William Oh:

Hello everyone. My name is William Oh. I'm the Chief Medical Officer for the Prostate Cancer Foundation, and I'd love to welcome you today to our program on Genetic and Biomarker Testing: What Does It Mean For Me? I want to thank Veracyte for their support on the section on biomarker testing. I'd also like to thank my colleagues, Dr. Maxwell and Dr. Hu, for their participation. And just remind the audience that their views are their own and not reflective of Veracyte.

As a reminder, the Prostate Cancer Foundation has been funding research for 30 years now. Our mission is to reduce death and suffering from prostate cancer. We support transformational research from all over the world, 2200 projects in hundreds of laboratories, and have been supporting the best and brightest young investigators.

We have a lot of resources for patients and families, so please go to pcf.org, sign up for updates. You can download free guides. You can view our past webinar series, and sign up for our online support group on Facebook. And very soon, June 1st, we're starting the Home Run Challenge. This has been going on for 27 years with Major League Baseball to support prostate cancer research and awareness. So please go to the website shown there, and keep that in the game.

Dr. Hu is the Ronald Lynch Professor of Urologic Oncology at Weill Cornell Medical College. He's the Vice-Chair for Clinical Research, Chair of Quality and Patient Safety, and has a research interest around surgical innovation and health services and comparative effectiveness research. He's been well funded for many years. He's a surgeon who does radical prostatectomies, with a robotic approach. He's been a colleague of mine for many years, and it's really a pleasure to work with him on tonight's program.

I'm really happy to welcome Dr. Hu to this section of the talk, which is really about somatic testing and really, biomarkers. So go ahead, Doctor Hu. Why don't you tell us what a biomarker is?

Jim Hu:

Sure. Thanks, William. Great to reconnect with you and the Prostate Cancer Foundation. We're going to speak about genomic tests, shift gears a little bit. And basically, genomic tests are biomarkers that analyze a sample of tissue. For example, that can be the tissue from the prostate biopsy, or it can be the tissue from the radical prostatectomy specimen. And really, it is to look at how active certain genes are, and the activity of those genes affects the behavior of the cancer, including things like how likely it is to grow and spread. And so, I think we'll highlight that with this particular case, and we can talk about variants of it or the opposite of it. So if we can go to the next slide.

So this is a 65-year-old gentleman who had a screening test with a PSA of 7.15, and then underwent to prostate biopsy. And for those who are very sophisticated, and I know many of the audience tonight are, of course, he got an MRI before the biopsy, and you can see that as the last labeled area. That's the MRI targeted area.

And so, in this particular case, this tumor was actually opposite the MRI suspicious area. And the MRIs, just as a point of reference, are only supposed to look for what we term clinically significant prostate cancers, which are grade group twos or higher, using the Gleason scoring system 3 + 4 = 7s or higher. And so, this incidentally picked up what we would call indolent prostate cancer, or grade group one prostate cancer.

And just highlighting one of the uses of genomic tests, and although we are sponsored tonight by Veracyte, there's other companies that make genomic tests, like Myriad as well as Oncotype.

But in this case, we went ahead and got a Decipher score, or what's called the genomic classifier score on the next slide. And so that's basically where the tissue block from the biopsy is taken and sent to this third party lab.

Basically, molecular sequencing is performed, and this test usually takes two to three weeks to run. And I think the graphic that one wants to key in on here is that, at least the Decipher genomic risk score is scaled on from zero to one as a continuous score. And in this case, you can see that as the continuous score approaches one, it's associated with a higher risk classification. And so, that's the continuous scoring you see on the left. And then in the right-hand side in the tables, you can see these likelihoods or probabilities. If this patient were to undergo, for example, radical prostatectomy, there's a 41% chance that with complete sampling of the prostate, that there's more aggressive cancer that's found. And that more aggressive cancer is defined in this case as being a higher grade cancer, or extracapsular extension, seminal vesicle invasion. Those are higher stages, where the cancer has gotten outside the capsule.

It goes on then to look at as well, the likelihood of death within 15 years. And in this case, it's 7.2%. And then again, with either radiation therapy or radical prostatectomy, there's a 2% risk of metastasis within five years, and a 4.9% risk of metastasis within 10 years. And so, this particular patient, given the genomic score that he received, decided to pursue treatment in the form of radical prostatectomy. And oftentimes, in a clinical setting, urologists, medical oncologists, radiation oncologists, are getting these tests to, for example, provide reassurance that active surveillance is the right thing to do. So for example, this person had a Gleason three plus three equal six, and I'd say 97% of the time, these tests come back concordant. That is, you would see the continuous score on the left, somewhere between zero and 0.45 following in the low risk classification. And therefore, just confirming that active surveillance or monitoring with curative intent is the right thing to do.

And I'll just briefly mention, William, we were talking a little bit earlier about a patient that we shared that, for example, had the opposite happen. He had a Gleason 3 + 4 = 7, or a grade group two on prostate biopsy, underwent this Decipher test, and then had a score of 0.17, which of course is very low in that blue low risk area, and therefore decided against definitive therapy and wants to do active surveillance longer.

So that's how we are currently, I think the most popular use of Decipher. It originally started actually just with the radical prostatectomy, post radical prostatectomy, run the Decipher score to determine what's the likelihood of, again, tumor behavior that you see in that table. And for example, it used to be that we thought that there was a advantage perhaps to giving what's called adjuvant radiation therapy, or radiation therapy as an adjunct to surgery. And so, if someone had high risk features, for example, on a radical prostatectomy specimen, or they wanted to look at molecular features, they would get a Decipher score. And if that risk came back high risk, that patient and provider may engage in shared decision making, and say, "We should consider radiation therapy shortly after the surgery."

However, there's been randomized controlled trials that have come out, and have shown that the cancer recurrence rate after salvage therapy that is waiting for the PSA to come detectable after surgery versus adjuvant, giving it as planned, that the salvage, that the cure rates are similar. And so that's why, really, I think the utilization in that setting has become less and less.

And third, I would just mention that, for patients who are thinking about radiation therapy, for example, and they have grade group two or grade group three disease, which is intermediate risk, Deciphers are being sent by the radiation oncologist, because if the Decipher score comes back unfavorable intermediate risk that is higher in that yellow area, or comes back as high risk, then adjuvant androgen deprivation therapy, hormone therapy, is going to be given with the radiation. Because level one evidence has shown us that the recurrence rate, or treatment failure, is going to be lower with the

adjuvant radiation therapy in that setting, as compared to no adjuvant, rather adjuvant hormone therapy with radiation is going to have a higher cure rate than no hormone therapy.

William Oh:

So just as a reminder here, we assess risk using numbers like PSA, Gleason score, now the MRI, maybe a prostate exam, a digital exam, and we put people into categories. They have low risk disease, intermediate risk disease, or high-risk disease, and we base it on those classic numbers that have been around since you and I worked in Boston 15 years ago, 20 years ago. Right, Jim?

Jim Hu:

Absolutely, for you.

William Oh:

Funny for me. And so, this test and other tests like it, are giving us, in this case, discrepant information. This doesn't correlate. So one of the questions I have for you, like this man based on the Gleason score and his PSA should be blue, but he's not, he's red. A, how did this test, how did this biomarker come to that result? And B, how do you, as his surgeon, change what you recommend for him?

Jim Hu:

Sure, absolutely. Great question. So basically, how I explain this to patients is that, number one, these genomics tests are a way of looking at molecular risk classification. So what we talked about, a central feature of traditional risk stratification, which we actually worked with Anthony D'Amico, developed one of the first risk stratifications. It really relies heavily on the interpretation of the pathologist looking at the tissue under the microscope that is grade. And grade is, I think, one of the most central features of the three components that make up risk. And so, one of the key differences, and I'm glad you asked this question, William, between the Veracyte Decipher test, as compared to the competitors, is that, this is independent of looking at other known clinical variables, such as PSA, clinical stage, the prostate exam, for example. The MRI features the stage.

And so, how this came about is that, there are existing biorepositories, where men had radical prostatectomies, their tissues were banked, and then these men were followed for 10 or 15 years out, to look at these subsequent likelihood of these events. And therefore, the molecular signature, and this is looking at 22 genes and seven pathways, these molecular signatures that are run on a microarray are then therefore associated with, and/or matched, with those patients in these biorepositories that you have 10 or 15 year outcomes on. And so again, it's an independent way of coming up with risk, that differs from the components of traditional risk stratification, that is PSA, the grade, as well as the clinical stage.

And then in terms of your question of the two-parter, which was, how did I help this man come to a treatment decision? Well, I mean, again, I think that one has to keep in mind this is not a perfect crystal ball. There are associations, and I'm sure you in your practice have seen cases where, for example, and I've seen this, a person who had pathologic T 3B disease, had high risk Decipher score, actually chose not to get adjuvant radiation therapy. This was years ago, when it was popular for that reason. And fortunately, six years later, has not had recurrence, which defies, and had a grade group four, or at least in 4 + 4. So again, there are going to be exceptions, and one has to understand that it's not a perfect crystal ball.

So in terms of this particular patient, I don't think that this patient, if he had an MRI or biopsy again in two or three years, we may not see high risk prostate cancer. But the way to interpret this is the statistical prediction, again, based on the association, and/or the matching of his molecular features to men in a biorepository, is that, he has a high risk tumor that's going to behave like this. And given that information, this particular individual, who is also in his mid 60s, decided that the potential trade-offs, in terms of quality of life versus cure, were worthwhile to go ahead and pursue treatment.

William Oh:

So this is a man who you might have offered active surveillance to, but once you saw this Decipher score, you leaned away from it.

Jim Hu:

Exactly right.

William Oh:

Because the Gleason score suggested he may not need treatment, but the Decipher score suggested that maybe we were missing something in the Gleason.

Jim Hu:

Absolutely. And more often, we highlight this as a discordant test. And just to reemphasize the point, I'd say 97% of the time it's concordant, and provides reassurance to both the patient and the provider, that active surveillance is the correct thing to do.

William Oh:

Yeah. It's like extra information. Prostate cancer is like a puzzle, and we're trying to get as much information as possible. This is molecular information, and it is genomic data that's put into an algorithm, really a single number, through a kind of formula that the company and we have, there's at least two other companies that do something similar. And doctors use this to help counsel patients about the best therapeutic choice forward.

Jim Hu:

Absolutely. And one other thing that we talked about, William, is just the fact that I think many of the Prostate Cancer Foundation supporters are obviously very sophisticated. And I know in the PCF literature, there's the recommendation, for example, if you get a prostate biopsy or radical prostatectomy specimen, to send it to a second opinion. And so, in this regard, as we're talking about, because this is a independent test that isn't dependent on those other characteristics, like the PSA, the pathologic, the original pathologic interpretation. And so, this can also be a proxy, if you will, as a second opinion for the pathologist interpretation, which may be subjective, as we've seen in our practices.

William Oh:

Right. I remember I had a patient in Boston when we were there, who had a Gleason six in one Harvard hospital, Gleason eight in another, and a Gleason seven at Boston University. So three different Gleason scores. You don't see that much anymore, but I think some people who read the Gleason scores are not

necessarily as experienced as people at, for example, at Cornell. So this is a way, what you're saying is, this is a way to kind of be sure that a Gleason six really is going to behave like a Gleason six.

Jim Hu:

Absolutely. And I'm sure you've seen patients after radical prostatectomy, they'll want to know, "Hey, what is my likelihood of cancer coming back in the future?" And the easiest way is, of course, to look at those nomograms, or predictive tools, or what's been termed the Partin tables, that originated at Johns Hopkins. But I tell patients who want to know, "Look, this is the most individualistic probability that you can obtain, based on a molecular signature from your radical prostatectomy specimen."

William Oh:

So let's answer a few questions, Jim, that we're getting from the audience. So one patient wants to know, he had a prostatectomy several years ago, can you actually run these biomarker tests on a sample that's a few years old?

Jim Hu:

Absolutely. The critical thing to understand is that, when one has, whether a biopsy or a prostatectomy, there's still a tissue block, meaning, tissue that's embedded in a paraffin block, that's separate from those that are made for the glass slides. The glass slides are what's sent around. If you get a second opinion, you send it to another institution. Whereas, the tissue block remains on file at the institution that either the biopsy or the prostatectomy was performed. So absolutely yes, you could request that. The patient will have to sign a waiver, and the pathology department will send it out for testing.

William Oh:

So there's another question. There's one person who had three different companies run their tests, and two of them agreed with each other, that surveillance was an option, and one of them suggested treatment. Do you know how often these tests disagree with each other? Do we have good data on that?

Jim Hu:

O haven't. I've probably seen, just I'm sure in your practice as well, as second opinions, I've seen a handful of disagreements, but I would say, most of the time the tests agree. But I would again, point out the fact that Veracyte, the Decipher score, is the most widely validated. It's the most often studied. It also runs, for example, I mentioned the seven pathways, whereas the other run, runs one to four. And again, this is independent of PSA, the light microscopy grading as well as staging. Whereas, the others take that into account to come up with a score.

William Oh:

Can the test results change over time? And have you had examples where you're running serial, let's say, Decipher or other molecular biomarker tests?

Jim Hu:

Sure, absolutely. And so, one of the Achilles heel of the Decipher score, particularly in the biopsy setting, is that, we know that prostate cancer is multifocal in about 75 to 80% of men. And so for example, in the example that I showed, it was grade group one, or Gleason 3 + 3 = 6, but a biopsy of the prostate

samples about 1/1000th of the prostate. And so, the point here is that, if you're not sampling the most biologically aggressive cancer, if it's present, then, of course, you're not getting the molecular signature, or the prognostic information that would come from that genomics of that cancer area. So that's really the Achilles heel. So the question of whether these things change over time... And again, I think that most of the audience tonight are probably prostate cancer survivors, but we can all think of the rare instance where, for example, I had a patient on active surveillance, did three biopsies. The patient had a high MRI score at PI-RADS four, and then on the third, the PSA kept going up.

And finally, one sampled an area that's clinically significant, instead of grade group one on active surveillance. And then instead of the Decipher score being low risk, it was consistent with the grade, which became a 4 + 3 = 7. And so, it's just one of those things where, and I don't want to mix what's going on in the debates that are going on the field right now. One of the debates is should grade group one be called prostate cancer anymore? But I think that one does have to keep in mind that, regardless of whether we call it cancer, or an idle lesion of epithelial origin or idle lesion, that acts of surveillance means monitoring with curative intent. It's like having a polyp and needing to go back for the colonoscopy, instead, just forgetting and saying, "I'm going to skip it." So I think that's the most critical lessons that come out of just a continued monitoring and being vigilant.

William Oh:

So when we use the term biomarker, we probably have the most famous biomarker in prostate cancer in all of medicine, which is the PSA test. These biomarkers are not going to replace PSA, are they?

Jim Hu:

No. So one of the differences I would just go back to is that, the other competing biomarkers with PSA, or I shouldn't say competing, but I should say supplemental, which is, there's biomarkers like the 4K score, or PHI, and those are used in the space of saying, my PSA is, let's say, between the four and 10 area, where it's indeterminately high, should I consider doing another biopsy? And those biomarkers just give you a probability of having prostate cancer. There's also urine based biomarkers now in the setting of a mildly elevated PSA that you can take. And again, it's just to help the man and his provider determine whether or not to pursue prostate biopsy as the next step.

William Oh:

So should every man who gets a prostate biopsy get a Decipher score or an Oncotype score? Does everyone need it?

Jim Hu:

Well, I think you'd agree, William, you only want to order a test if the results are going to help you with decision making. And so for example, if I have a, and again, I'm using extreme examples if you will, but if I have... But we see this not uncommonly in New York City, for example. If I have a 75-year-old guy, who again, guidelines would've said, stop doing PSAs and biopsies in men aged over 70. Let's say I find someone who is 75, and had this biopsy report, that is grade group one prostate cancer. Do I want to necessarily highlight the fact that in 10 or 15 years there's risks of metastasis, when this person's life expectancy may be seven years?

So again, I'm just using an example where, for example, that 3% discordance may not serve that person in the long term, because the mental anguish of knowing that there's discordance and actually high risk tumor behavior may cause that person regret from finding out and choosing to have treatment that may

not prolong life, but actually worsen quality of life. And so I think the point there is, order the test, if it's going to help the decision making or reinforce the decision.

William Oh:

Yeah. If it's not going to change what you do, don't order the test. Another example would be a young man, 50 year old man with a Gleason eight prostate cancer group grade four, you're not going to change what you do. You're going to treat that man aggressively, based on what we know about Gleason eight prostate cancer. If a Decipher score came back intermediate risk, you're not going to forego treatment in that man, because you already have a lot of knowledge about the behavior of that cancer. So I know some doctors, and it's actually some patients, would like to figure out a way not to do treatment if they don't have to. But the fact is that a lot of our traditional markers, biomarkers, like PSA, like MRI, like Gleason score, already give us a lot of information. These are additional pieces of information that help the patient and the doctor to make the best decision. So if it doesn't change your mind, then it may not really help, and probably shouldn't be done. Right?

Jim Hu:

Absolutely.

William Oh:

So let me ask about, and maybe, I'd like to hear your thoughts, and I can answer it as well. Kara showed a slide about tests like Foundation or Tempus. These are genomic tests of tissue, but they're different than Decipher or Oncotype. Can you just comment on what information you get from, let's say, a Tempus or a Foundation report that is different from what we're talking about here?

Jim Hu:

Well, I mean, I think those are definitely more whole genome sequencing tests, whereas, we're talking about the tissue related to radical prostatectomy or biopsy related tests. And so, the tests that I'm referring to very specifically, are to look at the likelihood of, or a prediction based on those biorepositories, of the likelihood of cancer being more aggressive, or things of that nature in the future. Some of those tests that you mentioned, for example, are looking at, and again, I think in the more advanced disease setting, are there somatic mutations that there's new therapeutics for that, for example, can help treat that particular? Is it a DNA for repair mismatch gene that a new drug can target? But I'll let you, the medical oncologist, comment about that.

William Oh:

Yeah. So right now, we're talking about really newly diagnosed, where the question is surgery versus radiation, versus surveillance, or the use of additional radiation, what we call adjuvant or adjunct radiation. And whether we, for example, add hormones to radiation. It's all kind of front loaded with tests like Decipher, or Oncotype, or Polaris. The sequencing tests like Tempus, or Foundation, and other companies that do this, are really for more advanced patients, where you're, as you said, you're looking for other therapies. And the best example of that is actually the BRCA genes, the BRCA1 and 2 genes. Just like Kara mentioned, when you find the BRCA gene in your blood from your mother or your father, that makes you a candidate for a specific type of drug called the PARP inhibitor, the most well known is called Lynparza. But there are others.

You might not have inherited it from your mother or father, you might have had two normal BRCA genes, and then you can actually damage one of them by itself, just by living in this world with whatever causes that kind of damage. So some patients do not inherit a bad BRCA gene, but actually have a bad BRCA gene in their tumor, and they are also candidates for drugs like Lynparza. So that is the other reason to test those. But that's primarily in patients with advanced disease.

Can you just talk a little bit about AI? Cornell has a big artificial intelligence program. We're all using ChatGPT, and we think that it might be coming into medicine. Do these biomarkers use AI? Should we trust them? Do you have a sense of where AI is going to be used for helping some of this decision making?

Jim Hu:

Sure, absolutely. So I use ChatGPT to anticipate these questions now. But no, in all seriousness, and you're aware of this. At least I think the most exciting work that I'm aware of that looks at some of this prognostication is, Felix Feng at UCSF has worked with, his backer is... What's his name? The founder of Salesforce. But essentially, they have a company which is looking at artificial intelligence in terms of better... We talked earlier about the subjectivity from pathology to pathologists. So they're using artificial intelligence to better grade prostate cancer specimens. And I think what they have thus far has improved the performance characteristics of, for example, predicting who's going to recur. It modeled on a lot of the radiation oncology trials, where they have, again, the biorepository of tissue, and long-term clinical outcomes of how patients did on radiation therapy trials. And so using that AI, they can go back and look at the tissue and learn from that. And then, have a training set where it predicted long-term recurrence, and then a validation set. So that's what I'm aware of most in the diagnostic setting.

In the research setting, for example, for surgery, I'm fortunate to collaborate with Andrew Hung, who's using machine learning to really explore, as we all know, surgeries now, robotic assisted surgery. And so, that's captured on videos. There's also a black box, if you will, of the robot that captures movements in the X-Y-Z dimension. And so, our grant from the National Cancer Institute is really to examine our certain technical maneuvers during nerve sparing. The part of the surgery, of course, that deals with preservation of sexual function, erectile function, or certain maneuvers associated with better recovery versus others. And so, those are the areas in which I personally have seen AI and/or are doing research in AI, but I'm sure there's many other areas. For example, we talked about MRI earlier. And so, there's plenty of machine learning that's going on to, again, enhance and take away the subjectivity of radiologist interpretation of MRIs.

William Oh:

Yeah. I think the fact that we're still using Gleason score, and that a pathologist is looking under a microscope, I think that's going to go away in the next few years. It's Marc Benioff, and basically, their computers will be able to read pathology slides, and probably radiology images, better than humans in the very near future. Whether your job as a surgeon or my job as a medical oncologist will go away because somebody makes better decisions than either of us? I'm not sure yet, but I think in the end, I think a lot of this is computer assisted, so I think we'll be okay before we retire, Jim.

Jim Hu:

Hope so.

William Oh:

There's a couple of interesting questions. Should it be standard practice for a biopsy sample to be tested for Decipher in a Gleason 3 + 4 patient who chooses surveillance? That's a pretty classic example. Should that be standard? Would you recommend it pretty routinely?

Jim Hu:

Well, so there's other things that have been, and I think this is a, if you will, a nuance of what you mentioned earlier with the Gleason 4 + 4 equals patient getting a Decipher. So I think the critical thing to understand is that, even though we're using categories of Gleason 3 + 3, then Gleason 3 + 4, then Gleason 4 + 3, it is a continuous spectrum from 3 + 4 to 4 + 3. That is the amount of pattern four dictates whether it's the minority 3 + 4, the majority 4 + 3.

So the short answer to that is, it depends on the amount of tumor volume. We showed someone with 13 different areas sampled, so let's say 12 out of the 13 has Gleason 3 + 4 = 7. And if you're confident of your pathologist, for example, if that's a Weill Cornell pathologist that I work with, or we can send it out somewhere else, that is going to give us... It's very unlikely, unless this person has significant comorbidities, or really values their current quality of life, erectile function, it's very unlikely that I would recommend that person for active surveillance.

And so again, that's just a literal example. But in the case of one or two course positive, it's five to 10% pattern four, I think absolutely it provides reassurance. And as you know, William, and the person who asked this question, I would say that the placements of men with favorable intermediate risk on active surveillance, has probably only become more conventional in the last two to five years. It used to be, okay, someone over 70, Gleason seven, okay, active surveillance. But now, I think we're increasingly seeing that in men as young as, for example, 50, to go on surveillance and follow them very carefully.

William Oh:

So yeah, I think surveillance is where these biomarkers are playing a particularly out sized role, as well as if you do intervene, how much intervention should you use hormones, for example, with radiation or not? That's time, Jim. Really appreciate your time. And Dr. Maxwell, I thought it was a very interesting discussion. There's more to come. I'm going to give you one last sentence about what the future of biomarkers holds.

Jim Hu:

Wow, that's a tough one. I mean, look, there's going to be more and more biomarkers. I think they're going to be better and better validated. For example, earlier, Kara said very nicely that, it's been largely tested, these biomarkers, in the White American population. And so, I'll just put in a plug for the fact that the National Cancer Institute is linking the Decipher and the Oncotype and other scores to the SEER Registry. The SEER Registry is largest population based tumor registry. So we're going to learn a lot more about how biomarkers perform in non-White individuals as well.

William Oh:

Thank you, Jim. Thank you all for joining us tonight. I thought it was a great webinar. And please, follow up with pcf.org for further information. Goodnight.

Jim Hu:

Always a pleasure. Thank you.