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Symposium**

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Session 2: Localized Cancer Treatment – E. David Crawford, MD, Moderator

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DR. CRAWFORD: Good afternoon everyone. We'll get started with our afternoon session.

I'd like to welcome the newcomers that weren't here yesterday. Who wasn't here yesterday raise their hand. Let's have everybody introduce themselves that weren't here yesterday.

BRIAN J. MORAN, MD: Brian Moran, radiation oncology.

JAMES LUGG, MD: James Lugg, Cheyenne, Wyoming.

MR. DANIEL TAUT: Daniel Taut with Allergan.

VIVIAN WONG, PHD: Vivian Wong, Progenics Pharmaceuticals.

MS. JESSICA JENSEN: Jessica Jensen Progenics Pharmaceuticals.

MR. CHRIS THIBODEAU: Chris Thibodeau, MDxHealth.

DR. CRAWFORD: You got Ken next to you.

MR. KEN COMIE: Ken Comie [phonetic] with MDxHealth.

MR. PATRICK SULLIVAN: Patrick Sullivan, Sanofi Oncology.

DR. CRAWFORD: Welcome. Chris attempted to make it. I think he got stuck eight hours in the Salt Lake City airport.

[Crosstalk]

Summary of Previous Day's Discussions

DR. CRAWFORD: Yesterday was a very action packed day. One of the jobs I have is to summarize the highlights and I can't obviously do everything. We had something like eight presentations and I felt bad that we were late getting started and a lot of other things happened. We didn't have enough time to have discussions after each one of those sessions but we will have time today if anybody wants to bring up some things to discuss.

Scott Lucia did a great job of moderating and introduced

Jack Shalken who has been at this meeting many, many times. Jack is the developer of PCA3 and he gave an overview of that and a little bit about where it really should be and why it isn't there and we don't know why it isn't there and some of the developments that have occurred. He talked about a new urinary test called QUATTRO which was dialed in for a high negative predictive value and discussed a little bit about that. We talked about the future would be. Some of the questions would be urinary testing and probably blood. Some people thought that, both Jack and Wim thought that blood and urine might be the first entrée. The next level when you have tissue is to work with tissue which made sense. Getting more information. That's where we are now and where we're going to be sort of the guess.

Then Wim went into a very detailed discussion on epigenetics and some of the development that's occurred there including the confirmed MDX assay and all the things that are associated with that and also a glimpse into the future in bladder and so forth. It was a very discussion, the discussion was lively afterwards.

Then we had a number of state-of-the-art presentations on many of the new markers which were really good and I compliment all the presenters for being comprehensive and on time.

Then Stacy Loeb did a very nice job talking about social media which I am not very good at. She was talking about tweets or whatever they were called and actually said that she and Laura had been tweeting each other, whatever that means. I assume that you can say that.

How many people at this table that are faculty actually have been involved with the social media on a regular basis where you've made a commitment? Any?

[Crosstalk]

DR. CRAWFORD: It's the younger people usually. Kane how about you?

DR. KANE: A little bit. I'm more of an observer. I don't enter many messages but I do read it.

DR. CRAWFORD: I wouldn't even know how to read a tweet. Maybe Laura you can tell me how to do it. Apparently I must have

a tweet site or whatever it's called. I thought it was interesting. She's absolutely right.

The other thing that you've got to watch out for is if-

[Crosstalk]

DR. CRAWFORD: You've got to watch your sites. If you Google yourself and then go to some of the ratings and sites and things like that it actually tags one bad thing to ruin your whole reputation, so to speak, you have one star instead of four or five stars and when you investigate it you find out there are three people and one's - - . I guess that is something really to work on. That was really an excellent discussion.

We didn't get to hear from Chris Thibodeau and he's going to speak here in a little bit on MDx so we'll get him up here.

Today we're going to delve into some of the local treatments and I'm moderating that. We'll have some discussions and then we have a couple of state-of-the-art presentations, one of which will be Chris. Then Dan's going to take over and we'll move into some of the other cancers including using radiation, cryotherapy, other things and talk about hormonal therapy and some of the progress in prostate, kidney, testis, and so forth.

Gerry Andriole, as I mentioned is not going to be here so I'm going to give a talk that I had the pleasure of giving in front of 12,000 people at EAU meeting and it covers the controversies of screening so we'll do that.

With that I want to invite our first speaker up here who has come to this meeting many, many times, Brian Moran.

Brian is a great guy. He's a radiation oncologist who is very friendly and works hand-in-hand with urologists in the Chicago area. He started this Chicago Prostate Center a number of years ago, I think 1995 or something. He is a graduate of Loyola and he has done a lot in the way of radiation therapy and apparently has done 12,000 seed implants and has proctored physicians all over the world. That's a lot of seed implants. Brian also has an interest that we have in parallel and that's why we got together and this mapping biopsy concept of the prostate doing more than

just transrectal biopsies and Brian's got a way to do it a little bit different than ours. It's probably a little more user-friendly and cost effective and he's been talking about that—how many years you been coming to this meeting?

DR. MORAN: At least 12. We were talking about focal therapy and everybody shook their head except for you and I remember?

DR. CRAWFORD: Right. We started it here. It was Gary Onik who's been here a number of times who is probably the guy that should be credited with it. He came here and we started bouncing it back around. What do you need to take it to the next level of interest? It has caught on. It is an alternative to active surveillance I think. It may, in fact, be more cost effective in the long run. We'll talk about that. That doesn't mean that you don't do the genomic markers to help you predict the risk factors but they're there and I think that the future we're going to see more of this.

Next year we'll be presenting sort of a turnkey operation to do these mapping biopsies with a 3D program and we have a needle that we've developed and patented which is instead of we get 17 millimeters with our needles now you can dial this needle to 25 or 30 and then you can back it off. You can measure the prostate length and then you can dial this thing in and shoot the needle. I think that will be neat, and then different ways to handle pathology we're working on that and some other things. We'll be starting clinical trials with this whole thing.

The other thing is we've got an optical biopsy needle we just went to the FDA on. Both of these things will be going next year and we'll have some new news there.

With that, just beginning I want to welcome my good friend Brian Moran up here. What is that trophy there? I've seen that before somewhere?

DR. MORAN: That would be our Stanley Cup.

DR. CRAWFORD: We had that twice in Denver.

DR. MORAN: Whatever year it was. It gets us through our winters in Chicago. Thanks Dave.

**Featured Lecture: The Future of Focal Therapy -
Brian J. Moran, MD**

DR. MORAN: I've been honored to be included in this meeting and more importantly the friendships I've developed with all of you. It was in this room probably 12, 15 years ago that we brought up—we were doing these mapping biopsies and it was really looked upon with some criticism at the time but Dave supported me and we've done actually over—now I should update my little bio—16,000 implants and we're coming out with our paper now on 3,500 of these mapping biopsies. I'm only going to briefly touch on that.

We're going to talk about focal therapy and focal therapy is really the product of patient desire. Whether we believe in it or not its here. Hashim Ahmed and Mark Emberton in the U.K. have done some really novel work and as I talk about it. That is our Stanley Cup. We're very proud of it.

We've also talked about this concept of the spectrum. We heard one size doesn't fit all. I think with all the increased technology with genomics and molecular markers technology is taking us on a different therapeutic course or approach to patients and you really have to look beyond the scope of low, intermediate, high risk. You have to consider volume. I'm very pleased to be at meetings today and see other speakers speak of the spectrum and also recognize the patients overall health spectrum. Their age, their comorbidities, it's not uncommon for us to see in the clinic an 80-year-old executive who's potent, walks the golf course, shoots his age and he doesn't want toxicity.

Why do focal therapy? Obviously it makes sense for the right patient with low volume, low risk disease. He is in a compromise between active surveillance versus radical homelard [phonetic] therapy. Can it achieve equal disease eradication? That's where technology is going to help us. It's going to help us identify this subset of patients. That's what we're struggling, all the focal therapists today, is to really define who's a good candidate for it. Obviously the one thing in its favor it has numerous salvage options. Patients are asking for it.

If you were to look at today's of the focal therapist, I

know I've shown this slide, but I can't emphasize it enough because undertreatment, overtreatment it's a balancing act and where the difference associations stand on it it's going to be slow to be accepted in the U.S. but it's taking over in Europe. Much of the new data is going to be coming out of Europe. Is there a precedent? Mike Brawer stole this slide from ten years ago. This is partial breast radiation and my colleagues in our society frowned on it five years ago. It's accepted standard of care today. It's here to stay. This textbook just came out if you don't have it I'd encourage you to—it's very well written. It's a nice little easy to read text. Hashim put it together with Peter Carroll and Mark Emberton and Mani, who I don't know, but I read it page to page and I think it's a very easy read and it will really make you think about something.

In Vail this year Mark Emberton came out and said brace yourself for the revolution. The revolution is going to be of not knowing where the tumor to knowing where the tumor is. In urologic circles there's just MRI, whether you do a transrectal or transperineal or fusion MRI is going to have a big role in this. The question is and I'll touch on it briefly when I get to the MRI slides, but instead I'll just keep going with this.

This is the patient's point. Cure rates, obviously, bladder/bowel toxicity, sexual function, time off work. Time of work, this recession's real. A lot of our patients come into clinic and they're like doc I can't be out; I have to work. Obviously cost is really going to have an impact on where we go especially with the new technology.

Like Dave said, I think we really have to streamline algorithms that are not only integrating all of our new technology but doing it in a costly manner. In Chicago it's taken off on this value concept that I'm not going to really talk about.

This slide I am going to spend some time on and this is out of the textbook and it's really brilliant what they did. We got LAT, HAT, and SAT and this is the way the focal therapists are starting to think. If you look at the LAT lesion is lesion ablation therapy. That's all you're going after and as these biopsy techniques become more sophisticated the clinician's confidence is going to rise

significantly. I am really excited about it. There are probably five different approaches but there's going to be a winner as to what's the best way to identify the dominant index lesions.

Hemi ablative therapy, that's where we are right now, we're doing a lot of hemis. Then obviously you can see the dominant lesions here and there's quite a bit of literature that they speak of in the textbook about what's significant. Maybe you don't need to treat these. That's what we're learning right now. Those three bars are self-explanatory on the bottom. Obviously the likelihood of cure the less aggressive you are. You might not be as likely to cure them however the number of candidates it just explains itself. I don't want to spend too much time on that.

The bottom line obviously is the effect on mortality. I would venture to say that much of the data out there on survival data I don't think it's going to have a negative impact. It's going to be every bit survival-wise, we all know that especially in these patients we view prostate cancer as chronic disease.

These are the current modalities. Gary Onik, as Dave said is really the pioneering work that I'll show you his data, it's the best data that's out there. HIFU really we don't have much. PDT Scott Eggner in Chicago just finished his protocol. We're excited to see his results. Then focal laser ablation. Then obviously brachytherapy, which there's a few of us in the country offering it non-protocol.

Who are candidates? This is a big debate. Is it the low risk, low volume? Everybody would agree on that. What about intermediate risk low volume disease, high risk low volume disease. In an elderly man toxicity is an issue. Every bit a candidate in my mind. Gary's data that I'm showing you here right now is great data. He did it with cryo. He really was doing this way before many of us were doing anything. You can see that the low intermediate and high risk patients they all did relatively well. He did use the Phoenix definition. I give him a lot of credit for that. He was ahead of his time on that.

This is the interesting thing. Doing focal therapy

recurrent patterns there's definitely value in a mapping whether you use MRI or not. The traditional extended sextant biopsy is not as accurate. It grossly underestimates disease; toxicity profile is very favorable for Gary's male lumpectomy.

Our experience how these patients got to us for one reason or another we treated them with focal therapy and 46 of them were done with the transrectal biopsy for which we're analyzing the recurrence data. It's really minimal; we haven't really seen any. What is important is the first five years experience look at the median age. These were healthy men; otherwise we never would have considered them. The last five years it's dropped and it's dropping precipitously. We're having men in their fifties and sixties as us for focal therapy. They're being put on protocol.

This is the breakdown of the risk groups that we're treating. You can see that they're not all low risk low volume disease. There's a significant portion of intermediate risk patients and they've done well. This is the big question; PSA response. You have to think logically about it. If you treat half the prostate you still have 50% remaining prostate that's PSA productive. This is a big debate at most of the discussions I've been involved with. I think that right now the Phoenix definition is still a good one to go by. That's nadir plus two.

This is new concept definition. We call it the impact PSA kinetics. Regardless of the modality of focal therapy that's used it's a logical approach as to the percentage of the gland that's treated should have at least some percentage impact on the initial PSA. We're analyzing this data right now and we don't have that data.

The key identify what area to treat, the dominant index lesion. MRI is doing that well in tumors over 0.5 centimeters. MRI is not of much value in tumors less than that. In fact, I just reviewed a paper that's going to be out in *Urologic Oncology*. It's a really great study out of Paris where they did MR transperineal mapping biopsies 380 patients and in the patients the that MRI were negative they then went back and did a comprehensive mapping biopsy and they found cancer in 40% of those patients, 70% of

which met NCCN clinically significant disease.

I think it's going to be a combination of both. I'm not willing to just throw out comprehensive 3D mapping biopsies.

This is an example just of a dominant index lesion and we're seeing more and more of it. The debate I think is going to be coming between multiparametric and then the comprehensive 3D mapping. I think the winner is going to be a hybrid of those two technologies. I think they both will benefit each other. Prior to this we only had radical, we all know the radical data, the upstaging, and it's significant. It shouldn't be ignored especially with today's diagnostic tools we have available.

This was just published in my society journal and it's exciting for me to see that the radiation oncology community is finally starting to get on board and consider this. This was just published last month.

This is Dave's data. I have very similar data but wanted to be invited back next year so I put this up. I'm just joking.

The bottom line is they do a 5 millimeter XYZ; we call it stereotactic because it is stereotactic, but I'm fine with 3D prostate mapping biopsy. I think that's the term most commonly used in the literature. It's very sensitive. It really doesn't miss.

The last bullet point they look at that whole mount radicals and it had a 96% concordance value. We found the same thing in Chicago in 107 patients. It was 96, 97%. It is value.

This is where things are going, just speaking with a few people, some of the new software companies are coming out and its I think, for all practical purposes address MRI, ultrasound, fusion technology. Again, symbiotic relationship between the different diagnostic tools. This is where the tumor was identified on a MRI and on mapping biopsy and then this is the implant needle going into target that area. That software is very exciting. We can't afford it. We're working with a company that's letting us use it.

This is my new study we just opened in April and you can see that the accrual rate is very fast and so I have no problem as long as patients go on study in informed consent we're going to probably finish this before the years out.

Our goal here is to really document that you really shouldn't even consider focal therapy based on transrectal biopsy. We did include those patients and that's just going to be a big question that we can all get out there and move focal therapy forward. We are using cesium on these patients based on its energy in the physics world. It has the most generous energy and my philosophy there was if I'm skimping on things then I definitely want to use a generous energy to avoid cold spots. I think a brachytherapy definitely will have a role in focal therapy.

We don't know optimal outcome. Follow-up is a problem especially with regard to the PSA and it's not the nadir so much as the PSA kinetics post-therapy. I think everybody's agreeing on that.

It is fun. We have a lot of people working on this around the world and listening to them put their heads together is exciting. This is exciting because it goes back to 2008 was the first international focal meeting and its happening.

I would say there's emerging evidence focal therapy will have similar disease control as whole gland treatments however the morbidity may be much less. In my experience without question it is. A partial implant versus a whole gland brachytherapy there's no comparison. I think it does have significant promise. I think that proper patient selection ideally treated on study, optimal modality I think there will be a few of them and salvage treatment.

We were at the meeting in Vail and the question was posed to a very impressive panel of urologic surgeons. Jim was up there, Alan and the question was posed to these guys; do you think there's a role for focal therapy. Across the board there was not one person that said no. I was blown away by that. When I saw the caliber of those individuals say yes, in select patients there probably is a role.

That's really I think. If you want to see the Stanley Cup I can show you that.

Thank you very much.

DR. CRAWFORD: While we have you up there let me ask you a couple questions. Yesterday I mentioned that I think there's really a role for using 5-alpha-reductase inhibitors in a lot of these people on active surveillance. What happens with active surveillance or focal therapy is their PSA goes up a little bit because it's BPH and then they all get worried and then they get re-biopsied or they want to go get a treatment and things like that. Are you using that? I think that's three things. One is that it may prevent cancer. We know that from a couple of studies. It may treat low-grade cancers. We know that from the REDEEM trial. It certainly treats BPH and if your PSA goes down you have a new nadir. Do you use that much or do the urologists you work-

DR. MORAN: [Interposing] That slide that I showed you LAT, HAT, SAT we are using it in the SAT group to take care of those microfoci that we're not treating and that's the rationale so it has been used. That's not on the study but we have been doing that.

DR. CRAWFORD: How are you ablating? With cesium now?

DR. MORAN: We've used iodine, palladium, cesium but I think we are right now going forward on the new study its all cesium.

DR. CRAWFORD: We use cryo, Honick [phonetic] cryo. You mentioned people were using other things like that. We'll have to see. Then there's electroporation and a bunch of other things that are out there.

Any questions for Brian?

DR. BRAWER: Nice talk as always. What is your thinking about- this may be ongoing treatment. You may need to hit them with radiation or something else again over time, right, especially if you start with a young person? There seems to be an advantage of cryo or maybe HIFU in that you don't cause enough tissue trauma of rectal, et cetera, so you could then after this do external beam or whatever. What's your thinking about using radiation upfront as opposed to a less perhaps injurious energy to - - .

DR. MORAN: That's the one downside of radiation. You commit

yourself to an implant you really can't re-implant the patient again in the same area; however, when we plan these patients we do two plans. We do the focal plan and then we do the completion plan. If they fell in the future it completes the implant to the whole prostate. We haven't had to do that yet which is really interesting. We have not identified contralateral disease that's been diagnosed.

MALE VOICE: [Off mic]

DR. MORAN: Ten years. That retrospective analysis goes back ten years but now we're going prospectively. Marc, and then I'll give it to you Frans.

DR. GARNICK: Are you using oncoType DX or any of the other genomic profiles to get a handle on which lesions should or should not be ablated instead of looking at those when they get their recurrence.

DR. MORAN: I think that one then Prolaris are being used going forward.

DR. GARNICK: But are you making any ablative or focal selection decisions based upon that.

DR. MORAN: If they fall into the more unfavorable categories the higher risk group I don't recommend focal. It's not part of the study but I think as a clinician if we suspect there's more aggressive disease there than the risk group predicts then we don't recommend focal. Did I answer your question or not?

DR. GARNICK: It seems to me that's a hypothesis you could actually test to see whether or not you can ablate the lesions that-

DR. MORAN: [Interposing] I think these biomarkers are without question going to have a huge part in the toolbox for focal therapy and that needs to be incorporated going forward. There's no question about it.

DR. GARNICK: You're not making a distinction on Gleason score of the lesions that have been ablated?

DR. MORAN: No. Right now we're looking at all risk groups. It's really volume. It's really volume and it goes back to these biopsies. Raoul and then I'm sorry, Frans.

DR. CONCEPCION: Brian, what if on the contralateral side where

- you had a negative biopsy you ran a confirmed DX and you had significant epigenetic changes there.
- DR. MORAN: I think that needs to be done. I've heard that proposed and we're not there yet but we need to be doing those things.
- DR. CONCEPCION: Would that sway you-
- DR. MORAN: [Interposing] It's a whole new frontier. That's an excellent question. It has been asked and I think that's one of the next steps going forward. What do you do with these negative biopsies? Are they truly negative? Are they higher risk for the future? Nobody knows that. It's funny the farther we get into this the more questions are coming up and the more little uses we're finding in this algorithm. It's defining itself as we're going forward. It's very exciting. Frans and then I'll get to you Dan.
- DR. DEBRUYNE: I had the opportunity recently to visit - - of course I've been - - department several times. I'm convinced that focal therapy is going to play a significant role. My concern however is two-fold. First of all that the technology and the experience that you need to have is quite sophisticated so it's going to be very difficult to penetrate at least in the general urological community. It's a very, very difficult part of concern at least as far as I am concerned. Second is the question can you do that like Fernando Bianki [phonetic] does under local anesthesia?
- DR. MORAN: You could. The only one that's done that is Ken Walder [phonetic] with perineal anesthesia and he was injecting lidocaine. You can do it but those patients threw a lot of PVCs at the VA in Seattle. It was kind of a scary experience.
- DR. CRAWFORD: Why because they used so much lidocaine?
- DR. MORAN: Yes.
- DR. DEBRUYNE: That's the second - - question. What about the sophistication of the technology?
- DR. MORAN: It is. Focal therapy has created an environment where less is more so not only to intervene it's less operator-it's more operator dependent but less labor dependent.

DR. DEBRUYNE: The technology the fusion is quite complicated at least for urologists.

DR. MORAN: This new software that I just showed you that I have no financial relate, that one slide I showed you-

DR. DEBRUYNE: [Interposing] We are using the - - software.

DR. MORAN: That's MIM.

DR. DEBRUYNE: We are using the MIM software and I can tell you this is, at least as far as I am concerned, there are probably 15 companies providing software for fusion. At least six in Europe and probably six or seven-

DR. MORAN: [Interposing] MIM is the future.

DR. DEBRUYNE: MIM financially they - - but we evaluated the model and came to the conclusion that probably MIM is the most advanced. The disadvantage however is that your MRI - - the guy who makes the MRI the multiparametric MRI needs to have the same software.

DR. MORAN: Right. They're making great advances and making it simpler for us. I think I'm done, am I? Dan, go ahead.

DR. PETRYLAK: It's interesting you did it with cryo and the question I have is about the PSA. Has anyone actually looked at immune infiltrates in the primary tumors after patients have had cryotherapy because there's data that suggests there's activation of dendritic cells? I wonder whether you could actually see that either at the periphery of the tumor or within the tumor cells themselves.

DR. MORAN: What was the question?

DR. PETRYLAK: Has anybody looked at dendritic cell or T cell infiltration in the prostate after cryo surgery?

DR. MORAN: We looked at dendritic cell infiltration during brachytherapy and after intratumoral injection of dendritic cells. That was published in 2011 and I'll show it to you. There is no tremendous immune infiltrates before 45 - - of doing that in intermediate risk implant.

DR. CRAWFORD: There have been reports going way back in the literature about spontaneous remission of metastases in men who had cryotherapy of their primary in patients that were castrate-resistant. We have a grant to look at measuring

immunological responses wherever in the hell that is because you try to find out what should we look at, what should we measure and talk to—and we actually hooked up with the people at National Jewish who are big in immunology to do that.

As you well know Dan, some of the ipilimumab and things like that I think—in the studies didn't they prime that with doing one dose of radiation. Cryo to me would seem to be a good option and do it. We're looking at that right now as you well know from the studies with Provenge that found immunologic areas of surrounding tumors when they did radical prostatectomies on some of these people. Michael.

MR. BRAWER: Jack Singer who is Tia Gano's [phonetic] husband, most of you know her, he's a medical oncologist—he went to the dark side, he's at CTX. This is 15 years ago and more maybe, of all the perturbations we could do to the prostate, this was when I was at the U, I gave him serum over time before and after cryo and compared to everything else that we did, radical, all kinds of radiation, brachytherapy, cryo induced the greatest pan-immunologic effect - - and Hawk and Rogby [phonetic] had a protocol going on in the Philippines which I've not heard anything about, of actually doing this in the metastatic setting. Cryo for exactly that reason.

DR. KANE: Great talk. I find a lot of young men who are thinking about focal therapy. The barrier is poorly defined secondary treatment rates. They're trying to understand what's the chance I'm going to get away with this versus be treated. Then if we use cryo or brachy it makes surgery as a second treatment more difficult. What do you think about things like laser or gene therapy, something other than cryo or brachy in the younger guys? Then you're getting into more morbid surgery if they're choosing surgery as salvage. I think it locks down that second and third treatment for the younger guys.

For older guys who are choosing whole gland radiation or whole gland cryo as their salvage not a big deal.

DR. MORAN: I can answer this. The younger men are really focused on salvage options and Josh Meeks in Chicago now does our salvage cases but we haven't had any to send him out of the focal group. I'm just waiting for either a

whole bunch of them to start fouling or maybe we are onto something. That's a great question but I don't know the answer. There's a question from industry. Peter Knapp.

DR. KNAPP: Brian you had mentioned that the volume was your threshold determinate as to which patients to go ahead with brachytherapy and which ones not to. What volume is it? Is it 4 positive cores out of a 12 core biopsy? Is it eight?

DR. MORAN: We do our biopsies based on octants. We divide the prostate into octants so our protocol is one quadrant or hemi. A quadrant would be ideal. We're really not looking at the number of biopsy specimens. It's the number of quadrants that's involved. All the studies today look at this concept of quadrants. What are you guys doing? You're doing quadrants or octants?

DR. KNAPP: No, we use the brachytherapy grid and go at 5 millimeter intervals.

DR. MORAN: For their biopsies but that's how we define the volume. It's a quadrant.

DR. CRAWFORD: Two octants, one on each side they would still be a candidate if you have three octants that's too much?

DR. MORAN: If it's contralateral yes. If you have quadrants it's all ipsilateral. Right now where we are we're in the ipsilateral world. Either whole anterior half, whole posterior half, whole right, or whole left. We haven't been able to split the gland base or apex. That's the challenge. The new software hopefully is going to be able to answer that with the - - .

DR. CRAWFORD: I think that the way we do it we've done probably now 50 to 60 radicals on men that have had napping biopsies that had worse disease and we've only reported probably on 30. Scott knows this very well. The correlation is outstanding between at least with the 5 millimeter. It's very time consuming. You've got to - - the proximal end and reconstruct it and everything else. I feel that it reflects what's going on. We'll take on more aggressive cancers than just the six now because we feel cocky or confident, whatever you want to say.

I think just to finish up and make some comments a lot of

people say you do all this focal therapy and its bullshit because basically its people that were candidates for active surveillance and you should have done the active surveillance and you're making a big deal out of it. I think that's true to a degree but also the patients like to get rid of the cancer. It does probably cut down on the follow up. The other thing is you mentioned confirmed MDX in doing that. What you're trying to do is spare the nerves and apex basically so what if you just did a biopsy along the nerve on each side and then you did the apex and you did confirm MDX on it and they're negative. There's no methylation at all. We're looking at that as a way to say we'll just treat the whole gland. That's another option.

As I get these people out seven to ten years that we've done and I'm starting to see some Gleason 6s back and failures and I get a little depressed but we save these guys ten years of having potency and so forth so I think it makes sense.

To answer the question that was brought up about surgery being more difficult I don't think it is. I've done enough of them to know. What makes surgery difficult are people that have a lot of transrectal saturation biopsies. The mapping biopsies do not, and I've done 50 or 60 of them, do not make it more difficult. I've done a lot of salvage prostatectomies after cryotherapy and we've had a few failures where we've done the mappings where we did them. I don't think that's too much of an issue. It's when people have a lot of transrectal biopsies and the saturation ones are the ones that you really have a difficult time. I heard Pat Walsh [phonetic] say how hard it was to do the radicals after that and I said I don't think that's the case. Then I realized what he was talking about people had saturation biopsies. Do you feel the same way?

DR. KANE: I agree completely I think that the mapping biopsies don't make it much more difficult at all. I agree; multiple, multiple, multiple transrectal. Cryo I've done a couple of salvages after cryo and those were pretty ugly. HIFU wasn't much and brachy - - anymore. Cryo and brachy both is a horrible - - .

DR. MORAN: I can probably say one thing. Speaking of the surgeons in Chicago the implants have become so

sophisticated keeping the dose almost right inside that gland that the surgeons are saying there's nice planes to work with and we weren't seeing that ten years ago.

DR. CRAWFORD: Let me ask another radiation oncologist next to me, Dr. Finkelstein just as a reality check. Do you concur with what he said?

DR. FINKELSTEIN: Brachytherapy is a wonderful modality. My father has Gleason 9 prostate cancer. When it was time to treat his cancer he was treated with brachytherapy combined with external beam. The question I was going to ask you would be having done a lot of LDR; my partner is Alvaro Martinez. Alvaro is saying brachytherapy is dying. I like the idea of HDR because it obviates the problem that you were saying of doing LDR seed implants multiple times. You could do HDR multiple times potentially. Potentially if you believe in, you get some credit for time served after the time after your implant you could give more radiation. Alvaro will tell you that he thinks brachy is dying I was going to ask you what you thought of that.

DR. MORAN: There are a lot of factors out there. The brachy use, the urologists just aren't referring patients for LDR brachy across the country now. Jim Morris's study, the ASCEND RT study that was just presented this past April.

DR. FINKELSTEIN: ASCO.

DR. MORAN: Yes. It's hot. It's looking at intermediate and higher risk patients treated with either IMRT and androgen blockade versus three-way therapy; androgen blockage, IMRT, and implants. There was a 50% BNED difference at five years. This is a prospective randomized - - .

DR. FINKELSTEIN: However, what I would say is in order to do a brachytherapy implant or focal therapy you have to be halfway decent as a doctor.

DR. MORAN: No question.

DR. FINKELSTEIN: In order to do external beam not so much. I teach the ASTRO contouring course. ASTRO, our professional society has a course in which they teach radiation oncologists how to draw the prostate. It's a ball, right, behind the pubic symphysis; how hard could it be. What do you think the pretest success is for board certified

radiation oncologists. Want to take a stab? Dave?

DR. MORAN: Seventy percent.

DR. FINKLETSTEIN: Oh, we're not that bad. We're a little bit better than that.

DR. MORAN: Ninety percent?

DR. FINKELSTEIN: No, we're not that good. It's 85% is the pretest which means what's the success rate of take all comers for prostate cancer for radiation? About 85%. My take would be if you go to see you and maybe me and you do external beam. You're going to hit the prostate. I'm not convinced everybody on the planet is going to hit the prostate but if you do brachy for a living you're going to hit the prostate.

If you do a trial, when I was a surgeon for ten years, we always wrote those papers; my outcomes are better than yours, right? How many times did we see those outcomes from Whipple's from Hopkins? Everybody is not going to have the same outcomes but I do believe that brachy in the right hands has the potential of being an incredible therapy.

DR. MORAN: It's a lost art form. Alvaro was right. At least LDR is. HDR is coming alive.

Thank you.

DR. CRAWFORD: Thanks a lot. We want to invite Chris Kane up to talk about robotics. We've had a number of different presentations over the years on robotics but we're glad you're here Chris. Chris is Professor and Chair of Urology at UC San Diego. He's done a terrific job there. I've been down to visit him a couple of times and the program there at the cancer center, the folks he has—are you the chair of surgery still?

DR. KANE: No, I'm not the chair. I was Chair of Surgery for two years. Now I'm just Chair of Urology. The counseling is over. Release the psychiatrist. Now I need counseling for three foot downhill putts after this morning's round.

**Featured Lecture: The Future of Robotics -
Christopher J. Kane, MD**

DR. KANE: Thank you very much for having me David. I really appreciate it and Marc beautiful organization for the meeting. Thank you so much.

I'm going to talk a little bit about future looking things in robotics. We'll talk a little bit about the XI. How many people are doing robotic surgery in the audience? How many people are very familiar? Not many. Okay.

We'll talk a little bit about the systems and I apologize there. By definition we have one major company so I'll be using some of their slides talking about their system. We're talking about the da Vinci robot which is by far the widely used system in the world. Then we'll talk about future looking, what are some of the applications of robotics that I think are coming both in standard surgical oncology and urology. It's really going to have to do with the robotics as a platform to enhance fluorescent imaging and I'll show you some work that we've done on sentinel node imaging with fluorescent imaging agents. There's also some really interesting work being done at UC San Diego and elsewhere of imaging of tumor and imaging of anatomic landmarks like nerves. The robotic platform and actually just laparoscopy in general is really nice for the new imaging agents because we can control the laser light source and the laser light source is unique to each of these fluoroprobes.

I think when we think about the future in the next 10 or 20 years I think we're going to be doing more image-guided surgery with the new fluorescent agents and I'll share a little bit of that with you.

I think the other thing that's going to be a bit of a revolution is public reporting of outcomes. I'll show you my public report. Public reporting of outcomes is now happening, not just in cardiac surgery but just in the past two weeks in urology. For radical prostatectomy for the first time.

DR. CRAWFORD: How as your - - ?

DR. KANE: I'll show you mine. I'll print it out for you. We can lament the process but it's here to stay and I think what public reporting of outcomes is likely to do is increase regionalization in the united states for elective procedures. That's what it did in cardiac surgery and I

think it's likely to do that for total joints, knees, hips, radical prostatectomies and other elective surgeries. I think that transition and revolution will happen in the next three years.

I'm not going to talk about the new robotic companies very much but there are four major competitors. There are about 100 companies in this space and they're each using robotics for different specific applications. Single port robotics, this is Titan Medical has an item that's likely to be cleared for use that actually holds the single port system and has an elegant flexible single port mechanism which makes single port laparoscopy much more straightforward.

TransEnterix is robotics and flexible instrument really around advanced GI so for ERCP and for advanced colonoscopy where they can do major resections and reconstructions intraluminally so it's really elegant technology.

AVRA Surgical is modular lightweight robotics so you can just use different sections. You don't have to buy the entire whole da Vinci system. MAKO robotics is for joint replacement precision and that's actually commercially active company right now. I'm not going to go into those in detail just for the interest of time.

The evolution of robotics, this is the first system that started with in 1999. It was awkward. It took about 15 minutes to dock the system. We put laparoscopic ports in and then we dock this robot to the laparoscopic ports and then through these ports go the robotic instruments.

The da Vinci S was quite a significant improvement in 2006. It had a better HD vision. The SI is the dual console which enhanced education and I think the safety of education. It also has the firefly system which is fairly primitive fluorescent imaging, had a single sight mechanism, not much single sights being done in urology but quite a bit is being done in general surgery for cholecystectomy. It also has a Skills simulator that's marketed. There's recognition about how difficult learning robotics and how many surgeons were struggling inside their first hundred cases so there's been a moment to try and enhance education through skills simulation.

The new system that just got released this year is the da Vinci XI and it really is quite a different system. This

patient-side console is very different. The actual surgeon console is quite similar but it has stapler, vessel sealers, future innovation for single port surgery, integrated energy. It's got some nice improvements.

This is just a little bit of the new system. The surgeon console is our surgical environment with clutch pedals and manual controls and that didn't change and that's really useful because when it changes like it did for the S to the SI it takes surgeons months in many cases to get comfortable on the new system. It's like having a new car and driving a new stick shift. It takes you awhile for it to become second nature.

The real advances are in the patient cart and in the energy and optical systems. Just real briefly the patient cart, this now can basically be positioned over the patient. One of the awkward things when you do a radical prostatectomy you position the cart between the legs. When you do a nephrectomy you position the cart over the shoulder and the cart is somewhat awkward and gets in the way of anesthesia so this is designed to come in to the side of the patient and this entire system can rotate so that we can position it for a nephrectomy or a radical prostatectomy or a nephroureterectomy or a colectomy where we have to actually operate two quadrants of the abdomen. The most significant advance is that new flexibility.

These arms are a little bit better than the old arms, better range of motion, longer instruments, just creates more versatility. This is a little easier for our nurses to dock. It's quicker. It has a little laser pointer so we position it over the patient properly. It has a height adjust which again are a little convenient advances.

The significant thing is it used to be a hassle for the nurse. You have to black balance, white balance, zero the image. It used to take quite a few minutes to standardize the camera. Now it's all automated. It's an 8.5 millimeter camera so the new camera can go in any of the laparoscopic ports. That's a real advance. If you're doing a nephroureterectomy you start with a camera low looking up toward the kidney doing a lap nephrectomy then when you go down to do the bladder cuff you switch the camera into a different port. It used to be the camera would only go in a 12 port and the instruments were in the

8s. Now the camera can go into any port so there's greater versatility. There are some nice and practical advances. Easier for the nurses. This is the new energy system. Bipolar and monopolar on the same cart. This is a new system that allows single port surgery that again, is beyond the time of this talk. Then new staplers, new seal devices. Really quite nice.

Future thinking I think we're going to do more image-guided surgery. I think this agent we're talking about here for lymphatic imaging is FDA approved now but the fluorescent version of it will be available probably within 12 to 18 months. Some of the tumor labeling antibodies with fluorescent imaging should be available in three to five years so this is in the near term horizon.

This is an elegant molecule that binds. It has a dextran backbone so it binds to lymphocytes and it's labeled with technetium 99 so this is in widespread use in breast cancer and melanoma now. It's injected into the primary tumor and then you can do scintigraphy or you can do a PET CT to see that sentinel lymph node. This goes to the sentinel lymph nodes, binds to lymphocytes, and does not go to the next echelon of lymph nodes for over 24 hours. It gives you a nice timing interval to image to choose that sentinel lymph nodes. It's the standard of care for breast and melanoma. It binds to CD26 which is a mannose binding receptor in lymphocytes.

Prostate cancer and bladder cancer, these are high impact areas for potential sentinel node imaging. Also I think gastric, colon, and gynecologic malignancies they're all cancers where fairly extensive lymph node dissections are currently done and they're only currently done because we can't accurately image the first echelon lymph nodes. The potential utility is to avoid these excessive lymph node dissections while identifying the patients at highest risk for metastases.

DR. CRAWFORD: What's the volume - - .

DR. KANE: It doesn't bind tumor cells it binds the lymphocytes so a very small volume of the injected agent is visible both on PET CT and on fluorescence. Less than a tenth of the injected volume.

What do we have now for fluorescence agents? We use this

ICG. In Europe it's mixed with Nanocol, that's a blood-based product that's not available in the U.S. It binds to plasma protein, it dissipates fairly rapidly so it's really not a sentinel lymph node imaging agent. It goes to the first echelon lymph nodes and then in 10 or 15 minutes it goes to the next echelon lymph nodes. It's been very well studied in Europe. We've done a set of developmental studies with the new tilmanocept labeled with a new fluorescent dye and this is IR800 dye and it's basically that same Lymphoseek molecule with technetium but now we put a dye on it and we've actually tested three different dyes. Just to show you how this works this is in a dog we inject into the prostate and then after the injection we do a PET CT and the sentinel lymph nodes light up beautifully because it's gone to the first echelon lymph nodes and then we can go ahead and do surgery. This is what the target lymph node—this in a popliteal rabbit experiment, a little different than that dog experiment but this is the first echelon lymph node and we've injected the agent into the foot of the rabbit and this is what it looks like on fluorescent imaging. This is really practical to do in the robotic system because you can change the laser wavelength.

In this prostate injection study in a dog this is us injecting the prostate, this is the PET CT of the dog. This will show you a brief video of the way it looks robotically. Let's try and run that fairly quickly.

DR. MORAN: Chris, does this just identify the sentinel node?

DR. CRAWFORD: No it doesn't identify whether it's positive or negative.

DR. KANE: Correct. It just identifies the sentinel lymph node. This is the injection site of the prostate. We just switched to the FireFly system. We have added a modification so that it is at the right wavelength to make IR800 fluoresce. That's the site of the prostate looking abdominally. This is in the dog looking toward the foot and we could see on that PET CT there was a pre-sacral lymph node so now we're going to go after the pre-sacral lymph node robotically. Again, the dog's foot's here. This is pre-sacral. The lymph nodes going to be in this zone. We can't tell where it is on white light. That's slow-mo. See if we can get it going a little quicker.

Just 10 more seconds I think we're going to flip to florescence. You'll see the lymph node is very easy to see in fluorescent imaging.

This is ready for primetime. What is in development, and again we have grants and work going on in cervical, colon, bladder, and prostate right now. That's the research team. This is David Vera who invented that molecule. That molecule is now FDA approved and its standard care in breast and melanoma and I think it's going to be ready for primetime in prostate and bladder. Our clinical trials hopefully will be ready after our safety studies in about a year or two.

The next wave is actually fluorescent imaging for tumor and for nerve and other anatomic landmarks. Much of this work is based on the pioneering work of Nobel laureate Dr. Roger Chin and he invented green fluorescent protein and his main collaborator is Quven Nguyen, who's an ENT surgeon. She did a state-of-the-art lecture for image-guided surgery at the AUA last year and it's excellent. She just received the Presidential Early Career Award for Scientists from President Obama and she has a TED talk that she did on this topic that has now had over a million views. Because I only have ten minutes I can't go into it but they've developed a bunch of elegant proteins and this is the site for the TED talk. If you just TED talk image-guided surgery you'll see her presentation and there's molecules developed that bind to the antibodies of every solid tumor you can imagine with different fluorescent wavelength markers.

This is happening fairly soon. This is from one of their *Nature* papers. This is one of the proteins that labels nerves and look how white light you barely see it and then given the two different proteins the nerves just show up beautifully. Can you just imagine seeing that in radical prostatectomy; darken the room and put the correct laser on the nerves would light up.

This is a recurrent laryngeal nerve just how easy it is to see and this is labeling a medullary thyroid cancer tumor model and just beautiful fluorescence so you can imaging seeing the actual prostate cancer, the capsule, the nerves, and being able to have image-guided surgery. This is certainly within our professional lifetimes I think five,

seven years away.

Public reporting and we've done experiments in rats trying to use their proteins to see nerves. You can see autonomic nerves but the autonomic nerves of a rat because they're not myelinated are very tough to see. I think in larger animals it's going to be better.

This is public reporting. Have all of you seen this data? How ProPublica has surgeon-specific data available. They use the last three years of Medicare data. You have to have at least 50 cases within 3 years on Medicare patients with data available. They only look at complications data which is readmissions or deaths so it's a very narrow definition of quality. We actually have a pathway that patients go home within 24 hours so our readmission rate is a little bit higher. This is my actual data, 107 patients who could fit in my little mark. It doesn't show up well. This is a continuum of risk and I was in the middle of surgical risk but the confidence intervals go all the way from low risk to high risk so it makes you wonder.

DR. CRAWFORD: The ones I saw - - didn't have the number of times you did it, I don't think.

[Crosstalk]

DR. KANE: It had to be more than 50, between 2010 and 2013, patients over 65 with no secondary insurance with data evaluable. We went back and looked it up. Between those three years I did 440 radical prostatectomies only 107 make the list because of the age and the quality restrictions.

DR. CRAWFORD: The one I saw had tic marks for other surgeons in the area and they had a map where they were.

DR. KANE: You just can't see it. There's little dots right here that are the range of performance. It didn't show up on this reproduction. If you go to the website it's pretty interesting. You can look up any surgeon in the United States. Right now they have data for total joints, cholecystectomy, radical prostatectomy, and - - . Unfortunately the original article and the highlight of the article in the *Wall Street Journal* named a very well known urologist at Johns Hopkins who happened to have a high complication rate and it's pretty damning and his names in the *Wall Street Journal* as someone who's pointed out. It

is supposed to be acuity adjusted.

MALE VOICE: Can you tell me what the validity of this is? If you're only taking a sample of a third of your cases. The public doesn't know this.

DR. KANE: That's a great question because it's really up to us. We have better data than this. We have a surgical score card, we're a NSQIP hospital, we have UHC data so I know hospitalization, - - transfusion rate, complication rate. we actually have much more rich data. We just don't share it publically because we're concerned about interpretation and if you do a lot of salvage prostatectomies you cannot judge. You're going to have a two or three times readmission rate so I don't think it's ready for primetime. The AUA, that American College of Surgeons both have a statement saying that this is data before the quality and the ability to interpret it. We think the data is a little bit ahead of the ability to interpret it.

DR. KEANE: Chris, great talk so far but I have to say I think this is absolutely bullshit. I do nothing but perineals so my group is—I think I had 45 during this time, I had no complications, but I was considered high risk because I didn't have more than 50. A couple of points these patients are all over 65-years of age. Typically we shouldn't be taking out their prostates in the first place if they have low to intermediate risk disease which is what everybody's moving towards. Second point it was readmissions as you said there was nothing else really about it, its absolute crap. I want to know how many transfusions our patients if they—why do they need a transfusion, how many rectal injuries, all of that stuff. None of it collected. I think that - - at this stage. We should have as a group we should have said you're going to pout this out then you better put something that's meaningful but not trash like this.

DR. KANE: It might behoove us to publish the data we have. We have higher quality data than this that we currently have available certainly for the NSQIP sites. For those of you who don't realize it, NSQIP is the American College of Surgeon's quality metric. They actually put a nurse in the hospitals and they actually really carefully adjudicate each of the complications and its very high quality data and the American College of Surgeons doesn't publish it for

those very concerns.

DR. KEANE: We should publish it I think it's becoming obvious. Otherwise we're going to get this sort of stuff published.

DR. KANE: But to the public it sounds like we're unwilling to be public about our outcomes. I think from a public facing perspective we're going to have to come up with a better solution than crap.

DR. KEANE: There's an old saying if you can't stand the heat get out of the kitchen. There's nothing wrong with publishing our complications. If we can't stand the glare of the light then maybe that's a good thing.

DR. KANE: My point for what's the future is I think public reporting is going to lead to enhanced regionalization because we're really controlling NSQIP outcomes when we're really working at our processes you need big teams and high volume to do that well and there's no way you can do that effectively in a community hospital. It's very difficult. That's not to say there aren't great surgeons but it takes complex systems to really drive outcomes. I think we're going to see more regionalization. That's my prediction for the future. The title is the future of robotics. I think we're going to become more regionalized with elective surgery.

DR. GARNICK: This was a great talk obviously. I assume you have the XI?

DR. KANE: We do.

DR. GARNICK: Nice. The public reporting is interesting though because when it came out last month I looked up people I knew and myself and those of us at the safety net hospitals, those of us at the academic centers clearly had higher scores than other people in our regions who had nowhere near the same numbers and I think I had 84 out of 400 I had done and my score was actually 3.4 so you're clearly a better surgeon than I am.

DR. KANE: The confidence intervals are huge. They go from 1 to 5.

DR. GARNICK: Any of us that work in those systems, UC San Diego, I was in Arizona at the time but UMass even more so the readmission rate is much higher just because the

patient population is - - . None of that is - - . Thoracic surgeons did a phenomenal job with SDS in their database and their data's out there and you're right, urologists and general surgeons should follow suit because we have to - - and that's obviously much more vetted, much better data.

DR. KANE: That's a great point and in the acuity adjustment, the typical acuity adjustment is - - and comorbidity index and most of these patients are zero and one so it doesn't do much for you. Also sometimes diabetes or renal failure. I know that when someone has heart disease and they've had stents and they're on Plavix I'll operate on anticoagulated patients and I'm the only guy in our region that will do that so if you're willing to operate on anticoagulate patients your readmission rates going to be a little higher. Those sorts of subtleties are unmeasured.

DR. GARNICK: - - which is now we have the same - - pathways we actually a perioperative surgical home and we're trying to get patients out within 23, 24 hours increased readmission rate absolutely with that.

DR. KANE: Any other questions?

I do think the intuitive surgical robots are evolving and improving, improved simulation and safety. The next horizon is fluorescent imaging for lymphadenectomy for tumor identification and for anatomic identification. That's going to be here during our professional and surgical lifetimes.

I do tin public reporting is there to stay whether we like it or not so it's going to behoove us to manage it.

Thank you.

DR. CRAWFORD: That was very good.

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

DR. CRAWFORD: Next we're going to have invited state-of-the-art presentations. Chris, are you ready? Chris Thibodeau who has been to this meeting a number of times is going to talk about ConfirmMDx. We heard a little bit yesterday from

Wim. Chris is a good friend and a brilliant guy. His title's always changing. You're Vice president Commercial Operations MDx in Irvine.

MR. THIBODEAU: Thank you very much and it's a pleasure to be here once again. I have a brief presentation. I'll just cover some recent data that we've developed and Wim touched on it a bit yesterday. It was presented at the AUA earlier this year.

We are a publically traded company so any statements I make which may be forward-looking you should take into consideration and do your research before any investments.

When we look at ConfirmDx and most of you in the room are probably familiar with the assay. It's a test indicated for men being considered for repeat biopsy. The ultimate goal based on guidance from thought leaders like yourselves, re received years ago, was really to focus on how do we reduce unnecessary repeat biopsies. By virtue of that we help identify men at risk for prostate cancer who might benefit from prostate biopsies.

The data we presented in the past which I'll cover, we've got over 45 published studies in over 4,500 patients. I'll cover a little bit of that here, just some of the recent data we've generated in the last five years. A meta-analysis on 35 studies in over 3,500 patients where we demonstrated that the genes and technology could yield a very high sensitivity and specificity for prostate cancer. We conducted studies on both health economics, on clinical utility. We have a lot of that work ongoing as we speak with additional studies. Recently in the last couple of years we presented some multicenter clinical validation data using a defined assay with defined cutoffs in two different cohorts, one European, one U.S., to demonstrate that the test performs in different cohorts. We'll talk about that a little bit.

The clinical utility study was really to demonstrate does the test have an impact on physician behavior. This is, as we've talked last year and the year before, significant for reimbursement and of course, we have to focus on reimbursement because ultimately we can't continue to offer the test if we don't get paid. Whether it's Dr. Jeter with the MolDx program through Palmetto GBA for Medicare

coverage or really if it's Aetna, CIGNA, any of the major providers healthcare insurance companies they're focused on clinical utility. This is a small retrospective study where we compared the performance of the assay in patients with a test negative results. The rate of repeat biopsy of those patients on a mean time of follow-up of about 18 months we showed a 4.4% rate of repeat biopsy in those patients as compared to what was reported in the PLCO study which is a rate of about 43% of men with an initial negative biopsy will go on to have a repeat biopsy so a ten-fold reduction. We hope to demonstrate that in a large prospective study that's underway. Neil Shore, who was here yesterday, I missed him, is the principle investigator in that study. Its 600 patients at 18 sites throughout the U.S. We expect to have those results in the first half of 2017 but again, 600 patients being tested and then following those patients to see if the test results influenced physician behavior. Dr. Concepcion is also one of the investigators on the study as well.

The health economics I mentioned earlier, this is a budget impact model we used as the basis of our submission for Medicare coverage and for other payers for that matter. We showed the application of the assay in the negative biopsy population for those men being considered for repeat biopsy could actually reduce healthcare spending on average about \$588 per patient. We have to be cost conscious about the type of testing we do. Is it going to improve outcomes? Most certainly we would need to but also can we improve health economics and that's really been our objective from the beginning.

Most of that data was used in submission for our medical dossier and review by Elaine Jeter in the MolDx program. We passed the technology assessment which was very rigorous. Dr. Dennis is here, Dr. Brawer is here. They've been through it as well with their assays and I think they can attest to the fact that it's a high bar. Since its introduction in 2013 you've had a very low number of tests actually pass the technology assessment. They're making sure that you have not only clinical validation but clinical utility data that justifies coverage of the assay.

What it does validate is the test is reasonable and necessary and that's I think a great description of how these tests are going to play and through Medicare's eyes.

Recently the data we just presented which Wim touched on a bit yesterday, in both the MATLOC and DOCUMENT studies we demonstrated that ConfirmMDx is the most significant independent predictor of prostate cancer detection on repeat biopsy. The test was designed for negative predictive value. How do we rule out the men who don't have cancer from undergoing unnecessary repeat biopsies but when we look at that test positive patients we can show that this test outperforms all the standard clinical risk factors for prediction of that outcome, that next biopsy. It's important as compared to PSA, high-grade PIN, age, even DRE.

When we looked at this data we have a cohort of 803 patients we developed a risk score. This has yet to be launched. We expect to launch it later this year. We developed an algorithm so test negative patients the results remain the same. For test positive patients we're introducing an algorithm to stratify those patients further to say these are the men that are at significantly high risk or high risk for significant cancer. These are the men mostly like where you would find Gleason 6 cancer upon repeat biopsy.

We developed this algorithm which we will publish the results I think fairly soon and we decided to improve the stratification of those test positive patients to really help improve the guidance for men who would benefit from earlier repeat biopsy versus those who may go on perhaps active follow-up. You follow them closely but you're not necessarily needing to perform a repeat biopsy immediately.

What we show here is area under the curve. I think the test itself the risk score, the ConfirmMDx risk score had an area under the curve of 0.72 alone which clearly outperforms PSA, outperforms the PCPT risk calculator. I'm not sure how many of you use that risk calculator. This is the 2.0 version, and when we combine the risk calculator with the ConfirmMDx risk score we get a little bit of an improvement in the area under the curve of 0.74 there.

In conclusion the assay what we just reported is the negative predictive value for clinically significant cancer with ConfirmMDx is 96%. For all cancers it's 90%. I think some of the value proposition with the tissue-based assay is it allows you to test a patient where you may have

concern and the test results are valid for 24 months out from the previous biopsy. It gives a little bit of a longer interval in terms of managing that patient and deciding on next steps. Lastly the new risk score which we plan to introduce will help you improve stratification, help you identify those patients that are at significant risk for aggressive disease that might benefit from earlier detection and treatment. There's a little bit of an algorithm how we see that actually fitting into clinical practice.

Any questions?

DR CRAWFORD: I know it's been an education challenge with urologists to talk to them about why negative predictive value is important but that's what people want when you talk to them. They want it to say we got a biopsy back and it was negative, there was nothing wrong. I found that was a challenge and in my practice and talking to others is when the test comes back positive in a way with one, two, or three methylated genes and now I think you're trying to address that.

What are your recommendations let's say that your SF1 is positive in the base and you're a little concerned, their PSA was 5. It was a 60-year-old man, it wasn't like it was a 40-year-old guy it's still a red flag. What do you tell them?

MR. THIBODEAU: I think that's an important question because anecdotally we have numbers of cases where we have one gene site in one core where that patient is later diagnosed with significant cancer. What we haven't reported previously which we will be introducing with this risk score is looking at the degree of methylation. We have four genes, a control gene, and three cancer genes. When we look at how methylated those genes are at our initial launch we were concerned more about cancer/no cancer for the high negative predictive value for all cancer. Now that we've sharpened the pencil a little bit and looking at if it's more important to identify those with significant cancer let's look at the degree of methylation.

There's been numerous reports, whether it's out of Johns Hopkins or other sites, who have reported on the prognostic values of these genes and whereas we're not using it in the

area of guidance for active surveillance, we know that the degree of methylation of these genes does actually relate to the aggressiveness of disease and we're looking at the number of genes positive, the number of cores positive, and the degree of methylation in that algorithm, which helps us differentiate those men that are at higher risk for significant disease.

Back to your question on the patient with today's test what we say is that's a patient who's at risk for prostate cancer. They have a 30% risk of prostate detection on repeat biopsy. Whether or not it is significant we're not giving you guidance on that yet but once we apply and look at even with one gene if we see the degree of methylation on SF1 is extremely high that patient will be at increased risk for significant disease.

DR. CRAWFORD: Are we getting in the report the degree of methylation back?

MR. THIBODEAU: It will be a part of the report as we launch this new - - .

DR. CRAWFORD: Of the three genes which one do you think is probably the most significant one?

MR. THIBODEAU: They all contribute. If we look at both the MATLOC and the DOCUMENT studies you can see that each gene in and of itself contributes to about 15 to 17% of the cancers identified, in and of themselves. Combined certainly there's a better performance when you have multiple genes positive. It's hard to say that one is more important than the other per se, however historically we always look at GST-Pi which has been the backbone of the assay if you will because it was originally published in 1994, it's probably the most sensitive or most specific for prostate cancer. I guess you could look at GST-Pi as one of them but really it's the combination of those genes and the degree of methylation.

DR. GARNIC: Have you looked at the any difference in patients that have anterior tumors that were diagnosed as a result of your test and then looked at the epigenetic profile of the peripheral zone versus the anterior portion of the gland?

MR. THIBODEAU: We have not but that is a wonderful question and

I think that we will be. We have a small study ongoing with an investigator now. It's a pilot study that's going to allow us to look at some of that information. In fact, Dr. Crawford that might be an aspect of the study that we discussed with Kevin looking at roughly 40 patients with transperineal mapping biopsies and cancer so we can evaluate the different degrees of methylation and the signal and the field effect.

DR. CRAWFORD: Why are you worried about that Marc?

DR. GARNICK: Because I'm concerned that we see patients that have PSAs in the negative biopsy and they get a second biopsy. It would be very nice to identify those patients up front so if you end up taking one anterior biopsy during your routine transrectal prostate needle biopsies and you found a different epigenetic profile of that particular portions that may signal an earlier diagnosis of an anterior tumor.

MR. THIBODEAU: We are investigating this because both the DOCUMENT and MATLOC studies I mentioned those are studies that were conducted with serial 12-core TRUS-guided biopsies. The likelihood of them reaching the interior part of the prostate is low but we have positive test results but then no cancer found on repeat biopsy. Are we wrong or was cancer missed on the repeat biopsy. I think it would be interesting to look at template-guided mapping biopsies as a way to predict whether or not there was an interior cancer and we picked that up, would that be more accurate in that regard.

DR. BRAWER: Great talk. I'd like the committee to recommend you for an honorary urology - - .

[Crosstalk]

DR. BRAWER: Don't do that study on mapping biopsies just do it on radical prostatectomies. We ought to map it precisely and to answer Marc's question you'll know how close you can get at each point. You might as well get all the data you can.

MR. THIBODEAU: That's a great suggestion. Thank you.

DR. CRAWFORD: I don't think it's that great because you don't have needle biopsies of the radical prostatectomy. This is

a prospective thing to see how it would work. Can you shoot a needle along the base and needle the-

[Crosstalk]

DR. GARNICK: Chris, my comment was when you showed the health economic outcome per patient benefit it was around \$580. But you know the tendency and the trend nationally is to MRI and MRI-guided biopsies. The potential savings is going to be 10 to 15-fold so that's where you need to go.

MR. THIBODEAU: That's a great observation absolutely. This is compared to the standard of care prior to MRI being introduced and if MRI is really taking root and people are using it more frequently we know the cost associated with those procedures is much, much higher.

Any other questions?

DR. CRAWFORD: Nothing else? Alright. Thank you.

We have one more presentation. We have Vivian Wong from Progenics speaking about targeting and treating cancer.

DR. WONG: Thank you. Good afternoon. Thank you Dr. Crawford. Thank you to the organizers for having me here today. I want to take this opportunity to give an update on some of our program relating to prostate cancer.

DR. CRAWFORD: One second. Please ask some questions on these iPads. We've got really great technology here. If you look at the iPad you can see the presentation, the agenda, faculty bios, you can ask questions, you can take notes on slides, they'll get back to you. Please use the technology.

DR. WONG: Just very, very brief intro about Progenics is a small pharmaceutical company located just outside of New York City. It's been a public company since 1997. Aside from having a commercial product Relistor which is for the treatment of opiate-induced constipation, nothing to do with prostate cancer, also right now a registrational study is ongoing for some rare neuroendocrine tumor, pheochromocytoma, and paraganglioma. Our R and D efforts pretty much focus in prostate cancer.

Our prostate cancer program primarily uses PSMA as a target. PSMA is prostate specific membrane antigen. This

is a good target. I think many of you are familiar with it. I just repeated it.

This is actually in normal prostate cells, PSMA is expressed intracellularly and in prostate cancer PSMA becomes expressed extracellularly so making it very useful as a targeted agent for therapy as well as imaging.

Here shows the protein expression of PSMA in prostate cancer is many, many fold higher than in normal tissues. It's very suitable to be target for prostate cancer.

Our PSMA-targeted pipelines we have two product candidates that are for imaging and two for therapeutics for prostate cancer. The first imaging agent is called 1404. We are planning to use it to detect prostate cancer in earlier lower grade cancer. 1404 is a SPECT/CT agent. PyL is a PET agent and we're planning to position it for higher grade more advanced stage prostate cancer detection.

Today I want to give you an update on our 1404 program. This is data from our Phase I study basically showing that 1404 scan can detect prostate cancer very nicely. Healthy volunteer versus somebody who had prostate cancer. Our investigators and our readers told us that 1404 scan was very easy to read and they feel that it's very comparable to MRI in terms of their ability to detect prostate cancer.

In our Phase II study we enrolled patients in all range of prostate cancers and they were given 1404 scan prior to them going into prostatectomy. That means that we have the histopathology as a true standard to compare to our images.

Our data shows that 1404 scan can detect prostate cancer in the prostate gland with high degree of specificity and sensitivity. We have derived a semi-quantitative method to read these images and that we were able to show that the uptick of 1404 to the prostate gland correlate very, very nicely to Gleason score. On top of that, what we saw was patients who had received prior treatment and then had 1404 scan we saw that there was a reduction in the uptick. We think that it might be in the future maybe usefulness in monitoring treatment for prostate cancer patients. We got the true standard in our SPECT/CT scan and then this is the same MRI.

Based on what we have learned from our Phase I/Phase II

studies we spoke with FDA and we're proceeding to a Phase III study. It's a pivotal Phase III study and this is the study design that we have agreed with the agency.

We're going to enroll patients who have biopsy confirmed low-grade prostate cancer and they are eligible for active surveillance but also decided to go for radical prostatectomy. We'll dose them with 1404 agent which is a technetium-labeled small molecule that is targeted for PSMA. Then they received SPECT/CT imaging CN and then they go into prostatectomy and at the end the scan needed to be compared to histopathology because that was required. FDA said we have to have a true standard.

We are planning to enroll approximately 450 patients and the primary endpoint is specificity and sensitivity and that was also agreed and required by FDA. However, we were told that we were not required to do a clinical outcomes study. One of the very nice comments from the agency the almost first sentence from them is that they see the clinical utility of this 1404 imaging agent. They asked for specificity and sensitivity. Of course safety and tolerability and also from the scan we're able to look at the location of the disease as well.

This is our upcoming study. I hope that some of you will be interested in participating. Very exciting. We hope to get it running by the end of this year. If anybody is interested please reach out.

Thank you so much.

DR. CRAWFORD: In this study for your endpoint how are you going to handle somebody who has three plus four non-organ confined disease? That would be considered clinically significant cancer.

DR. WONG: Yes. It's a very tricky point. Three plus four and confined they would be enrolled. But three plus four that extracapsular and all of that we would consider that clinically significant. From our Phase II data the semi-quantitative scan we're able to distinguish that and the uptick. We feel comfortable with that and apparently the agency allowed that as well. That is our cutoff is exactly what you just mentioned.

[Crosstalk]

DR. GARNICK: Are you planning to do whole mounts in all the prostatectomy specimens?

DR. WONG: Confined to whole mounts?

DR. GARNICK: Whole mounts.

DR. WONG: No, I don't believe so.

DR. GARNICK: How can you possibly get any meaningful data from your study if you don't do whole mounts?

DR. WONG: Whole mounts we do sections.

DR. CRAWFORD: Explain it Scott.

DR. LUCIA: The deal is that prostate cancer tends to be a multifocal disease process. You may be picking up an index lesion and if you're only sectioning that side you may prove your point that you can match your grade with your index lesion but it doesn't tell you exactly how accurate you are at picking up the other lesion within the prostate.

Whole mounting means cutting through the prostate like a loaf of bread, all the way through, keeping all the anatomic locations intact and then comparing the volume of the foci that you set on both sides of the prostate with what you got with your imaging.

DR. WONG: I'm sorry. The answer is yes, we are doing that.

DR. KEANE: How stable is this? I do a lot of work on ProstaScint in the past and we had a lot of trouble and still it can get taken up in the liver. How is your product different? Are you having problems with it? Have you seen it being inactivated? Once you see a white liver you know your antibody's gone. How are you doing with that? What percentage of your studies is interpretable?

DR. WONG: Our molecules clear very quickly. ProstaScint is a monoclonal antibody so I think the clearance is very different and we don't seem to have the same problem.

DR. KEANE: Have you used this to take a look for lymph node involvement?

DR. WONG: Yes we did.

DR. KEANE: What did you find?

DR. WONG: We found that it detects lymph node metastasis quite well. There's a difference between how big the lymph node is and the intensity of the uptake also has to be taking into consideration so we're still working on the algorithm to decipher it more accurately. That's why in this trial we are looking at just the prostate gland first.

DR. KEANE: I would encourage you to use it in lymph nodes as well because if you get even a small amount of uptake in lymph nodes we know that if you stain some clinically negative lymph nodes that have been said to be negative but if you stain them for PSA you can find uptake of PSA-type cells or cells containing PSA and I would say that could be the same with this if it's that specific. I would encourage you to use that. We know that prostate has cancer. What we really want to know is it outside the prostate and if so, where.

DR. WONG: Right. In our Phase II data we definitely saw lymph nodes it's just that we have to look for a good algorithm to semi-quantitate it because this is SPECT/CT. That's why we have another program which is PyL which is a PET agent. That would definitely be used to evaluate a lymph node involvement.

DR. KEANE: Are you using a 16 slice CT scan? What are you using?

DR. WONG: I don't have that answer. I don't know. I will look.

DR. CRAWFORD: What's the difference between a 16 and a 14?

DR. KEANE: One of the problems with ProstaScint early on is the CT scan - - fused to are six slice so you could miss quite a lot of stuff going through it. They were just not very useful. Much more accurate today.

DR. CRAWFORD: We've discussed ProstaScint in CT scanning at this meeting many, many times including the Vail meeting too and we've had, what's the guy from Cleveland Clinic, Bruce, the guy that was the guru from that case Western Reserve on ProstaScint. I can't remember his name. You have talked on it. Lots of other people.

[Crosstalk]

DR. KEANE: It's back again. It's coming back. The company—
[Crosstalk]

DR. GARNICK: Can you provide what's the difference between your test and the previous ProstaScint. Just go through the differences.

DR. WONG: ProstaScint is also a PSMA targeted agent so that is a similarity but it's different processes as an antibody and the specificity and sensitivity that is in the literature at this point is much lower from what we have seen in our Phase II studies. Another disadvantage of ProstaScint is that you get the dose right and then you have to come back a week later I believe it's a week to be scanned.

DR. CRAWFORD: Not a week.

DR. KEANE: Three to five days.

DR. WONG: Three to five days.

DR. KEANE: What is your compound then if it's not a radiolabeled monoclonal antibody? What is your PSMA compound?

DR. WONG: It's a PSMA targeted small molecule. It's targeted to the similar domain but it's a small molecule so the pharmacokinetics and the clearance and all that is somewhat different from a monoclonal antibody.

DR. GARNICK: I thought there was some issue of ProstaScint that you needed dead cells to express the intracellular domain from the antibody.

DR. KEANE: But that was because there was an internal epitope and an external epitope and there was that battle over the—I can't remember the company, but they had an external epitope and ProstaScint was an internal epitope so you wanted the cells to die and then it would move in. We were meant to look at that with hormonal therapy to see if it would upregulate. It was interesting to see that yours downregulates that — treated down, after treatment that yours drops down which was different.

DR. VESTAL: Has your company given some thought to this model agent being to gadolinium. Everything's going to MRI scan. It would be very nice to see a compound like this fused

with an MRI scan to enhance our ability to detect significant cancers.

DR. KEANE: We've actually published on that with ProstaScint fusing with MRI.

[Crosstalk]

DR. CRAWFORD: I think we're a few minutes ahead. Thank you.

DR. WONG: Thank you.

DR. CRAWFORD: Why don't we take a ten minute break and then we'll get back and get started on prostate, bladder, and kidney cancers.

[Crosstalk]

[END Day_2_Session_2.mp3]

[START Day 2 Session 3.mp3]

**Session 3: Future Approaches to Prostate, Bladder,
and Kidney Cancers – Daniel P. Petrylak, MD,
Moderator**

DR. PETRYLAK: It's my pleasure to introduce Dr. Steven Finkelstein who's going to be talking about the combination of radiation therapy and immune therapy for prostate cancer. Dr. Finkelstein.

**Featured Lecture: Radiation Combined with
Immunotherapy – Steven E. Finkelstein, MD**

DR. FINKELSTEIN: It's a pleasure to be here to speak today about the state-of-the-art connection between immunotherapy radiation therapy, where are we now, and where are we going. It's a little different than some of the topics that we've talked about today.

To take Dave's mission I'm going to try to make this a little bit more interactive. It's late in an afternoon where multiple lectures have been given.

As many of you know, I took the helm of 21st Century Oncology's research about four years ago, built the TRC, the Translational Research Consortium, where our mission is

to build novel approaches combining radiation therapy and other therapies to elicit radiation-induced personalized systemic therapy.

My journey has been an interesting one to date. As many of you know I did general surgery, then surgical oncology and immunotherapy at the National Cancer institute. I'm happy to say I'm alumni with Gomella over there.

This slide shows that I've aged visibly since you can see this young pup here on the left who has more hair although not everyone in my group has had more hair over time.

Our group was very productive looking to build immunotherapies for cancer going from the bench to bedside and back again. You can see here we have a track record of numerous publications of which we were able in vivo models to not only cause regression of large established tumors, something that in the surgery branch we had tried for 25 years to accomplish within the same models using a tripartite three component system of immunotherapy coupled with a vaccine approach, adoptive cell transfer, and an immune stimulator coupled with radiation therapy. Indeed these tumors not only went away but in a melanoma model they went after not only the melanoma, but since there's melanoma differentiation antigens in the coat would actually have these animals have vitiligo and turn white.

Trying to be interactive with Dave, Dan asked a question earlier, I put in some slides on the fly. Back in 2003 we published that using an advanced transgenic model in which we could tag T cells were able to show in this model the infiltrate of T cells using that approach. Those T cells were CD8 positive T cells. Indeed when we looked at the same in humans, this we published in PNAS we were able to achieve similar outcomes.

My journey was interesting. I was a dumb surgeon, right? I knew nothing about radiation so with Steve's blessing I went back to school after ten years of doing surgical oncology and immunotherapy to get boarded in radiation oncology. The classic teaching for radiation oncologists is that you should never do radiation with immunotherapy. Radiation is immunosuppressive. We use it for bone marrow transplants but that's when we give whole body not we do 99.9% of the work which is focal radiation therapy.

Classic teaching suggests that radiation works through double stranded DNA breaks. However, that's not the whole story.

We've known as immunologists, as surgeons that the immune system is important in the interaction that causes regression of cancer. There's upregulation of various molecules such as Mac Class 1 and Class 2 enhancement of androgenic presentation of dendritic cells and when we radiate things what we actually do is not only hurt the cancer but cause danger signals, so-called DAMPs, damaged associated molecular patterns. Through this mechanism we can induce the expression of cytokines, chemokines, and inflammatory mediators, so when we think of what actually happens when we radiate things it's probably not just DNA damage, which made a good story 60 years ago and made us a modality but this, which we published back in 2011, with Bob Timmerman who created stereotactic body radiation therapy, of which when you radiate things you get upregulation of class one molecules, adhesion molecules, costimulatory molecules, heat shock proteins, inflammatory mediators, immunomodulatory cytokines, and death receptors. This manuscript trended as the number one manuscript in radiation oncology for three months back in 2011. This was before people were talking about PD-1 and checkpoint inhibitors. I was lucky enough at NCI to be one of the first to give Yervoy before it was Yervoy, when it was Medarex's compound.

We want to go from bench to bedside to bring immunotherapy into the clinic in relevant ways.

When I had my fellow review the manuscripts that had been done about combining immunotherapy and radiation two, three years ago there weren't that many. In 2014 when I had them write this, I'm happy obviously some of my papers are here, but we need to have more studies done. This was one of the first manuscripts in prostate cancer, an analogous manuscript in sarcoma. When you look histologically, when you have gigantic tumors growing, this is a sarcoma model, in vivo in humans, when you have gigantic tumors growing you actually look immunologically with respect to their histology you don't see an influx of CD3 positive cells, T cells et cetera. However, with radiation coupled with immunotherapy you can see CD3 positive T cells. I'm a T cell chauvinist. I showed you that mouse model which that

influx with CD8s actually here its CD4s so depending on how you elicit immunotherapeutic effects you may get very different responses immunologically.

We want to go from the bench to bedside and back again to build clinical opportunities to combine immunotherapy with radiation. My group is 21st Century Oncology. We've coupled with TGen, Jeff Trent's group, to build an approach to do animal work that mimics what we do in the clinic. TD2 which is the drug development arm of TGen and 21st Century teamed up for rapid testing of anti-cancer drugs as combined with radiation therapy. 21Cs footprint is quite large with over 500 sites and 700 physicians.

We built ARIEL, the animal radiation imaging immunotherapy experimental lab which harbors a SARRP unit which at the time when we put in we were one of six units in the U.S. This facility is that same facility which we share with Dan VonHoof [phonetic] from U.S. Oncology.

You ever see a SARRP unit? I'm going to show you what it looks like. This is my head physicist and my head therapist. The unit behind it is a SARRP unit. It is essentially a shielded unit which mimics what we do in clinical radiation. You image as you would so animals go on the table like we put people on. We call that a couch. I have no idea. As a surgeon who became a radiation oncologist I still don't know why we call it a couch. It's a table. Nobody laughed at that joke.

We can image using CT scan, find the spot we want to treat, and then have clinically relevant setup and treatment of which we aim beams of energy where we want to. Here's a subcutaneous model.

For those in the audience wanting to test relevant agents before they get to the clinic this is an approach which we believe has incredible utility remembering that we are a private practice group who has an advanced animal imaging laboratory.

Clinical trials in the clinic. Again, when you look at the panel of trials that are in Clinical Trials dot gov there is an infinite number. I'm happy to report that at least there are some trials combining radiation and immunotherapy currently as this is one of the hottest areas in the field.

I'm going to show you what is the largest immune monitoring trial to date. We wrote a trial to combine what is clinically available radiation with what is clinically available Provenge. Obviously I don't need to teach this group about prostate cancer. We know in men with recurrent diseases androgen deprivation is the current standard. Until recently docetaxel was the only therapy that existed. Our research hypothesis that radiation in combination with Provenge may improve outcomes.

Provenge is essentially an autologous cellular immunotherapy. It's pretty much analogous to adoptive cell transfer. We wrote about this and where we thought this was going back in 2011.

Provenge was approved based on seminal works. There were multiple trials that showed Provenge's efficacy leading to the IMPACT trial which showed a 22.5% reduction in the risk of death with an improvement in median survival. I'm not going to debate the nuances of Provenge but Provenge is the clinically available treatment with immunotherapy for prostate cancer. PD-1 is not. Yervoy is not. However, those things when coupled to adoptive cell transfer approaches may yield very interesting utility if coupled with things like radiation in the right way.

Obviously Provenge was tested and very safe. Now radiation, as I talked about, we believe involves DNA damage plus more. We believe the dying of the cells—remember when we radiate prostate cancer in some cases we do it over nine weeks. Name another therapy that you have nine weeks of treatment. When I was a surgeon I cut things out, it went into a bucket. Not very immunogenic. However you sit and you radiate something for nine weeks or you use a stereotactic approach in which you give big doses of energy in a short period of time your body is going to have a natural response to healing.

We call this in the past the abscopal effect. We've known about this for 60 years. I didn't think this up. The abscopal effect is the idea that if you radiate over here, over here, somewhere over here the tumor goes away. How does that work? In the past we said we didn't know but it's probably and elicitation of immune responses.

This involves lymphocytes with a great deal of nuances and

dendritic cells with a great deal of nuances. How are we going to test this? As I talked about on Saturday the fact that you could image prostate cancer is a key aspect now in the management of patients. As the last lecturer alluded to this is advancing. We used to have technetium 99 bone scans and CTs. Now we have better imaging that can actually tell us where sites of disease is. I don't know if Bela is in the audience. Bela said radiation oncologists how do you sleep at night? You sleep at night because you can image where the sites of cancer are and then treat it.

Within this study we not only built immunologic monitoring before and after every step but advanced imaging which included sodium fluoride PET CT bone scans with a sensitivity specificity over 905 and next generation C-11 acetate PETs. For those of you who have heard the C-11 choline story out of Mayo this is C-11 but acetate. There are only three sites in the U.S. which have currently capacity to do such. What does that look like?

FAT and PET CTs image bone sites of disease and probably very well in the right hands of those who read it. However, it doesn't image soft tissue sites of disease where C-11 acetate can come in. The future of radiation and surgery is both anatomy is destiny and if you could image sites of disease you should be able to effectively build the right therapy.

C-11 acetate was actually not a new thing. It was around in the eighties. C-11 acetate was built for cardiac imaging and then they found all these guys with prostate cancer. The problem is that you need two \$12 million cyclotrons you have to make the agent and then basically deliver it within 30 minutes. Here's what a C-11 acetate looks like. It can image both bone and soft tissue.

This study will assess the effects of radiation coupled with immunotherapy. It's a multicenter trial to have enrollment of a hundred patients. They get immune monitoring and C-11 acetates and F18s before and after each step with long-term follow-up.

Inclusion criteria is nothing exciting, except essentially you got to be eligible for both radiation and Provenge. Exclusion criteria is like most immunotherapy trials. You

can't be on systemic immunosuppressives.

The endpoint is to compare immune stimulation in patients receiving radiation following 28 days of Provenge with secondary endpoint is to look at the imaging.

The primary endpoint is percentage of subjects who elicit a two-fold increase in peripheral immune responses and post-treatment time points. This is currently enrolled. I'll finish with my best data.

I'd be happy to entertain any questions.

DR. DEBRUYNE: I missed your talk I'm very sorry but I have a question. Radiation therapy impacts negatively on the immune system.

DR. FINKELSTEIN: Let me be clear. If you radiate a whole person you're going to knock down lymphocytes and cause immunosuppressive. We use that clinically for bone marrow pretreatment conditioning. If you do focal radiation, my friend here you want to do focal therapy? It's not. We did pelvises and we published our data in higher risk setting, we published that at ASTRO that it's not immunosuppressive.

When you focal radiation what you achieve is you essentially upregulate certain molecules and leave blood in the water so that the immune system can do something and come in. I would caution those in the audience who think they want to do immune studies with just one component of how the immune system we've done that for years. We did that for years at NCI. We did vaccines by themselves. They didn't work. We did IL-2. It only worked a little bit. We did adoptive cell transfer by itself. It only worked a little bit. Only when you put the different pieces of it together will it start to work. My friend Chuck Drake did a very interesting trial which had negative results. It's coupled eight gray which is not a lot of radiation to a target coupled with Yervoy. There are better ways that we're probably going to do this and I'm happy to discuss it afterwards how might that affect you.

DR. PETRYLAK: Thank you. It's my pleasure to introduce Fernando Kim from the University of Colorado. He's going to be talking about cryosurgery.

Featured Lecture: Cryotherapy – Fernando J. Kim, MD

DR. KIM: Thank you Dan. It's very tough to follow all the speakers. David, thank you very much. All the jokes aside I think you've been a mentor for a lot of people in Denver but your pioneer work and things that you've created has been great. You actually pushed me to do cryoablation and see where we are 15 years later. David was also responsible to create a very successful medical cancer, surgical cancer clinic. Then I had the pleasure to work with Harry Drabkin. Now Harry is - - so they kidnapped him - - plays saxophone. This is a pleasure to get invited again and this year I made it, so thank you very much.

What I'm going to do is not be very controversial. I'm going to try to go to the point, tell you a little bit of about our story. Denver Health is a safety net hospital. We take care of the uninsured. We've been extremely—that's what I really did after I left Baltimore Hopkins. My passion was in trying to understand the minorities since I do believe that I belong to one group so trying to understand what are the differences that we see. We've have been creating a very good liaison.

With the permission of Dave and Marc I'm just advertising Jackson Hole Centers going through 36 years. Ralph Hopkins passed the baton to me before he passed away about two years ago. David was one of the first speakers. There are a lot of winners here. - - is between the first and second column there. That's what they were looking for. Lenny Gomella and Chris Kane, Waldo Winters, and there are a bunch of guys here that attend the meeting. I invite you to come and have some Kentucky lemonade. That is bourbon with some lemonade that Ralph Hopkins always had in his room and we used to have a lot of fun. Next year it's going to be a great program and people tend to have some fights during the scientific meeting, but no fistfights. After that, only if they get drunk.

I'd rather start talking a little bit about what has been evolved with my life in terms of laparoscopy. That's all I did until they showed me that cryoablation was something that I would like to do and this is where the visual par is important because this is what you see with cell

destruction and if you decrease the temperature less than minus 19.6 degrees Celsius you can not only kill - - cells, PC3 cells but also RCC with sarcomatoid and so on.

We aren't the only place that we have patients match cellular primary cell culture and that means we took kidneys from patients with cancer and the normal and we did primary cell line culture without being passed eight times or ten times immortalized so it's very, very similar to what the parent cell is and we did a lot of studies in trying to see a lot of different things. Apoptotic reaction is one of the things that we saw trying to see some immunological effects of cryo with some metabolic degradation.

I'm just going to talk about our clinical findings in terms of how cryoablation changed the way of our patients in the African American community particularly seeing aggressive therapy for prostate cancer.

What is interesting is that about 50% of our population that we treated for prostate cancer or biopsied for prostate cancer they were minorities; African Americans and Hispanics. You see the profile of the insurance companies and how they pay the - - is basically they are underserved. If they are indigent or - - care or Medicaid or less than that or if they don't have anything they are what we call CHS, is that the illegal undocumented aliens that don't have anywhere to go. If you see all that and then you pay attention about the Gleason score of those patients you see that African Americans have, for whatever reason, a little bit more aggressive prostate cancer. The risk category also is higher.

If you see the - - risk stratification, PSA, the only thing that really matters is that you understand that our African American population men had a higher risk. They tend to have more mets at diagnosis. The PSA didn't really matter and the volume of the prostate. What was interesting is that what kind of treatments they were looking for.

When I started laparoscopic prostatectomy I thought everybody would go for that in 2000. That didn't change in the African American community. I went to the black church initiative a hundred black men in Denver, Colorado Coalition, the American Health Institute of African

American Studies and I used to go almost every week and nothing change. When we started to do cryoablation what changed was that the majority of the aggressive prostate cancer African American men we diagnosed with prostate cancer they liked the idea of the less invasiveness. This is not a validated questionnaire whatsoever but when we questioned what triggered you instead of doing radiation or active surveillance had cryoablation. It's less invasive. That was the message of this paper.

Here another thing is the visual part and Stacy did a great presentation about the social media, this is a YouTube that Lenny is the CJU editor and we have a section that we do the techniques and more than a hundred thousand people linked to our video and this is the - - view after we placed the needles. If you've never seen cryoablation it's a simple thing. It doesn't really demand to be a great surgeon but if you know how to use the - - those games that you put the AC, A3 or it's a grid you just have to put the needles and understand how to read ultrasound. I'm part of the American Urological Association Ultrasound Group so you can get certification also with us. This is the beauty of using cryoablation particularly on the specific group.

In terms of collaborate or what I like to present and add to this group of great brains that we have here is what we've been doing the last 12 years. Steven - - and Dr. Ware [phonetic] are brilliant guys and collaboration with the School of Mines, we were able to create a nanoparticle that is gadolinium base, created a polymer on that gadolinium and it's being the last five and a half years we've developed the aptamer which is a DNA sequence for PSMA. So far from more than 250 samples we were able to get 5 sequences. They're also patented and this is my disclosure. From those five we had to create a different geometry to link to the - - cap cells, PC3s and when we did that with BPH cells and washed out there were no read at all in the MRI. This is where I like to see is being able to focus the foci where the prostate cancer cells are and this I think is going to be a major breakthrough in terms of visualization, then we can talk about focal target therapy or MACs or trying to identify something better. I really appreciate the PSMA talk.

I think it is still painful to develop this DNA sequencing. Other colleagues from Hopkins tried to develop the - - but

it was RNA and it was degraded at the first pass as soon as it's given to the animals. Those are the challenges that we have.

This is about prostate. What happened with cryo in the kidney? We saw two years ago my last surgery laparoscopic partial nephrectomy versus robotic. We performed faster, more cost effective and that's not the issue. The issue is about cryoablation. Cryoablation can be - - time about 50%. This is an update from our publication that in this group of patients with T1A there is a methodology that you can decrease the chance of recurrence because you create a halo and definitely with the next slide I can show the technique. This is from one of the physics major students that PhD that showed if you use three probes instead of one you will increase the area of kill zone and definitely with the ultrasound you can ascertain you are treating that.

The beauty of doing this is for those patients that have chronic renal failure already. You're not clamping. Ischemic reperfusion has been a long term research for me and we even created a chimeric SOD with the Webb-Waring institute. That didn't really diffuse the oxidative stress and injury to the kidney. With this you can just plug it in. It easy and decrease the temperature.

Not only that what we did was if I biopsied the kidney tumor before I freeze is there a chance I can spread. Yes. How about we biopsy after we do all the freezing. Can we still diagnose kidney cancer? In this paper that we published in the *American Journal of Pathology* we compared after the first freeze and the second freeze. What we were able to determine is that the only thing you cannot determine is the Fuhrman grade. Scott Lucia can comment on that. I don't know if that is key. It's pivotal for you to follow-up or determine what the prognosis of that patient will be.

In terms of literature in the world you can see that cryoablation percutaneously or laparoscopically still a very good methodology. That is comparable to open partials or laparoscopic partials is just another organ-sparing methodology that can treat small tumors.

One of the things that always I have an emotional attachment to cryoablation is this patient who was treated

at the University of Colorado during the Drabkin years, had a nephrectomy on the other side, came to our clinic with this met and you can see the CAT scan the met here and the met that was encompassing the whole - - there. We sliced open, sat there a sarcomatoid renal cell. Got the solus [phonetic] also and we just-I put so many probes that day that the distributor was very, very happy we used so many cryoprobes. We treated in September of 2006 and in 2014 she passed away with mets to the lungs, to the bones and Benny Leveque [phonetic] is an orthopedic surgeon that does only oncology and after cryo was introduced to me by David, I introduced to Benny and Benny loved that and he's been doing all the cryoablation of the bone, just can be any kind of tumor. The technology is extremely good and kills and creates an apoptotic reaction. The problem when they recurs probably is because you're not placing the probes in the right place.

In conclusion I think it's not very scientific what I'm showing as a conclusion but cryoablation is a technology that when you apply it very well, not freezing for one or two minutes but at least for six minutes and we know that from a bunch of people, Baust [phonetic] and others that have been doing this for a long time, basic science research, you can create the kill zone. Then apoptotic reaction. You can have immunological reactions but the important part is six minutes then five and then freeze it again. Two freeze and two thaws. I think this is a good technique. I think the future will be more organ-sparing technology and techniques to treat cancer.

I'd like to thank David again for this great meeting.
Thank you.

DR. CRAWFORD: We were, I think, the third group in the country to start using cryo a long time ago with the old CNS machine which is archaic and then we stopped it because of a whole bunch of reasons. One, we lost the urethral warmer which led to a lot of complications but the person that actually deserves the credit for us getting back into cryo is someone who is at this meeting, Cliff Vestal. Cliff Vestal was my fellow. He left me, went around, and started doing cryo on his own when the new machines came out and came back and retrained me. He is the really the person responsible for that current cryo crisis.

DR. PETRYLAK: Terrific. My pleasure to introduce Dr. Tom Keane who's going to be talking about androgen blockade or androgen ablation.

Featured Lecture: ADT – Thomas E. Keane, MD

DR. KEANE: Thank you. That was a remarkable lecture Fernando. I have not heard of cryo for palliation particularly in bony lesions and presumably they have to put some kind of a nail through it as well to stabilize the time but I'm going to talk to my orthopedic guys. This is future directions in urology but that was future directions in palliative care. That was really impressive. Thank you.

I've been asked to talk about basically androgen deprivation therapy and what we know about it and what we don't know about it. We've been dealing with this since 2002, the 2000s when abarelix came along as an alternative to an LHRH agonist and then we got to 2008 when we had degarelix and basically you can see the differences that are listed here. I don't need to go over them but just to say they are dramatically different compounds and they have different affects in terms, particularly of surge of testosterone, of microsurgues of FSH suppression the two products differ fundamentally. As a result of these differences I think combined androgen blockade has been around for many years and we've argued it left and right, we've had numerous meta-analyses but combined androgen blockade in summary does not abrogate the initial testosterone surge which is intrinsic with LHRH agonists.

Marketed anti-androgens do somewhat inhibit but do not completely inhibit the cytoplasmic androgen receptor and there is a possibility that when you expose it in that manner you may be inducing a resistant phenotype by partial blockade. Again, needs to be proven but one of the first maneuvers that happens when the testosterone rises and someone's on CAB is you with draw the anti-androgen and you do see a 25% drop on average overall in PSAs which is short-lived because the androgen receptor does change and come back again.

Again, we don't know if FSH is involved in the development of prostate cancer. There's a lot of basic science data which would indicate that it is but it has to be proven and

these are the future directions that we'll take.

The antagonists were developed to completely avoid the testosterone surge to cause a more rapid reduction in testosterone. It doesn't affect the androgen receptor; it's devoid of the anti-androgen adverse events and it does cause we now know more profound suppression of FSH.

A couple of questions that have become answered in recent years; what is an appropriate testosterone level. Its 20 nanograms per deciliter. It shouldn't be 50 and I think in future directions going forward we, as urologists, should insist that that gets changed, that we have an effective reduction in testosterone not something mandated by the FDA as being okay.

The other questions that we ask are do differences exist between the efficacy and benefits of GnRH agonists and antagonists particularly in terms of time to castration and castration onset and PSA suppression. Also PSA progression, is that different? Are there significant differences in the safety profile? These are all things that are currently being looked at.

In terms of testosterone the question is answered in my opinion. We had the Morote data, we had the Perachino data which were teasers, there wasn't enough to draw any conclusion; they were hypothesis generating and then we had the data from the Canadian data which really proved the point in over 600 patients and those patients who had a testosterone level you see it at the bottom there that's 50 or more compared to those who had a low testosterone of 20 or less on the top there was a profound difference in the rate of progression of their disease so I think 20 is the accepted number.

Then we look at what's the difference between an agonist and antagonist. It takes one amino acid change to make an agonist it takes seven to make an antagonist.

There has been a head-to-head comparison. It was a non-inferiority trial, it was a CS21, and you all know the data. As I mentioned it also had a number of secondary objectives. When you look at the primary endpoint it succeeded. It was non-inferior so the antagonist was non-inferior to the agonist in terms of testosterone suppression below 50. Big deal. The secondary endpoints

however were really interesting. The proportion of patients with testosterone surge between the two agents significantly different. The proportion of patients with testosterone less than 50 at Day 3 significantly different. The percentage change in PSA from baseline to Day 28 and time to PSA failure significantly different. Frequency of PSA progression, significantly different and no difference except for injection site reactions in terms of toxicity.

When you look at reducing the risk of death, and this was an unexpected finding, we found that there was a substantial difference in terms of PSA progression, or castrate resistance or death. It was found that it was more prominent that you saw that in the patients with the higher PSA or the higher volume of disease. Also Vin Schroder showed that serum - - phosphatase control was considerably different. If you're on the antagonist it stays down over the year of this study. If you were on the agonist it gradually comes back up to normal as you get to the last four or five months.

Then the FDA mandated an extension study. In the extension study they said we want you to stop the patients on the agonist and convert them across to the antagonist because we want to make sure in view of previous data that there's not a more profound escape phenomena which was seen in earlier versions of the antagonist.

What happened? Basically when they converted patients over from the LHRH agonist to the antagonist we saw a surprising drop in FSH levels, 63% further drop. This was not new data. Marc Garnick could show them this in 2002 that the antagonist had a much more profound control of FSH.

I know I'm sitting here talking about FSH and you're saying what the hell does FSH have to do with prostate cancer. This was a study that was produced by Radu - - . It was in the *New England Journal* and it showed that they stained for the FSH receptor, they also stained for the vascular endothelial cell markers, and they found that they were in the identical areas. They were at the leading edge of the tumor and there were more vessels of course in the tumor and where was the location of the majority of the vessels? At the periphery of the tumor which is exactly where you would expect them to be if this is an invasive tumor.

Getting back then to the crossover study when the patients were crossed over there was a difference in PSA progression between the two arms of the study and once you converted patients across from the agonist to the antagonist you saw the event rate drop back to what it was with the antagonists themselves. The failure curve shifted to benefit the patients.

The overall summary was that the antagonist offers faster castration onset and PSA suppression with no risk of clinical flare, longer PSA progression-free survival. The five year extension study the therapy was well tolerated and PSA progression was improved after crossover.

Then we need to look again and see what is the disease control in cardiovascular outcomes. We don't have many randomized control trials but we have a number of Phase III trials which we can put together in the form of a pooled analysis and that was what was done here. There were three long-term studies and three short-term studies. All of them as you put them together had a large number of patients in the agonists and on the antagonists. I wanted to show patients were well balanced, there were 1,263 patients on the antagonist, and there were 657 patients on the agonist.

This is Larry Klotz's data which was published in 2014, he was the lead author on the paper, and there was a superior overall survival for patients on the antagonist compared to the agonists. That doesn't make sense. Very few patients died of prostate cancer of the year of this study so what did they die of? Cardiovascular complications. They also looked at the rate of musculoskeletal events which was significantly different and the rate of urinary tract infections.

Now we need to focus in perhaps on the cardiovascular events and see what's going on. Is the risk of cardiovascular events increased with agonists versus antagonists?

You have to look at the ADT and the risk of cardiovascular event. ADT is associated with an increased risk of cardiovascular events when you use LHRH agonists it was linked to increased cardiovascular morbidity compared to orchiectomy. Men with a history of cardiovascular disease

were the most at risk. The antagonist has a distinctly different mechanism of action so we may not see this difference if we're using an antagonist.

This all started back in the late sixties when the estrogen data came out from the VA and you did see an improvement in survival from prostate cancer in patients treated with estrogens but this was muted by the rate of death for cardiovascular events by giving estrogen. There was no essential difference between the two.

Further studies, and this is a study which was published I think in 2011 showed that GnRH agonists also have an increased rate of cardiovascular events and CAB had a small amount, orchiectomy has a small amount too.

Then we have the D'Amico data which showed that men over 65 years of age receiving 6 months of ADT had shorter times to fatal myocardial infarction compared to radiotherapy alone.

Based on the studies what have been said so far if the increase in risk of cardiovascular disease in men treated with ADT that is orchiectomy, estrogens, or GnRH agonists appears to be 20 to 25% which is the same risk if you're looking at a smoker versus a nonsmoker.

This was the pooled data. Over 2,000 patients, 1,401 on degarelix, the antagonist, 837 on the agonist. They were well balanced and as you looked at it this was patients with a history of a cardiovascular problem. There was a very significant difference in any cardiovascular event occurring when on the agonist versus that antagonist and the death rate was three times higher.

This is not a huge death rate but it may be a 4% difference. That's four patients in every hundred. Also this is just a slide showing the same; it was a highly significant difference. When you looked at the common cardiovascular variables and you basically adjust them it still held true.

In summary when treated with degarelix compared to a GnRH agonist, patients with preexisting cardiovascular disease had significantly fewer events during the first year of treatment and had a relative risk reduction in death of 50% and an absolute risk of 8.2%? Why? We know it had metabolic changes. We might have GnRH receptor activation

or we may have differences in FSH levels. The metabolic syndrome and the metabolic changes induced by ADT are different and the differences are highlighted here. I'm not going to go through them for the sake of time.

When you do look at plaques and all of us are at an age at this point when I look around that we may well have these plaques. I certainly want to have the plaque on the left rather than the plaque on the right is a stable plaque. You have a big cap, it's rich in SMHC and matrix. You have poor lipid and you have little inflammatory cells present.

This is a GnRH receptors which are located in the smooth muscle cells in atherosclerotic plaques. Starting to see the message? This is how T lymphocytes are the key drivers of collagen metabolism in atherosclerotic plaques. You can see down on the bottom you have the T lymphocyte which release interferon gamma which interferes with collagen formation. You also then have CD40 which is released into the monocytic phagocyte there which then releases collagenases, et cetera, which breaks down the fibrotic cap. The result is a disruption of the fibrotic cap, plaque instability, and increased risk of thromboembolic complications.

Here it is in a cartoon form. There's your GnRH receptor and the agonist on the T cell increased proliferation of activity, fibrotic cap disruption, the antagonist complete blockade, no increase in activity, no disruption of the cap.

I just want to show you these here. One of the reasons for explanation it's difficult to attribute this to testosterone. It's more than likely what I've just explained and there might be a punitive cause for FSH which is another future direction that we need to go in the next few years.

What does it mean for our patient? We should consider which therapy will treat the prostate cancer effectively, consider which will control the disease symptoms, and consider minimizing effects. If you don't have cardiovascular disease history it probably doesn't make a difference which one you're on. If you have a history then you probably should be on the antagonist. If you have a high PSA you probably should be on the antagonist. If you

have—again, this is tentative data it would appear as if you do better.

Finally, we've heard about future directions, where do we go. What do we do with abiraterone? Where do we put that? Where do we put ensalutimide? We have AFFIRM, we have PREVAIL. Everything's moving forward. I just had this up, I'm not going to show them but these are the key differences and it is a slide that's available to you between the two studies. There were differences but both were dramatic in showing that the earlier you give it; you can give it pre-chemo, so you move forward. Now we have CHARTER. What's going to be the future? Now we're going to get chemo upfront. Probably a patient who presents with heavy volume metastatic disease is going to see LHRH therapy of some form be it an agonist or an antagonist and they're going to see chemo and do we put abiraterone into that mix? Do we put enzalutamide into that mix? I would put it to you that the future is very exciting in how we manage this disease. There's a load of work still to be done but the title of this is future directions so the future directions in the control of metastatic prostate cancer looks very bright but there's a lot of work to do.

Thank you for listening.

DR. CRAWFORD: Thank you. Unfortunately we don't have time for questions but that was excellent. We've gone from being ahead to being behind by 45 minutes now. I know Mitch is going to save us. He's a great guy.

**Featured Lecture: Management of High Risk Prostate,
Kidney, and Testis Cancers – Mitchell H. Sokoloff,
MD**

DR. SOKOLOFF: I was given the topic of talking about the future of high risk prostate, kidney, and testis and was going to show basically about three or four slides on each of them.

Definition of high risk prostate cancer most of us as urologists use the D'Amico classification greater than 20 nanograms per ml, Gleason score of 8 through 10 and clinical T2C disease. There are some people who want to bring that to clinical T3. The other cases represent about 10 or 20% of screened men so it's a large population of

what we see. Also moves to expand this into including lymph nodes, seminal vesicles, or mets but I'm thinking more of that high risk localized disease. In this setting what really needs to be addressed. One the earlier and best identification of patients, we talked a lot about this yesterday and more on that in a minute, and to get them the most effective treatment early on. The second is obviously to improve therapies to prevent recurrences or to treat that progression or recurrences when they develop.

Screening tests have improved clearly. A lot of great talks yesterday. One thing I would say, and this would be the main topic of today's talk, is we need to move a little bit beyond the PSA platform. I feel, at least in central Massachusetts our experience and some other studies we've recently put together in Detroit that PSA is getting a little bit soured and we're losing the battle in prostate cancer screening in part because PSA is involved. We had wonderful talks yesterday in the different molecular assays which have enhanced stratification. I use a lot of these different genetic signature-based biomarkers, I think they're wonderful but all of this is moot because the family practice, the primary cares and the general perception is that prostate cancer is not harmful.

When I got to UMass I was asked to do a couple little videos. They have the videos in the cafeteria on the hospital. They have the Facebook pages and they came up pretty spontaneously and said talk to us for a few minutes on prostate cancer also men's health and some other things. I did two videos. I thought it was very balance, they put text with it, and I even in the text links to AUA guidelines, the American Cancer Society guidelines, Massachusetts Department of Public Health. They came out on a Friday morning. I was operating, I did a couple of prostatectomies that day and when I got out of surgery there were about 50 or 60 emails from irate primary care physicians in the system saying that I've just set everything back and I'm an expert in the field and how could I even imply that prostate cancer and PSA screening was important and how could I support it? My secretary told me that they were standing at my door with pitchforks ready to come after me. It's a big problem.

I've met with the different groups and these are slides I use when I speak to prostate cancer support groups and

advocacy groups and I showed them the same things as we've got advancements in screening beyond just PSA and free total and density and velocity. We've got PHI, we've got 4K, we've got PCA3, ConfirmMDx for stratification. We've got all the different genetic-based markers. There's a lot we can do. More importantly we've really made this conscious effort to separate the diagnosis from the treatment. Across the board, doesn't make a bit of difference. I think that perception is really out there. I think that despite all the wonderful research, the wonderful tests that have been discussed in the last couple of days, robotics, some of the new basis for the immunotherapy and cryotherapy that until we change the conversation back again that prostate cancer is potentially a lethal disease all of this is unfortunately a little bit going for nothing.

We have one of the first AUA data grants I got last year with one of our MD PhD students and we're comparing just the rates of screening in the last two years for prostate cancers compared to a control group of about five or six years ago using one of the managed care networks in central Massachusetts and also the Henry Ford database as well. Its preliminary but there's a significant decrease in screening and diagnosis and anecdotally I'm seeing a lot more worse disease presentation and not the low-grade men that I'm seeing as much.

My take-home point for this is until we change that paradigm back that prostate cancer can be a high risk lethal disease a lot of this unfortunately is falling on deaf ears.

That said, once we do have those patients who are identified in the future we definitely need to identify which of those men will respond to which therapies. There was a nice talk yesterday on using genomics to identify the best therapeutic targets. Obviously it's not a new concept but if we could develop a wonderful personalized genetic or molecular fingerprint for each disease type and say this is when we use abiraterone, when we use enzalutamide, this is when we use hormones or non-hormones. That's going to be crucial for the future.

As a surgeon I think we need to use more extensive local therapy for oligometastatic disease both radiation and

surgery. I think there needs to be that addition of multimodality and systemic therapies early in the course and not a monotherapy but multimodality and using some form of genomics to optimize that treatment so that our therapies are truly target-specific.

Switching to kidney cancer since I've just used up half my time on prostate. High risk disease I'm considering that to be more recurrent after treatment. We have had successes. I think surgically we do a wonderful job with localized disease and even with some low volume metastatic disease. We have good systemic therapies for early metastatic disease but what needs to be addressed is that early identification of metastatic disease and improved treatment once a patient has metastatic disease and fails the first several layers of systemic therapy.

What do we need? We need tumor-based predictive markers much like I mentioned for prostate cancer. I think we need to better understand those mechanisms of immune escape and there's work being done here. Working on further downstream targets and putting in a play for my own institution more on RNA-based therapeutics as we have a huge center for that.

I don't think we've exhausted adjuvant therapy despite the recent negative studies that have come out. I think we need to look at very specific profiles for that and I also think we need to have a look at autologous vaccines in immunotherapy. I trained back in the days of Tills [phonetic] with Arie Belldegrun those days are gone, but there are much better understanding and opportunities for vaccine and immunotherapies for renal cell.

There are other molecular approaches that are being studied now in Phase I, II, and III studies. Checkpoint inhibitors, I know we're going to hear a little bit about that in bladder cancer to follow, programmed death ligand, the PD-L1s, HIF2, alpha inhibitors, the CAR T cells and also some - - addressing codes as to medical conditions and there's some thought that if you treat hypertension in some patients and you treat LDH, and hypercholesterolemia you can actually improve the response to the systemic therapies for metastatic kidney cancer.

Last couple of slides just on testis cancer. That poor

risk or high risk are those patients with the mediastinal tumors, very, very high tumor markers in the non-seminomatous subset.

Testis cancer is a success story in general. It's an amazing success story and chemotherapy works wonderfully. There are those rare patients with metastatic disease who ultimately fail so identifying them earlier would be an important thing for the future. Better treatments for those recurrent chemo-resistance advanced disease and there are some new genetic and molecular targets that are being developed.

Within the urology community especially at the last couple of SUO meetings, there's been a lot said about the toxicity of chemotherapy. How can we reduce that? Either by maybe reducing chemotherapy dosing or developing these new genetic and molecular targets that might be less toxic systemically.

That's really all I wanted to say in a very brief seven or eight minutes. I'll welcome any questions, and David thanks for inviting me. I appreciate it.

DR. CRAWFORD: Michael?

DR. BRAWER: Mitch, great talk. On this study that - - try and get the data from five years ago and now for screening from the managed care that's a great setting. Are you going to be able to control for patients that are being worked up for - - or patients - - actually going to interrogate the charts so it's really pure - - .

DR. SOKOLOFF: Yes. We've really started diving down on that with all the different CPT codes and all the different codes and working with statisticians in our quality outcomes department who always understand these things, really trying to clarify whose being-you have to include some men with BPH because if they get screened for prostate cancer and they come in with symptoms if someone's thinking of local therapies so really trying to hone in on those different categories of CPT codes to make it as pure a population as possible. But you're right; there can be a lot of confounding for people present with different things.

DR. CRAWFORD: One more question.

DR. FINKELSTEIN: It was an excellent talk. I think especially in renal cell cancer where immunotherapies work but lost traction because of various other things we just put a concept into SWOG to combine radiation and immunotherapy in the same way that I was discussing which energy has taking a liking to as well. I would like to see those kinds of things involved.

DR. SOKOLOFF: Right before I left Oregon they were going to start some SBRT for renal cell which looked really promising. They haven't done much with it but it definitely looked extremely promising.

DR. FINKELSTEIN: We have that data for SBRT for renal cell. You obviously have data for immunotherapy for renal cell and if you're going to build something build it for prostate first so we've taken that to trial to SWOG and hopefully - - .

Featured Lecture: Checkpoint Inhibitors for Bladder Cancer - Daniel P. Petrylak, MD

DR. PETRYLAK: My talk is on checkpoint inhibitors for bladder cancer. There hasn't been a major advance in nearly 25 years. This is Alan Yagoda who was my mentor. There's a gentlemen in the room here who is photo bombing Alan Yagoda on the right here, Dr. Debruyne, it was probably about 20 years ago. This is from a meeting in Brazil and Alan is in his usual state of telling a joke or pontificating and he was really the major force in driving this treatment for this tumor.

Unfortunately even though his best efforts showed a survival benefit for M-VAC the long-term responses of this disease are fairly poor. If we look at the 6-year survival only 9 of 133 patients survived and basically most of our patients will go on salvage therapy afterwards.

Where do we look for salvage therapy? The immune system is one area. There are monoclonal antibodies that are engineered to interfere with the PD-L1 and PD-1 pathway. The tumor cell can secrete PD-L1 which will bind to PD-1 on the T cell and basically inhibit its activity.

The antibody MPDL3280A otherwise known as atezolizumab will

interfere with that particular binding and allow T cells to recognize tumor cells and then kill them.

It seems that mutations are important for the activity of the immune system. If we look at the tumor types that are active, lung cancer, melanoma, renal cell carcinoma, they tend to have a high rate of mutations, and they tend to be chemically induced tumors. Bladder cancer, chemical carcinogens we also know that smoking is a risk factor and it has a high mutation rate. It certainly makes sense to look at checkpoint inhibitors in this particular area.

The results that I'm describing were originally published in *Nature* about a year ago and I'm going to show you some update. We've looked at the staining of PD-L1 or PD-ligand in immune cells and found that this correlates with overall response and it does not correlate in the tumor cells. We've stratified our patients in this particular study based upon their immunohistochemistry in the immune cells, not in the actual tumor cells which may have a pd ligand. The overall prevalence of PD-ligand in translational sub - - is low and about 30% overall will express it in immune cells.

This was part of a large Phase I trial that we performed. Ninety-two patients were entered with varying levels of PD-L expression. These ere patients predominantly who had failed platinum-based therapy; they're predominantly bladder as their primaries. Visceral disease in 79% of patients, 37% had disease in the liver. Cystectomy was present in 61% but 94% of patients had prior platinum-based therapy.

If we also look at other poor prognostic factors less than three months from last chemotherapy or hemoglobin levels those are present in 42% and 17% of patients respectively. This was a very well tolerated drug. Atezolizumab was given every three weeks at 1,200 milligrams or 10 milligrams per kilogram. Fatigue, asthenia, nausea were seen but you don't see neutropenia and neutropenia fevers nor were there any toxic deaths. There were some immune-related side effects, these included transaminitis, hypophysitis, and hyperbilirubinemia.

If you look at the response rates in our patients based upon their IHC status of the immune cells two plus is more

than 10%, three plus is more than 20%. We see here that half of patients who were two plus or three plus had a response. The zero to ones it was 17% and we did see complete response in patients who were two plus or three plus.

This was the first patient we treated at Yale a gentleman with a supraclavicular lymph node as you see on the right. That basically disappeared after six cycles and he stayed without relapse for nearly two years and he relapsed in his retroperitoneal lymph nodes. That actually was surgically resected and he's continuing to be on ED.

We saw responses in 55% of our patients. There are patients who are PDL zero or one in the immune cells who responded so I don't think at this point it's ready for primetime as a selective factor.

If you respond you tend to respond for a long time. the median duration of response has not yet been reached and that's irrespective of those patients with either high levels of expression or low levels of expression and 20 of the 30 responding patients had ongoing responses at the time of the date of cutoff.

What's most impressive is the progression-free survival and the overall survival. Thirty-nine percent of patients had a one-year progression-free survival in the two/threes. It was 10% in the zero/ones. The median survival has not yet been reached in the two/threes and this is at a median follow-up of 14 months. It's going to be higher than that. Consider again systemic chemotherapy for these patients often shows you a median survival of eight months. That's what we see in the zero to one group.

How do we confirm this? This drug was granted breakthrough status by the FDA last year. The INVIGOR trial is completed accrual and looked at patients who had prior platinum-based therapy or who were platinum and eligible. A total of 400 patients were treated. You didn't have to require PD-L1 immunohistochemistry but we collected this for correlation.

Genentech had a press release on the 12th of July of this year basically saying that they were encouraged by the responses and they're planning on presenting this at a medical meeting in the near future. That's now under

preparation for a major medical meeting. I can't say which but it will be presented hopefully within the next several months.

Pembrolizumab is also a PD-1 inhibitor. It's also showing activity in metastatic bladder cancer. A very similar trial was presented at ASCO this year by Betsy Premac [phonetic]. Thirty-three patients were evaluated. They were treated with pembrolizumab every three weeks and again the survival seemed to be very similar to what we saw in our trial. These patients were selected for PD-L1 expression and we didn't have the gamut of patients that we saw in our previous study but overall the median survival is 12.7 months. What she's also demonstrated is there seems to be a very similar theme between patients with bladder cancer and melanoma as far as the immune signature are concerned. What she looked at was the same panel that's been looked at in melanoma. These include expanded immune panels, T cell receptor signaling as well as de novo proliferation markers. What she found was that T cell receptor signaling in a 13-gene panel correlated with overall survival and response with these patients. We clearly need better markers to understand that.

Finally and the last portion of this talk it's important to try to move forward because as we saw before only about a third of our patients respond to anti-PD-L1 therapy. One of the areas we're exploring is VEGF blockade. If you look carefully at these stains the T cells are on the periphery of the bladder cancer cells. Perhaps by opening up the door by using VEGF inhibitors we can let those T cells go and move in. VEGF R2 is expressed in bladder cancer in the tumor but not in the normal urothelium. We just recently completed a randomized trial looking at chemotherapy combined with a VEGF R2 inhibitor ramucirumab, also a VEGF R1 inhibitor icrucumab and this was in second line chemotherapy. We found in this trial, and this was presented at ASCO GU this year, that there was a significant improvement in progression-free survival when ramucirumab was combined with docetaxel, we didn't see this with the VEGF R1 inhibitor.

This is now moving into a larger Phase III trial which is being sponsored by Lilly. It was launched about two months ago comparing ramucirumab plus docetaxel to docetaxel alone and that's looking at a primarily survival benefit. We're

allowing patients with prior checkpoint inhibition therapy to go on this particular trial.

Most importantly the concept of combining anti-VEGF with immune therapy is going to be evaluated at Yale. Roy Herbst and I leading an effort in lung cancer, bladder cancer, also the Farber is going to be doing a gastric cancer portion to this where we're combining RAM plus the anti-PD-1 pembrolizumab and we hope to see at least an increased response rate with this particular combination.

There are trials that are now being designed looking at adjuvant post-cystectomy for those patients who are PD-L1 positive and that study is being sponsored by Genentech and it's accruing patients at this particular point. Patients have to be PD-L1 positive to go on this trial.

In conclusion checkpoint inhibition therapy demonstrates significant antitumor activity in cisplatin treated metastatic urothelial carcinoma. Phase II and III trials are ongoing to confirm initial observations of anti-PD-1 and anti-PD-L1 in metastatic urothelial carcinoma and we still don't understand the marked patterns at this particular point. I don't think that they're ready for primetime to select patients but you may be able to use these markers to at least stratify patients and go forth with more aggressive therapy rather than just imply treat them with PD-L1 if they're negative. I'll stop there and entertain any questions that you have.

DR. FINKELSTEIN: Dan that is an incredible overview - - bladder needs help. PD-1 might be the right drug to accomplish it. the part that you talked about is a key part which is the neoantigen piece which is. For those of you who don't love immunology immunotherapy, your immune system was never meant to go after you. It was never meant to go after self. It was meant to go after non-self. If you create a mutation or you give radiation and you hurt something, you give chemotherapy and you hurt something but if you put the things back together in the wrong you create non-self of which you should go after it but we don't go after it very well unless you give something to break tolerance which is what PD-1 does. If you have the right situation where you have those things you'll go after it. If not you won't

There's another piece of it which is the adaptive piece of

- the immune system and for those in the audience Dendreon had a product they were developing, Nuvenge [phonetic] which was an adoptive cell transfer platform similar to what Provenge was, can you get maybe a comment from you and maybe from the audience about maybe the desire to develop an adoptive cell transfer plus PD-1 or a VEGF agent.
- DR. PETRYLAK: I think there are a lot of different combinations that are out there right now and I think that the question is what's going to be based on the biology. Certainly there is a randomized trial of Nuvenge versus placebo that Dendreon is sponsored. This was in HER2 new positive bladder cancer patients who had undergone a cystectomy. They could or may or may not have had neoadjuvant therapy. That trial is now pending and we'll see whether that concept-
- DR. CRAWFORD: [Interposing] Where is it? Is it completed?
- DR. PETRYLAK: It's completed. The follow-up is pending.
- DR. FINKELSTEIN: The question again is adoptive cell transfer by itself probably shouldn't work. Even Steve's data was not impressive until he brought in other parts, the vaccine approach, the immune signaling approach. Now you'll have data that shows probably the PD-1 is useful and maybe Nuvenge's resuscitation will be used coupling adoptive cell transfer platform with take a drug of your choice.
- DR. PETRYLAK: Certainly that's one way of going about it. VEGF is another way. The question is what's the right sequence to go forth with chemotherapy. There's actually data that suggests that PD-L1 is upregulated after neoadjuvant. M-VAC and that was actually published from the University of Michigan so we really have a lot of work to do in trying to sort out what's the optimal sequence, what's the optimal combination and this is why your participation in these clinical trials, particularly the adjuvant studies I think are going to be crucial to understanding what's going on.

Screening Controversies - David Crawford, MD

- DR. CRAWFORD: This is really weird on these questions. All of a sudden 15 questions from yesterday came up that weren't answered. Hmm. That's too bad. We'll try to get to these

because these are actually a lot of good questions. There was one for Dr. Keane. Let me try to remember what it was.

It was about start with an antagonist then go to an agonist long-term what are your feelings about that. That, to me that just undermines the whole idea of what an antagonist does.

DR. KEANE: That's because the one month versus the three month issue and the six month issue and if you ever sit down and have a talk with Marc Garnick he still uses the one month LHRH agonist because he does not favor-

DR. CRAWFORD: [Interposing] I hope he uses the one month degarelix.

DR. KEANE: I don't know what he does with that because he still has abiraterone but he certainly doesn't use the three month or the six month and I'll leave it to him to answer that question but the idea of converting across yes, it's been done a lot and it's being done because people don't want the flare and they don't buy into the mini-flares and they don't buy into the FSH control and that's what I meant about future directions that we need to confirm these findings. We need to show that FSH is an important thing. I can talk about it all you like but until I can come up with some clinical evidence, which hopefully is coming within the next year that we can link FSH results to outcome in patients. I think that will be a terrific way forward.

As regards crossover I gave you the data on crossover going from an agonist to antagonist doesn't make much sense to me go to the other direction.

DR. CRAWFORD: If we get done here in a couple of minutes there's ten questions on molecular markers from yesterday that were good that somehow appeared on this screen a little delayed.

As mentioned ,Gerry Andriole can't make it and he has been here many, many times and we know he had a serious issue otherwise he would have been here.

What I'm going to do is pitch in and do a talk which is very similar. This is one I gave at the plenary session of the AUA. I'm a Professor of Surgery, Urology, and

Radiation Oncology at the University of Colorado. I did not give up being a surgeon to become a radiation oncologist. That was a weekend course and I did it and I am not a radiation oncologist. It's not that hard. You just have to know how many dollars you charge per rad but now it's per something else.

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

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

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

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

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

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

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

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

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

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

What did we do? A couple of years ago we went to the Henry Ford database and we combed that database found 350,000 men in the system. We had some data from the PLCO trial about PSAs and we knew that somewhere between 1 and 5 we wanted to look at. We wanted to find a PSA level that was a very little risk within five to ten years of you having a significant prostate cancer. The median age we round

21,000 men eligible that had to have a follow-up of five years and no 5-ARIs and we set an initial PSA between 1 to 5. We have a high percentage of African Americans in there, almost 30%.

This paper was rejected by the *Journal of Urology*, it was subsequently published in the *British Journal of Urology* a couple of years ago and it won the best clinical paper of the year in the *British Journal of Urology*.

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

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

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

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

How do we improve the performance of the tests and find

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

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

That was one of the criticisms of the U.S. Services Preventive Task Force the number of re-biopsies and what happened when you did that. this can be identified by the epigenetic field that both Wim and Chris mentioned earlier, the field effect that's there that looking at these three genes that are methylated that help determine who is going to have a positive biopsy. As you well know this was dialed in for a negative predictive value to provide actionable information to rule out prostate cancer free men from undergoing unnecessary repeat biopsies.

There are a number of publications this was the latest one the DOCUMENT thing that Alan Parton did that looked at how ConfirmMDx fit there. It fits in previous negative biopsy, ConfirmMDx negative, life goes on. If it's positive we heard Chris talk a little bit about that.

Here's how I think we go forward. A man comes in sees family practice doctor. PSA is a routine lab that is done. We can set the guidelines over the age of 50 over the age of 45 maybe up to 75 or so routine PSA. Less than 1.5 a green light; come back in five years. Greater than 1.5 a yellow light; maybe refer to a urologist at this point. That would be about 30% of men. Or know what the next test is. The next test might be one of these new PSA forums like PHI, PCA3, or certainly 4K and if they come back low risk then you back into the routine follow-up. If they come back higher risk, whichever test you use, then the patient obviously in the hands of a urologist will get a

TRUS biopsy or at least an ultrasound because we know that a large prostate also produces PSA from BPH. Then if the biopsy is negative this is where I think ConfirmMDx comes in and if that comes back negative we know that there's a 94% negative predictive value that there's no high-grade cancer to 90% negative predictive value that there is not a significant cancer. If it comes back positive this is where I think multiparametric MRI comes into being where you focus on an area and look for it and do targeted biopsies. If the biopsy is positive, Pattern 4, healthy person treat them. If it's Pattern 6 or 3/4 that's where your genomic markers come in. That's where mapping biopsies come in and if it comes back high risk then you treat the patient. If these markers come back low risk then you follow them in active surveillance. That's what I think the way forward. It's simple. It doesn't have to be hard. Know there's not going to be uniform acceptance of this. There are people who say I think cutoff should be 2 or I think the cutoff should be 1 or I think the cutoff should be 2½ and I hear that when I go talk to people. We've been saying that for ten years and we haven't gotten anywhere. All we've done is confusion. We need a simple, simple, simple message for family practice and internal medicine so they go forward. I think in their heart of hearts they believe the early detection of prostate cancer helps in spite of the folks in Massachusetts that try to crucify Mitch when you said that. I think that will happen in academic centers.

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

The PLCO trial there was an arm where people weren't screened and the result was that was as good as people that were screened. There were some problems with the trial we

overran the sites but when you separated out people that were healthy, and I did this with Anthony D'Amico and his biostatisticians group we found out there was a benefit.

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

Thank you.

DR. LUGG: If you're going to use 4K or PHI or PCA3 and you're going to pick them completely different population of high risk patients why are you doing a TRUS biopsy. Why wouldn't you then want to find the high risk cancer anywhere it exists in the prostate because if you biopsy with say for example and MRI-guided biopsy as opposed to a TRUS-guided biopsy you find the Gleason is 3 plus 3 and you missed the three plus 4 that was the thing that was making the 4K test or PHI test - - in the first place you're going to still want to do an MRI to make sure you're not missing that cancer because your diagnostic test told you that you have a high grade cancer so why do a TRUS biopsy at all? Why not switch to MRI-guided biopsy for everybody.

DR. CRAWFORD: Because I haven't drunk the MRI Kool-Aid, I don't believe it. Sorry.

Who was up here talking said they were just reviewing an article on MRIs they have 30, 40% miss rate. Brian Moran. I don't buy it Jim. Maybe in your hands. They're still missing significant cancers.

DR. LUGG: What's the miss rate with TRUS biopsy compared to MRI for high-grade cancer?

DR. CRAWFORD: I don't know that has been really studied off the block yet. People have done it retrospectively. Samir Taneja has done it. Emberton and that group have and they claim it's really good for high-grade cancers. Then other people are finding that they're missing 30% of the high-grade cancers.

DR. DEBRUYNE: The problem with MRIs, the meaning of the MRI by ideology is [background noise] 30 to 40 minutes to read an MRI properly and - - each time that the radiologist stands in from of an MRI is ten minutes. That's the point with MRI you need expert radiologist for that. we follow your scheme but we do the multiparametric MRI because was such a

center just prior to the TRUS biopsy - - .

DR. CRAWFORD: I don't know if we have to get into the argument about that. The first part of it to me is more important is the message to the family practice doctors. Thompson and the group just came out last month with a large cohort from Texas where they say a cutoff of 1 less than 1, noting happens for 10 years, come back in 10 years. I'm fine with that. We just have to go with some message and say at this level we think that the relative risk is not there. At this level it is. If you feel comfortable as a family practice guy to order a 4K test, or order a PHI whatever you're going to do fine. If not send it to a urology but by god, the urologists better grow up and not just do biopsies on everybody that walks in with a PSA of 1.5 and above and they have to evaluate for BPH and other things like that. I know Marc's about ready to lay into me but go ahead.

DR. GARNICK: No, I'm not laying into you at all. I just want to share with you my dilemmas about the whole screening issue about prostate cancer. We've got PLCO, we've got a European randomized study that did not show any improvement in survival. The dilemma that I have is that if indeed in the randomized study there were populations of men that had adverse risk features in both groups and the treatment was done then we should have seen a survival benefit by the earlier treatment of men with adverse features even those we did not have the molecular characterizations that we have now. Obviously we're not making any difference in survival in the indolent cancers that don't need to be treated. I think actually the biomarker data needs to be applied to developing actionable drugs that can identify the mutations that are driving the Oncotype DX and the Prolaris data that's leading to the adverse outcomes. What we're doing is you're adding more precision of who should be biopsied. I don't think that's the question. To me the question is what do those genes that have led to the quote unquote need for additional biopsies how can they be actually identified and acted upon. Otherwise in the screening studies these adverse patient populations would be equally identified in both populations yet treatment did not result in any survival benefit and that to me is the critical question of why the screening studies have failed. I think the future for the use of molecular markers is to

work with drug therapies that could potentially modulate the genetic abnormalities that are driving progression and metastasis and death.

DR. CRAWFORD: When that happens let me know.

DR. GARNICK: That's what I think needs to be done.

DR. CRAWFORD: I think it needs to be done too. We could be here until 10:00 at night arguing about PLCO and ERSPC and all the other things and I can argue it either way pro or con. I understand what you're saying. I do believe that there are men that benefit from early diagnosis.

DR. GARNICK: I don't disagree with that. We're obviously trying to figure out who those men are and what treatments those men should receive.

DR. CRAWFORD: I agree. I try to take the PLCO data and start backwards with the people that died versus those that didn't and figure out what's the phenotype of those people were and I could never get our biostatisticians or anybody to even think about that because they said it wasn't legitimate, it wasn't randomized in a trial. You find out information from that.

We've got Brawer and Finkelstein and then we quit. We have to be out of here in five minutes.

DR. BRAWER: Just a comment. Your 1.5 is eloquent, simple, beautiful and highly impractical because what you're going to do is 30% of men now are going to be referred to a urologist that don't have the bandwidth to evaluate those patients. We learned with complex PSA and free to total that the primary care doc cannot deal with anymore than simple PSA so its going to have to be either a midlevel practitioners that decides who get Confirm or 4K or we automate the laboratory system and it gets done and gets interpreted by some—it's a good startup idea, you could probably do this on an app—and they do it for the primary care doc because it will never happen.

The other thing that the people that are working on a more specific PSA, which I applaud, what they want to be able to charge for it will never solve the need to show economic viability.

DR. CRAWFORD: I think you're right and there are companies that

are working on that very thing that you're talking about to a degree and that can be automated and can be in a family practice office. It's hard to know what's going to happen with all the reimbursement now but it is a possibility.

DR. FINKELSTEIN: Can you put the great slide he has that summarizes? My question is to my colleagues in urology, which there are many very, very bright guys here. On a radiation side there's one piece of that that we don't think of in the same way and I'm wondering if we - - . The part about Gleason 4 plus 3 equals 7 we treat. But the Gleason 3 plus 4 equals 7 send for genomic markers, yeah that part. Gleason 6 I can, but for Gleason 3 plus 4 equals 7 I think most residents will fail their boards if they don't get treated in radiation oncology.

Of the urologists as you are sitting here if there's a guy with Gleason 3 plus 4 equals 7 are you thinking not treat them?

DR. KEANE: Larry Klotz has a large cohort of patients with 3 plus 4 disease who are on active surveillance.

[Crosstalk]

DR. CRAWFORD: Three/fours with enough disease should be treated.

DR. FINKELSTEIN: I'm trying to get a consensus of the gentlemen who are here. A Gleason 3 plus 4 equals 7 in general is getting treated unless it's minimal. Is that the general? That's the one thing about that where it makes it look like everybody, 3 plus 4 equals 7.

DR. KEANE: If you had 4 cores of 3 plus 4 you'd probably-

[Crosstalk]

DR. CRAWFORD: Let me ask Wim. You've been awful quiet. You know more about all this than a lot of people. What do you think about this way forward and the genetics and can we be doing 23andMe on everybody and getting an answer.

DR. VAN CRIEKINGE: That's a completely different story. Marks are probably going to be able to help distinguish who of the 3 plus 4s really need to move onto therapy and who can be waited for. The 23andMe is completely different story probably. It's about risks and genetic profiles and it's

going to be very minimal in contribution.

DR. GOMELLA: I think one of the things you have to put in here is patient characteristics too. Patient characteristics, ten-year life expectancies. Not to make it more complicated but consider individual patient characteristics. I think it's a great outline but I think you got to just say consider individual patient characteristics at certain junctions.

DR. KEANE: But that's not true because if you look now at the number of patients who we're seeing who are 76, 77 years of age who are being diagnosed with prostate cancer there's a whole group of people out there who you're wondering what was your PSA, 3.5 and you had a biopsy? And you're 78?

DR. GOMELLA: You're going to show this to a bunch of family practice doctors a 95-year old is going to come in with a PSA of 4 asymptomatic.

DR. KEANE: Congratulate him.

DR. GOMELLA: That's all I'm saying. Just somewhere in here individual patient characteristics have to be considered. That's all-

DR. CRAWFORD: [Interposing] This thing could be getting so complicated-

[Crosstalk]

DR. DEBRUYNE: You have to be careful today because you see a lot of patients that are 75, 76 and you say don't do a biopsy, don't do - - , you are not going to die but they say my mother was 90, 95, 100 you have to treat me. You have to diagnose it. I remember a patient just before I came, 82-years old and he had a PSA of 6 and he wanted absolutely an MRI. I said its nonsense. He insisted and if I refused he would probably feel discriminated. Patient characteristics are very, very important in both senses. That's the danger because we are going to be forced to treat more and more patients over the age of 75 that feel and are assured that they are going to survive another ten years and will demand treatment.

DR. KEANE: The biggest reason that people sue is not because they weren't diagnosed it's because nobody discussed it with them. Nobody sat them down. If you say I don't

believe you should be biopsied and I'm not going to do it but you're very welcome to walk out the door and go and see another urologist who probably will. That's most of the reason people get sued is because patients are pissed off and there was no discussion.

DR. DEBRUYNE: It's not a question of suing in Europe you know that. It's a question of emotional discrimination.

DR. CRAWFORD: Tomorrow I want to discuss with everybody. I don't know if you saw the *Wall Street Journal* on Saturday but it says FDA dealt setback on off-label use. Did anybody read that? This is huge. Basically it was about Ameren Pharma and a decision of the Southern District New York Federal Court about they had a lipid lowering drug and it was for people with really high triglycerides but they also said that it worked for people with lower triglycerides basically and they had some data on it. Basically what they said here is that as long as a court ruled that a drug company can tout other uses as long as the claims are truthful, which is huge. To me that opens up a lot of stuff. If you do a study and you're truthful to your drug off-label use it's going to be interesting to see where this goes.

[Crosstalk]

[END Day 2 Session 3.mp3]