've done a Point Counterpoint debate on this that are on active surveillance programs have enlarged prostates, BPH, that's what triggered the biopsy, we all know that, is that maybe they ought to be considered to be on 5-ARIs because I think it takes PSA out of the picture. If you believe in the Canadian trial it eradicates low-grade cancers. That's what it did in prostate cancer prevention trial and it does prevent cancer. I think it really makes sense to put a lot of these active surveillance patients on 5-ARIs. Jack, do you agree?

DR. SHALKEN: I agree.

DR. KEANE: All of these studies do—your risk of prostate cancer mortality or your risk of harboring higher grade disease you saw a 25% risk and that was considered okay by the patient. It comes down to the patient in the end. If you've got a Gleason 3 plus 3 and one of these tests shows you have a 2% chance of death in the next 10 years you'll probably take that. But if you're up at the other end even though you're still in the low grade that may be 10% and if you're 55 years of age and somebody told you that you've a 10% chance of a prostate cancer death in 10 years you might have a prostatectomy. What's the mortality for prostatectomy; 0.2% or less? With a good surgeon you can probably maintain some potency and you can probably maintain continence. It becomes a different conversation that's set up with the patient. I don't think these are

standalone tests. These go along to help you have an informed conversation with the patient and I think no matter which one you use they're useful. It's just a question of getting the right information to be able to counsel your patient as to what they feel is the best thing to do.

MALE VOICE: [background noise] and you're asking yourself - - can I believe this report? - - is there a 40% chance that this is - - high-grade cancer there's a test to answer that. if you're looking at a guy who's 50 that's got a Gleason 8 and you're wondering about his 10-year survival there's definitely another-

DR. KEANE: [Interposing] Yeah, he's having his prostate - - .

DR. LUCIA: Moving on we're going to go next to Phillip Ginsberg from MDxHealth.

MR. GINSBURG: I'm not giving you a presentation today. We had a change in our scheduling. One more - - I just thought to put things in perspective in terms of biomarkers and the implementation in clinical practice. I think we need to recognize that the whole industry biomarker development, utilization, et cetera, is an evolving thing and we need to move away from trying to be too drastic in thinking we can take the leap on an informed additional tool to be able to replace certain procedures in entirety. This is something that takes time but we are faced with stakeholders as people mentioned earlier as in the litigious side of it, insurance companies, who pays for what, what is standard of care and so on. I'm just saying at this point in time in this industry I see we have [background noise] tool rather than necessarily a replacement.

This meeting here we talk about the future and how things are developing and where they're going and I think with time there we will be a good rationale for maybe not necessarily with - - procedures but from being able to for example do fewer cystoscopies. Being from the time between cystoscopies as an example. I've been in this industry for enough years to have seen that there was a time where we - - put people on short-term therapy for lung cancer, for colon cancer anymore. We're going to use - - lung cancer patient we - - doing a - - patients or EGFR or - - patient on there.

I gave a talk in 2004 at the - - tri-conference in San Francisco where in 2004 most of the audience was saying this is pie in the sky, it's going to take years and years which it did. It's taken a long time but when it takes hold it will, in my personal opinion become standard of care. We need to recognize it's an evolutionary and incremental process. I just wanted to say that just in general terms - - .

DR. LUCIA: Thank you for your comments. Anyone have anything to add to that?

DR. CRAWFORD: That comment made me think is that from going through medical school and residency in my right-hand pocket was the early diagnosis of the acute abdomen. I memorized that book. Today you get a CAT scan. Can you imagine this conversation with general surgeons 40 years ago saying we've got this scan that can tell you whether you got something going on or not and they would say yeah but we're going to miss out on a lot of exploratory laparotomy.

DR. LUCIA: Mitch Steiner is up next. We've actually heard from him so I'm going to cut his time in half.

DR. CRAWFORD: While Mitch is getting up here Neil Shore and I put together this prostate biomarker grid with Wendy and the PCEC and we have a couple of them. We have different flow diagrams on the back and one of them is going to be one I'm going to talk about tomorrow. I'll pass these out while Mitch is getting ready and is talking there.

DR. STEINER: Thank you very much. I thought I would get extra time now because we just lost a slot. We'll figure it out.

Actually I'm going to talk about the 4Kscore test. This is a blood test that identifies the risk of aggressive prostate cancer following a suspicious PSA. I can only say so much in ten minutes but I'd like to set up the problem. The problem is that there are over a million biopsies done each year. There are complications related to the biopsy and we shouldn't take them lightly but what's really more important is that 75% of patients that undergo biopsy will have low-grade disease or no prostate cancer at all. If they have a Gleason 6 because what Bela said we're worried about that a third of them will have a Gleason 7 or above nearby we take them to surgery. What we now know is that

66% of those patients that go to surgery will indeed be confirmed to have Gleason 6. Those patients went through a lot for no clinical benefit. Then comes in the United States Preventive Services Task Force they make the point that we have a problem here. For every one patient we find high-grade disease, four of them have to suffer and as a results they said no-go.

We're now going back to the dark ages in my opinion because to stop PSA screening misses an opportunity to detect and treat men with high-grade disease, the aggressive form of the disease. The impact of the United States Preventive Services Task Force is now being felt in a couple of ways. This is recent data that just came out over the past few weeks.

One what we're finding out is yes, the overall rate of biopsies are going down but even more concerning is the detection rate of high-grade disease is also suddenly decreasing. That means good news with stopping biopsies; the bad news is we're also missing cancer. Interestingly another study, a different database said that men are now presenting with more aggressive disease. We're seeing like almost during our residency people coming in with metastatic disease.

What we need to do is to figure out better information after an abnormal, serious, or suspicious PSA to help make a better clinical decision. That means identify patients who harbor a high-grade disease that would benefit from treatment, but avoid prostate biopsies in men with indolent or no cancer to avoid overtreatment. We need something in between the suspicious PSA and the biopsy.

The 4Kscore test is a test that accurately identifies the individuals risk for aggressive prostate cancer. When I say aggressive prostate cancer that means the detection of high-grade disease but also prognosis in that you're talking about the rate or risk of prostate cancer metastases. The study is based on 10 years worth of work, 20,000 patients, 12 peer review articles, both in the initial biopsy and the post-negative biopsy.

It is recommended in the NCCN guidelines and it's a test that's now in this concept of reflex testing meaning if you have a suspicious PSA before you go to biopsy there's a new

thought and that is maybe we need more information, sit with the patient and use that information. To get to David's point who cares about the NCCN guidelines it's internationally recognized, it's considered the standard of care when 21 experts sit in the room and tell the world this is okay. It's level two data but the insurance companies which ultimately dictate what happens has made the decision that is standard of care and how could they not pay for standard of care. As a result companies are very interested in being in the NCCN guidelines because there are no other guidelines that they really recognize so it's artificial but it's real at the same time.

What's the 4Kscore test? The 4Kscore test uses four kallikreins and the total PSA and free PSA—we use that now, that's nothing special about that—what that does is get you to the point that you can distinguish prostate cancer from benign disease. Intact PSA in human kallikrein two or two proprietary kallikreins that are measured in our laboratory and intact PSA is just not made by normal prostate. Normal prostate doesn't like PSA when it's secreted because that's a nasty enzyme. It complexes it with protein or it fragments the hell out of it and you end up with fragmented PSA or complex PSA. If PSA is put out intact that means the prostate itself has become so poorly differentiated it doesn't care what it puts out. As a result because of that misprocessing we are able to pick it up. Human kallikrein two goes up when disease is more poorly differentiated. The 4Kscore test is actually looking for the aggressive form of prostate cancer based on these markers.

Then we add in clinical information; age, DRE, and prior biopsy states. I must say the prior biopsy status is probably one of the most critical clinical pieces of information you can put into an algorithm. Doesn't it makes sense if somebody's whose never been biopsied before is going to have a higher risk of high-grade disease than someone whose had a prior biopsy and it was negative. That information is critical when you start thinking about it.

This is a commercial test and this commercial test is intended use is as a follow-up test for patients with a suspicious PSA and you're considering an initial or repeat biopsy. It is in the NCCN guidelines where patients and physicians who wish to further define the probability of high-grade disease not to distinguish prostate cancer from

benign disease and the panel consensus is the test should be considered prior to biopsy and for those who had a negative prior biopsy for men thought to be at higher risk for clinically significant prostate cancer. We're extremely excited that this is considered standard of care and it's a very critical component when you go out to meet with payers to pay for a test.

The study was validated prospectively in the U.S. The AUC which represented the accuracy of the test is 0.82. Interestingly the biopsy itself has an accuracy of 0.82. In other words we probably should be validating our tests on radical prostatectomy specimens and the presence of high-grade disease not really on whether to biopsy as high-grade disease because you still miss it 20%, 30% of the time. Put that aside for a moment.

The key thing here is the calibration curve. What's the calibration curve? This study was prospectively designed to look for high-grade disease. That was the primary endpoint. It wasn't a subset analysis. That was the primary endpoint and as such on the Y axis and the X axis what you see is the predicted score. What the 4Kscore test does it gives you the percent risk that that patient on biopsy will have Grade 7 or higher. That's what it's predicting.

The Y axis is the actual biopsy result. When you look at that it's a near-perfect calibration. That means when you say somebody has a 40% chance and a hundred people in the study looked at their biopsy results 40% will have high-grade disease. It's not just the low numbers all the way to the top. This is really the best you can get in terms of trying to predict what the patient has. What the patient results they get back is basically a number and that number is that patient's individual risk. If the risk is 5% for a patient who is 75-years old and has comorbidities they may not want to go forward. In somebody's who's younger than that 5% is still extremely low risk, which I'll show you in just a moment.

You won't be able to see this but let me tell you it's 12 studies, 22,000 subjects, unscreened, screened, prior biopsy, the test has high accuracy between 0.8 and 0.9.

Clinical utility and we use the terms interchangeably, we

should not. Clinical validity means that your test picks up high-grade disease, that's what the test does. Clinical utility means how does it change your practice. In this setting the way it changes the practice is if you think that patients going to have less chance of high-grade disease then you just decrease the chances of a biopsy. That's clinical utility. Utility here is that you're avoiding biopsies and the avoiding biopsies is about 40 to 50%.

This is theoretical so we are currently conducting studies so we're currently conducting studies where we're looking at do we actually change practice and if it matches the theoretical then you can bridge into that data.

This data just came out. It's probably one of the most compelling pieces of information as it relates to prognosis. If the 4Kscore test is telling you what's going to happen at your biopsy more importantly what's going to happen 5 years, 10 years, 15 or 20 years. at that point that's really going to help you temper what you're going to do for the patient not in terms of chasing aggressive disease but the safety side; whether or not you can follow the patient and follow the patient safely.

What you see here is this is from the Vasterbatten [phonetic] study, 12,561 patients and this particular graph is looking at patients that have a PSA greater than 3 and the age of 60. They have given blood 20 years ago. This is when they're 60-years old and they're 80 years here. What you can see if you use just PSA, PSA shows you indeed they're at high risk with a higher PSA and that all patients are going to be followed aggressively with biopsies. If you use the 4Kscore test and you cut it off at 7½% for example you're not going to miss those patients that you're supposed to pick up but look what happens here. At low risk at year 10 you have a 99.8% chance of not having symptomatic mets. By year 15 it's 99%. That means if somebody has a score of less than 7½% you can look at them and tell them you have a 99% chance of not having symptomatic prostate cancer in the future. That gives you time to decide whether or not how you want to follow them and some comment was made about maybe just changes the frequency at which you look at the patient whereas these patients you'll probably be more aggressive. If you look at the groups patients with less than 7½%, that's 40% of

the patients, with a single 4K score 20 years ago 90% of these patients if they were deemed low risk from a single blood test, would have low risk for a symptomatic mets and therefore prognosis.

In summary it's validated based on a decade of research. Clinical validity is highly accurate at 0.82. Clinical utility it reduces unnecessary biopsies and men who are determined to be at low risk and safely avoid a biopsy because their risk of disease is less than 1%, in the guidelines, and finally the 4Kscore test is a useful cost effective diagnostic tool to select men who are at high risk for aggressive cancer and would benefit from prostate biopsy, and to select those men at low risk who may avoid a prostate biopsy and the possibility of overtreatment with no clinical benefit.

Thank you.

DR. LUCIA: Next we're going to hear from Peter Knapp from Strand Know Error.

DR. CRAWFORD: I think a lot of these things we're talking about than what Mitch just mentioned about 4K, if we would have had some of this stuff and implemented it years ago we wouldn't have all the crisis we have right now with U.S. Services Preventive Task Force and the over-diagnosis and overtreatment and things like that, that stuff the Brawer presented and Bela and that. Now the issue of is it really your biopsy.

DR. KNAPP: It's a significant question. Strand Diagnostics is a company whose roots were in forensic pathology doing crime scene investigations, specimen identification with DNA testing for FBI and other law enforcement agencies for many years.

I became involved with them about seven, eight years ago and was interested in seeing if we could take that technology and bring it over into healthcare to help specimen identification on biopsy specimens to really improve diagnostic accuracy and an ultimate goal of eliminating diagnostic errors due to specimen switches and contaminations and essentially provide the first step in precision medicine.

I'd like to cover with you a few thins today in the few

minutes I have to talk. One is to recognize that the occult specimen provenance complications do exist. Second is to define the rate of the occult specimen provenance complications or SPCs in routine clinical practice and also in NGS testing. Third, I'd like you to have some understanding of the clinical utility of DNA specimen provenance assay testing which is DSPA testing, in current clinical practice and emerging molecular diagnostic tests.

Dr. Mary Kroner [phonetic] at Cleveland Clinic, a pathologist, outlined in a white paper at the Cleveland Clinic a number of years ago 18 different diagnostic steps that are involved in the specimen handling from the time a biopsy is obtained to the time it's transported and delivered to the laboratory and goes through the various testing in a laboratory, and also identified the key touchpoints where specimen switches or specimen contaminations could occur. The added steps in molecular diagnostic testing that occur after the histology has been determined the specimen is re-cut and then sent to the molecular diagnostic lab for biomarker testing adds to the complexity and adds to the risk of a specimen provenance complication.

The clinical significance of these untested specimen provenance complications can include transpositions which are switching errors, simply where the wrong patient gets the wrong diagnosis and is administered the wrong treatment, possibly a toxic treatment, and also contamination where you have admixtures of DNA from one patient to another that can confound pathologic diagnosis and also confound biomarker testing.

A clinical solution to this problem is DNA specimen provenance assay or DSPA testing. It's a molecular diagnostic test that uses STRs and establishes specimen provenance as well as specimen purity to provide diagnostic accuracy with a DNA certainty.

There are really three steps in the process to do this. The first is to obtain a reference sample. Our system, the Know Error System, does it with a buccal swab. It's obtained at the same time the biopsy is done in the office and that is sent to the DNA laboratory and saved until the positive histology comes from the histology lab; whatever histology lab the specimen went to. The specimen is either

re-cut or we get the histology slide and it comes to the DNA lab to be matched with the reference sample prior to the diagnosis being given and prior to any treatment being implemented.

The first published report looking at the actual rate for occult specimen provenance complications in routine clinical practice was published in 2013 in the *American Journal of Clinical Pathology*. Dr. Pfeifer, et al, at Washington University reported that there was an occult error rate of 0.8 to as high as 3.5% in pathologic specimens.

What they did was we gave them free access to the databank at Strand Diagnostics and they came in and reviewed the first 13,000 Know Error specimens that had been done, all on prostate cancer biopsies. All of them had had DSPA testing performed prospectively to identify occult specimen provenance complications. The histology was received from 54 different laboratories. They were all divided into five different laboratory categories. They defined complications or errors as two types. Type one being transposition or switching errors. One specimen is mixed up with another from another patient, and type two errors, which were contaminations where the patient's tissue specimen actually contained either tissue specimen and/or DNA from two different specimens and two different patients.

The results of the study showed that if you combined Type One and Type Two errors that nearly 1%, 0.93% overall error rate in these 54 labs. In addition they found that the complication rates could be as high as 3.5% in some laboratories and this group of labs were the large independent reference laboratories. The other point that was made was that no lab was free of errors if they performed over 200 tests. If you've gotten to the point where you're doing a number of tests, prostate biopsy specimens every single one of those labs that had over 200 specimens handled had some combination of Type One and Type Two errors and no laboratory was really immune.

Another article that addresses the same issue was published in the *Journal of Clinical Oncology* looking at biopsy misidentification identified by DNA profiling in a large multicenter study. The study was the REDUCE trial which

we're all familiar with, looked at the effect of dutasteride on the risk of prostate cancer. These patients in the study all had biopsies done initially and at year two and year four. The first phase of the study it was recognized that there were some specimen switches and some contaminations that confounded their test results. They went back and used the DNA profiling to look at all of those specimens and identified that 0.4% transposition rate or switching rate with a 13.4% contamination rate from foreign sources of DNA.

In the study midstream they implemented the DNA profiling that we're talking about and they eliminated these problems in the second phase of the study.

A very recent article by Sehn et al, at Washington University in St. Louis, it's in press now in the *American Journal of Clinical Pathology* as looking at occult specimen contamination in routine clinical NGS testing. They found, looking at and evaluating 296 consecutive NGS cases that 6 cases or 2% were contaminated with greater than 5% human-to-human contamination called allocontamination confirmed by SGR analysis.

When we look at their bar graphed analysis you see a couple of interesting things. One is the light gray numbers are the six cases that had greater than 5% contamination. The black bar graphs are addressing the other patients that had contamination less than 5% that still may be significant in certain labs or in certain tests. The second point to take away from this was that the contamination rate increased with lower DNA yield. For specimens that had a DNA yield of less than 500 nanograms 5 of those 46 patients or nearly 11% had contamination that was over 5% and if the DNA yield was less than 200 nanograms it increased to 23%. This is significant because a lot of the biomarker testing and NGS testing that's being done are being done on small aliquots of DNA and may be at higher risk for having contamination errors.

The authors concluded that human-to-human specimen contamination occurs in clinical NGS testing. They said the contamination rate increased with lower DNA yield and that the tools for detecting contamination in NGS testing should be integrated into clinical bioinformatic pipelines. Interestingly CMSs website on molecular diagnostic

analytical performance specification guidelines also recommended that post-analytical testing requirements that the bioinformatic pipeline must include specimen contamination as a source of identified variance. There's a movement to have the testing qualification requirements put in place that will exclude specimen contamination as a cause for those variants.

In conclusion I think the data shows that occult SPCs exist in every laboratory and they have not been eliminated with the best QA measure. Our kit that we use where this data was analyzed by the Washington University group actually includes forensic chain of custody going along with the forensic background of the company and also includes bar coding. Despite those safety measures we still saw the error rate that I mentioned earlier and the occult error rate is 0.93%, nearly 1% and as high as 3.5% in some lab settings even using those measures.

The biomarker NGS testing are exposed to compounded risk of the SPCs in both histology and the biomarker work flows. What you receive from the biomarker company or the NGS company receives from the histology lab is already been exposed to those switching errors there and there are additional steps that can come into play.

I think in today's world with precision medicine with patient safety and diagnostic accuracy being the focus of our attention D spot testing with STR analysis can be used to establish specimen provenance, confirm purity, and eliminate diagnostic errors due to occult specimen contaminations and switches.

Thank you very much.

DR. LUCIA: Thank you. Our last speaker from industry today will be Robert Den from GenomeDx.

DR. CRAWFORD: Scott, while Robert's coming up there this is actually a question for you. I assume that pathology labs are certified somehow, right?

DR. LUCIA: Sure. Absolutely.

DR. CRAWFORD: - - certified and have a 13% contamination rate.

DR. LUCIA: The contamination rate from DNA is an issue that has not been addressed by lab certifications yet and that's why

I'm saying the handling of the specimen goes back to an earlier comment that I made that we have to deal with how specimens are handled better. I will venture to say that in a study that we looked at that a lot of the contaminating DNA was not patient-to-patient it was handler DNA that was actually used. We know that from the fact that it's very hard to get XX DNA from a male and we actually knew that a female handler had contaminated a particular specimen. It's handling DNA.

In terms of specimen switching and those kinds of things there are measures that should be in place to prevent those errors and we still deal with humans.

DR. CRAWFORD: That stuff that - - in your clinic when you're doing biopsies and people switch them.

DR. LUCIA: That's absolutely right.

DR. CRAWFORD: It's happened to me more than once.

DR. LUCIA: Starting in the clinic there's pre-analytical variables.

DR. CRAWFORD: You get somebody down there that's not used to doing biopsies with you, or somebody's sick, they bring somebody in that doesn't know what they're doing things get switched.

We are really behind on time here I want to get Stacy in so we'll put off the welcoming reception by about 15 minutes. You got ten minutes. We'll get ten minutes on GenomeDx here and get Stacy up.

DR. DEN: Thank you very much. My name's Robert and I am an Assistant Professor of Radiation Oncology and Cancer Biology at Thomas Jefferson and I'm speaking on some of our joint data with GenomeDx. These are my disclosures.

Given that this is a future directions I wanted to talk about the shifting paradigm in prostate cancer care. This whole meeting has been about the integration of genomics and biomarkers. The past has really been the use of clinical and pathologic features to assess risk, Gleason score, and PSA alone. At present I think you've heard a lot of very good discussion about prognostic information based on tumor genomics. The question about the future is can we use this genomics then to optimize targeted

therapies.

Here's the classic current patient management that we have. Patients who go to radical prostatectomy with adverse pathologic features if they are present there's always this large debate about should radiation be integrated, when should radiation be integrated, what should be the PSA thresholds. This uncertainty which I think is what prevails within the room is reflected in multiple guidelines, not just NCCN, but as Dr. Crawford mentioned AUA and ASH and there's really a lack of clarity about patient selection.

I think the thought now about increasing the role of genomics is can we use genomics to determine which patients need further intensification of therapy and so if you use a genomic test like Decipher you can show that in low risk patients these patients can go onto observation. Essentially these are the patients that we've known from multiple Phase III clinical trials that surgery has cured even in the presence of adverse pathologic features. It's really those patients with the high risk by genomic scores that can't be differentiated clinically those are the ones that need further therapy.

Just to talk about the GenomeDx platform which is trademarked as Decipher, it's a 22 gene marker panel. It's derived from formalin fixed paraffin embedded tissue. DNA or RNA is extracted, it's put against a gene chip, and you get this large genome analysis. The interesting thing about this platform is that it's able to integrate multiple different biologic pathways including cell proliferation, adhesion, motility, immune system, cell cycle, and androgen signaling all of which are very important.

This is the assay printout that is seen by the physician and can be shown to the patient where you can see the patients are stratified into different risks, high risk, average risk and low risk. This is currently in the NCCN guidelines. It's also been Medicare approved.

Timing matters. We know this as urologists talk to your patients about this all the time there are benefits and disadvantages to both adjuvant and salvage radiation. The idea of adjuvant radiation is that we can delay or prevent metastasis but it comes at a cost of increasing acute and

long-term toxicities. Salvage radiation you're avoiding or delaying a irradiation so you can increase time to regain continence, sexual function but it can be associated with decreased PSA survival, freedom from hormone therapy, and metastatic onset.

This is a list of the various publications you can see this has been a platform that's been applied to multiple academic centers and been validated in multiple different cohorts.

I'm just going to bring your attention to one of our papers. This was recently published in the *Journal of Clinical Oncology*. What we saw here was that if you just use a clinical nomogram and look at all patients who receive radiation therapy it's very hard to differentiate and distinguish the patients who will benefit from adjuvant radiation therapy versus those that can be carefully watched and undergo salvage radiation therapy. By CAPRA you would argue that all patients should receive adjuvant therapy, although we all know in our clinical practice and from multiple clinical trials that this is not the case.

What we've found is that through integrating this Decipher score we were actually able to distinguish patients that benefit from adjuvant radiation therapy versus those that could be carefully watched with salvage radiation therapy. You can see from the graph on the left that those that were low risk by the genomic score there was no difference in the development of metastasis. I think it's really important to stress that this was a metastasis endpoint which is a clinically significant endpoint for those patients with low risk whether they received adjuvant or salvage. Whereas for those that were high risk there was a clear 80% reduction in hazard with the receiving of adjuvant radiation therapy. This is perhaps the first indication that these tests can not only be prognostic but also predictive of therapeutic intervention.

We've also done a subsequent analysis in a larger cohort bringing other groups together particularly in the setting of only salvage radiation therapy which is the current trend within the genitourologic community. We find that early salvage versus late salvage in the low risk patients has no difference whereas for the high risk patients early salvage clearly has an advantage. I think this data speaks

to the challenge that we will face in the future when we think about a lot of the clinical trials that are being looked at in this post-prostatectomy space and how do we understand and interpret the data when it comes out.

I think what I've shown you briefly is that for men with high risk disease there is clearly evidence to support aggressive early treatment but we know that there's likely a need for further systemic therapy and really the unmet need is to determine the optimal treatment for this patient's particular prostate cancer.

The question is can we use genomics to find that ideal targeted therapy and could we use this platform to help us with that. What I mean by that is when you look at this platform you're able to get over one million expression markers but when you use it only for its prognostic and predictive value as Decipher you're only looking at 22 of those markers. Granted many of the markers on the AFI chip may be uninformative but if 1% of those markers are informative for another question you're talking about a hundred thousand or 10,000 genes. If it's 0.1% it's a thousand. You can see the power using an - - platform in being able to look for other expression signatures and to try to find other ways to advance precision therapy.

One thing that we're partnered with GenomeDx with and this really works thanks to Lenny, has been to move into this new format of GRID which is genomic research information database and this allows us to get the entire spectrum of the genomic analysis for our patient and it can be shown in multiple different ways depending on the level and sophistication which you would like the data. You could actually query for specific genes to see if they've been upregulated or downregulated or you can actually get the raw expression values and do more advanced bioinformatics.

The idea is to discover novel biomarkers and signatures for true patient care. For example to find a hormone therapy biomarker panel. This would allow us to determine should the patient be receiving radiation and hormone therapy? Should they be receiving only hormone therapy alone? Or should they be going directly to something like chemotherapy? Can we use these biomarker base for clinical trial selection, discover novel cancer pathways and discover new druggable targets within urologic cancers.

I just put this up as some examples where you can find levels of SPINK1. These can be targeted with EGFR inhibitors. There is a paper by the group out of Michigan showing this. C-Met, which can be targeted with tyrosine kinase inhibitors, for example cabozantinib, and then PD-L1 where you can look at the integration of immune therapy. I think this is the future where we have to think how do we carefully select and how do we bring this kind of information to bear to the right patient so that we don't do thousand patient trials and hear the NCI steering committee tell us we can't do your trial. Whereas if we carefully select the patients upfront and get that data then we can actually do the trials so we don't run into these conundrums that I think Dr. Crawford was alluding to.

Just to conclude; this metastasis signature is been validated for men with intermediate high risk following prostatectomy. It's how they validated at CMS covered, it provides a rich environment and resource for further investigation and integration through this grid and it's allowing for further biomarker research and may help us to deliver future tumor specific targeted treatment options.

I would be remiss in the last moment if I didn't acknowledge the team. We talk about a lot of these projects and these are actually team science based and I really have to give a lot of credit to Lenny Gomella because a lot of our work if you think about it these were specimens that we collected 20 years ago and if it wasn't for the foresight of a lot of people in this room to be very meticulous in their collection and their categorization of this in building these database we wouldn't be able to now to go back retrospectively 20 years later and actually be able to do this. I'd like thank my collaborators from the Mayo, Johns Hopkins, Duke, Cleveland Clinic, University of Michigan, UCSF and of course patients and their families.

Thank you very much. I appreciate it.

DR. CRAWFORD: I was going to say that's beautiful work. We've been using Decipher for quite awhile. You also didn't mention that the PSA failures is a group to look at.

The biggest challenge I face though with our second opinion, and Scott's there, when we talk about Decipher is

our radiation oncologist shoot us down. They say we have level one evidence from your SWOG study that says that you should use post-op radiation. This test hasn't been validated enough or whatever. I think there needs to be some acceptance of that. I don't know, Lenny do you experience that?

DR. GOMELLA: No, but I think Dave for years and years we've been—those of you that know this but the RTOG was born at Jefferson so there's been this long history of trials done at Jefferson and for many years David used to criticize a lot of our work we did with Rich Valecenti [phonetic] and others about using early radiation therapy. I could tell you of all the things I've seen lately and this interface between your SWOG studies with radiation and these now recommendations from ASTRO and AUA concerning this. I personally think this is the most practice changing thing that we have in this space that we've ever had and I think it's going to do a lot of good to cut down on the thing you used to criticize, the unnecessary radiation.

DR. CRAWFORD: You're telling me I was partially right, is that it?

DR. GOMELLA: Just partially. Just a little bit.

DR. CRAWFORD: We ought to write that. It's taken 20 years for this to come out. Okay. Great.

DR. LUCIA: It's my pleasure to actually change subjects completely here a little bit and talk about social media. This is a talk we haven't had at this event and I think it's well overdue. I'm very honored to welcome Stacy Loeb who's going to be speaking to us on it. Stacy.

DR. CRAWFORD: We'll give you till 7 and then we'll get out of here.

Featured Lecture: Urology and Social Media - Stacy Loeb, MD

DR. LOEB: The last thing I want to do is stand between everyone and happy hour. At least it's a light topic and then you can all have time to practice tweeting at the happy hour. This is really something that has taken hold very firmly.

Back on 2006 when it started there were only 23 healthcare professionals on Twitter and literally now there are more than 75,000 generating more than 150,000 tweets per day. This is taking hold and there are many reasons to use social media in urology. Some of them include finding out about news, research, conferences. There's a journal club on Twitter, advocacy for causes, networking of course with colleagues. Crowdsourcing if you ever want to pose a question to a bunch of international experts and advertising. I'm going to give you an example of each of these starting with major news.

I actually don't read the newspaper at all anymore. Twitter is my tailored newspaper because any paper that I would read or anything that I'm interested I follow on Twitter. Instead of just flipping through the *New York Times* to find out what you want to know about it's very fast to just scroll through the tweets and they're limited to 140 characters so it is just a sound bite. I find this much faster. I'm a Syracuse basketball fan so I follow the Syracuse basketball Twitter stuff and instead of looking through the whole sports section I get exactly the team I want to know about coming. I think really it is a great way to find out what's going on and within the medical world there's pretty much no instance where there's a new drug approved or something big happens that I don't hear about within a few hours.

This is also possible to do to some extent on Facebook but really it's not as rapidly dynamic as Twitter but nevertheless you can sometimes see when different things are approved or when the FDA issues a warning about something on Facebook.

Emerging research is probably my favorite use of Twitter. All the major medical journals have Twitter feeds so it's a very condensed way to scroll through. What came out in the *New England Journal* this week? Oh my gosh. It just so turns out that the CHARTED trial finally came out after a year of waiting. These things all hit Twitter immediately. In fact the embargo lifts the journals put these things on Twitter and then you can see how everybody reacts to it. It's very interesting to learn about it and to see the reaction and discuss the study. This is what we just discussed this week on the Urology Journal Club on Twitter. If you're following along with that you can hear what

people think about it and if they plan to change their practice.

It is something that's being taken up more and more by urology journals as well and actually it correlates with the amount of citations and with the impact factor of the journals themselves. It's no longer something that's being ignored or on the fringe or for people who follow Kim Kardashian this actually has real scientific impact that's even being demonstrated in terms of citations and impact factors. It's even becoming mandatory now. Some of our journals are requiring that you write a tweet about your paper when you submit the paper. I just submitted something to *European Urology* and you have to write up two tweets that can be published by them on Twitter if your article gets accepted. A lot of the journals are doing this now because the ultimate goal is dissemination. If nobody ever reads about your work or hears about it then it really didn't do any good so in order for us to have impact with all of the hard work we're doing it is nice to spread the word and this is a great way. There are tips that are published here, if anyone's interested, by Grayson [phonetic] on how to construct a good tweet about a scientific paper.

The next major use of Twitter is for conferences. Now all the major urology conferences have their own Twitter feed and in advance they'll tell you what the hashtag is. I'm not sure if everyone knows that a hashtag is. Maybe it's disseminated somewhat into the popular lexicon even for people not on Twitter but it's when you put the pound symbol in front of a word. A pound symbol with EAU15 or AUA15 as long as that's in there somewhere then you can search for all of the tweets from that particular conference. Hashtag prostate cancer would have all tweets related to prostate cancer.

These conference feeds are really growing. There were more than 9,000 tweets at the AUA last year and it nearly doubled I think this year. This is a great way to keep up with what's happening at the meeting. There are so many sessions going on. Maybe you missed the meeting. You can definitely see it on Twitter. Here's a tweet that I wrote this morning actually. Thanking Dr. Crawford for inviting me and that we're very excited about hashtag FDU15 so I invented a hashtag for this meeting. It's good to have one

and if you're going to be posting anything you can use it too.

Twitter is also really good for medical education. One example that I already mentioned is this monthly urology journal club but many of the other specialities are taking them up also. There's one for radiation oncology, et cetera. This is held the first week of every month. It's a 48-hour asynchronous discussion. We've got participants in the U.K., Australia, all over and as long as you use the hashtag EuroJC then you can read everyone's tweets whenever you happen to sign on. They just pick one article and everybody discusses it every month.

There's also some other educational options available on social media for trainees. For example, some quizzes, like this one is showing transillumination of the scrotum and asking what's the diagnosis or some imaging findings so the uses in medical education are definitely expanding rapidly also.

This is a project I've been very involved in over the past year. We have put all of the EAU guidelines into tweets so we sat there for days taking every EAU guideline and making them into 140 character tweets. I think this is actually a really visionary initiative of the EAU and we're still working on it. We have some new projects planned doing quizzes of different important points in the guidelines so this is definitely another great place to find out about changes to the guidelines is through Twitter.

Advocacy, this is really a wonderful forum for advocacy because in the past let's say you were upset about something. If united lost my luggage for example I might call somebody, be on hold forever, probably nothing would happen. But if you tweet at them they will respond to you right away.

I was at a urology conference about a month ago and somebody had no hot water in their hotel room so they tweeted to the Hilton and literally someone was up at their room within minutes and they got like a hundred dollars off their bill. These things are big for PR and if people do not show good customer service they don't want negative stuff on social media. Whatever it is that you want to advocate for, whether it's some issue you're having or

something like legislation, this is discussing U.S. Preventive Services Task Force reform which is probably something a lot of us feel strongly about. What are you going to do? Write to your congressman? You can also have a big Twitter campaign and these people often will write back on Twitter which is amazing.

Networking; it's really been a fun way to meet a lot of interesting people. Even Laura and I became friendly through Twitter really. I think it's nice for people who are in different geographical areas perhaps slightly different specialties to become friends. There's everyone from medical students to trainees to urology chairs, industry, you name it. It is a level playing field where everyone can have an open conversation. If you're going to meetings or other events it's a nice way to spread the word about networking activities.

Crowdsourcing this is nice for clinicians. Of course, you don't want to use any patient identifiers. You don't say Mr. Jones a 58-year-old man. But if you have a general question like is BRCA related to prostate cancer you will likely get answers back from at least ten other urologists all over the world within an hour.

It used to be if I had a question I'd figure out which of my mentors I'm going to call up on the phone and maybe they'd be available. You don't even need to phone a friend anymore. You can crowdsource to the world of urologists.

Advertising, why not use social media. It's a huge platform to disseminate information about whatever you want to advertise. If it's your clinical practice, a course you're doing, you're going to be on TV, whatever it is that you're doing again, there's no point of doing it in the closet with nobody knowing about it. You want to tell people because the people that follow you choose to follow you. You're not telling people stuff that they're not interested in. These are people who also are interested in prostate cancer if you are tweeting about prostate cancer so if you're doing something related to that or there's a course this is exactly the target audience.

I host the men's health show on SiriusXM so on Wednesday nights when I have my show I write that the lineup is going to be and that way if someone wants to listen to me they

know what we're talking about and what time. It's a good way to promote what you're doing and hopefully interested parties get the information. This is with Dr. Concepcion right here. His course next week in Los Angeles is about prostate cancer and the AUA has been tweeting about it. It's a good way to find out about things like course offerings, conferences. You always want to include links. You'll notice these all have links. If you're going to promote something you want to tell people where to go; they shouldn't have to work for it. If you have a new article that you're talking about include a link to the article so that people can actually read it if the sound bite is interesting. A really targeted place for advertising.

Some people express concerns about social media use. This was a survey that we sent to AUA members and about 71% had a social media account but some of the people that didn't thought maybe there's no added value or expressed concerns about privacy. We did a little survey to address is there added value? Are the people using it thinking that it's actually improving either their clinical or academic practice.

We sent a survey to all of the people that use Twitter at the EAU and the AUA in 2014. Of the respondents you can see very high percentages felt that it was useful to them for networking, disseminating information, research, advocacy, and career development. Only 38% for physician/patient communication but for all the other items that we asked more than 50% found it useful. Obviously this is a highly selected and biased sample because these are the people that use Twitter at a conference. The point of this was to find out do the people using it think that it actually enhances things and they do. That was good news.

There are some codes of conduct available that I think are worth being familiar with before undertaking this activity. The AUA code of conduct of course you always want to be very professional, not using swear words or ideally not posting photos with alcohol in them which can actually be really difficult at urology meetings so when I'm taking the picture I say okay everyone put your beer down because we're not supposed to technically have it in the picture.

Protecting confidentiality is number one. This is the kind

of stuff that people get fired over is if you take a picture that has a patient in it or you say something that breaks HIPAA so that's what you never want to do. I'm not sure I would even recommend taking pictures in the hospital. At conferences and other public events it's totally fair game unless you signed an agreement at an ad board or something like that. Being courteous. I have seen some pretty negative interactions on social media and I think it's very important as professionals that we act how we would want to be treated. You don't know who's out there and whose going to read this so just have discretion, support the identity of our profession, and be thoughtful.

BJUI has similar types of social media guidelines and it's always important that you consider that this content can be around forever. Even if you post something and you delete someone may have taken a screenshot. These things disseminate pretty quickly. Sometimes I've taken a screenshot when I see something that I think is really crazy so just think before you tweet just like you would think before you say something.

For the physicians many hospitals are fine with you having your own Twitter account. You're just supposed to state on there that your views are your own and that may be the case for industry also. If it is your personal Twitter feed that you're not representing the official position of your company.

EAU is the other urology organization with social media recommendations. All three of these are online and available and very useful before you start using. In fact, the EAU specifically recommends that you should consider understanding better how these work before you actively engage. There are quite a few people who just are passive users of Twitter where they follow the people that they want to and they use it as a newspaper but they don't write back or interact.

I think it is actually great to be an active user but it's a nice way to start as a passive user to get an idea how it works before you start engaging.

They say treat it like the hospital elevator. Just like you wouldn't talk about Mr. Jones and his situation in the hospital elevator in front of people. They again mention

saying that the views are your own, being open and honest, assume it's permanent, and maintain limits.

In summary social media I think, is extremely useful for finding out about news, about research updates, participating during conferences whether you're there or you're not. That's how I got started. I was giving a lecture on prostate biopsy complications in Australia and at the end of my talk in the questions and answer session they told me we got a question on Twitter from a guy in Canada and he's wondering which antibiotics are you using now for prophylaxis. I thought how the heck does someone in Canada know what I'm talking about in Australia. They literally took my answer and tweeted it back to the guy in Canada so I thought maybe there is something to this because I was in the group who thought it was all about Kim Kardashian before and I realized it really does add value.

I think of the social media Twitter is the most useful of all the platforms at least in the professional context of urology but it's useful to review all of the professional guidelines for social media first.

If you want more information about this a nice summary is on the Urology Match website and there's a webinar, Dr. Andriole checked my webinar which was nice from the AUA and they've now posted it on the website for free.

In conclusion I would say that Twitter has taken urology by storm and is here to stay. There is just a ton that you can do with it so get in on the action now or get left behind. The next time you can press this button and I will see you on Twitter.

Now it's time for happy hour.

DR. CRAWFORD: Is there any sort of a moment for professional Twitter feeds to require registration so that in the urology prostate cancer Twitter feed it's not the trial lawyers who are following you?

DR. LOEB: No. Not really. There are physician only social media platforms for example Doximity is HIPAA compliant so if you want to have a discussion about something that you wouldn't be able to have on a public forum you could use just a different platform altogether. There is a feature on Twitter where you can protect your feed so you can

actually lock it. You have to approve people to follow you but nobody that I know in urology actually uses that because the whole benefit is that anyone can read it. You don't even know some of the amazing networking opportunities or the things that come along. It's amazing some of the people I met and if I protected my feed they would have never even known to reach out to me. I think you should be aware that anyone could be following you. Honestly if you're professional and you're just tweeting about what interests you in an open way and there's nothing inappropriate, I don't care if it's trial lawyers or my patients or my mom or whoever because there's nothing to hide.

MALE VOICE: What are the percentages of urologists that have an account?

DR. LOEB: It's 71% as of about a year and a half ago and our AUA survey had a social media account. The numbers dropped. Twitter, honestly I'm not sure what it is now because there's been such an increase recently. I think it was in the forties that had ever registered but active use is very different because a lot of people just have an account that they signed up for or someone on their faculty signed them up but they don't actually know how to use or use it. I think we could use some new metrics on that because so many more people are joining. If anyone, by the way, wants individual help feel free to come up to me or email me.

MALE VOICE: That's what I wanted to say. I have an account but it don't know how to use it.

DR. LOEB: You can check the webinar online.

[Crosstalk]

DR. LOEB: Yes, I tweeted a thank you at you this morning so you should have gotten a notification.

DR. LUCIA: Thank you so much that was wonderful. I'd like to thank all the presenters and participants today.

The reception tonight is at the Golf Club Porch which is across the bridge to the main building and then down.

[Crosstalk]

[END RECORDING]