Dr. 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, 2,200 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.

So it's really my pleasure to introduce our two speakers. I'm going to introduce them both now, and we're going to start with Dr. Maxwell. She's an assistant professor of genetics and medicine at the University of Pennsylvania. Also a staff physician at the Corporal Michael Crescenz VA Medical Center. Dr. Maxwell is an expert in the area of inherited cancer syndromes and she focuses on both breast and prostate cancer. And we'll talk a little bit about how those two diseases are really linked, more than we ever realized. And she's also very passionate about increasing access to genetic testing for veterans with a study that's going to be published this week. And we're really proud that she's PCF Young Investigator and has also received a challenge award.

Our other speaker after Dr. Maxwell will be Dr. Jim Hu. 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.

So I'm going to go ahead and ask Dr. Maxwell to talk a little bit about the first part of our discussion, which is really germline or hereditary cancer testing, and to give us a little bit of an overview. Dr. Maxwell.

Dr. Kara Maxwell:

Thank you Dr. Oh. It's a real pleasure to be here. I always very much enjoy any educational session the Prostate Cancer Foundation does because it really does bring home how important the partnership between those of us doing science doctors and our patients are. So as Dr. Oh mentioned, we're going to talk about genetic and genomic testing with regards to biomarkers. And so it's important to sort of start out with just a foundation and nowadays, DNA and genetics, our kids learn about it in school, it becomes old hat. But just as a reminder, what I'm going to be talking about are tests that are reliant on testing the DNA in your cells. And so we're all made up of many cells. Those cells have chromosomes in them. DNA is the letters of the book that we use to write all of our stories.

And so within that DNA, DNA can be changed. That's what makes all of us individual. That makes our different hair color, our different eye color. But those changes can also contribute to disease. And so

mutations or variants are basically any change in the DNA. And this is a complicated slide, but it really just goes to show that there are a lot of different types of changes in that story that is your DNA. So you can think about deleting one letter could change a word that changes the whole story. You could delete entire pages, you could add pages, and all of those things will change the instruction manual. So when we talk about DNA-based biomarker testing, what we're talking about is looking for one of these many different types of variants.

So when we think about genetics and genomic testing, it's really important to distinguish between germline testing, which I'll focus on, and tumor testing, which will be talked about more in the second components with Dr. Hu. So germline testing is testing the inherited changes in your DNA, things that you inherited from mom and dad that in this case, when we're talking about prostate cancer, what we're concerned about are those changes that increase the risk to develop prostate or other cancers. This type of testing is typically done from a blood sample, but can also be done from a saliva-based sample or even skin cells that we grow in the lab.

And that's to be distinguished from tumor testing, when the surgeon or a somebody else does a biopsy and gets a piece of tissue. That DNA can also be tested, but those changes are things that developed in your cancer as it grew. But because the cancer it came from, you, came from the person, the germline changes are also seen in that cancer.

So just to make it a little bit complicated, many patients who've had cancer or another diagnosis have also undergone what's called liquid biopsy testing. And I draw this arrow here from the blood because even though it's a blood sample, what those specific tests are designed to do are to look for the tumor DNA that gets shed out of the tumor and into the blood. And so just because you get a blood test, it may not have been for germline, it could have been for the tumor as well. And there are a lot of companies that do this testing, and that can be what's very complicated and confusing for both patients and doctors alike actually.

So some of the companies that do germline testing are listed here on the left. The more commonly seen companies that do tumor testing are listed over here on the right, but there are many other academic labs depending on where you're seen that may also do tumor testing. And what's important to note is that these tests are different from some of the other biomarker based tests that you may see. So for example, things like Decipher or OncotypeDx or Prolaris, those are different types of tests using different materials than DNA. But what we're going to focus on now for the rest of my slides are about germline testing.

So the real question right now in prostate cancer and many other cancers is which patients should undergo germline testing. So if you're in this space right now or you're a loved one that is supporting somebody with prostate cancer, the question is, should I get my germline tested? Could I have something that I could maybe pass on to my kids or could be in my family? And we think about who we should do genetic testing. We could test people who have very advanced disease down here on the bottom, metastatic prostate cancer patients. We could test patients maybe that have high risk of prostate cancer. We could test low intermediate risk prostate cancer, or we could go into the population and think about testing people before they were diagnosed with cancer.

And when we think about who should be tested, we should think about why we're doing the testing. So if we're testing the population or people with a family history, if you're sitting on that end of things, the reason why you would do germline testing is it may impact whether or not you do prostate screening. And more and more we're seeing it may impact at what level we should consider doing biopsies. But it doesn't really affect at that point, prostate screening clearly isn't going to be impacted if you do germline testing if you already have prostate cancer. But because so many people with prostate cancer

do well, germline testing for all populations, either people with or without prostate cancer, may benefit by others cancer screening that may be indicated by the germline mutation that you could have.

In the treatment setting, what's been really, really amazing is that now germline genetic testing can impact the types of treatments we can give men who have metastatic prostate cancer. And we and others are trying to move that into the high risk setting where some of these targeted therapies that are based on germline mutations may also be implicated in men who have high risk prostate cancer. And then of course, germline genetic testing always impacts the family. So pretty much every prostate cancer risk gene has risks of other cancers associated with it, risks in both women and men. And so any change that is found in the patient with prostate cancer will impact their family.

So how likely are you to have a genetic change in a gene that we currently know about? Well, it basically is inversely related to the way I presented this slide, where metastatic prostate cancer patients, 10% to 15% of them may have a mutation in a gene that is inherited. In the population though, these changes in these genes are not infrequent. 1 in 50 individuals are walking around with a mutation that affects cancer risk. And then the other categories in between. There's still some debate on this, but probably 3% to 5% of localized prostate cancer patients have a mutation in one of these genes that we consider to be important for germline testing.

So then the question is, that's who we should test. And hopefully that gives you an idea for yourself if germline testing is important. So then the question is how do we choose the genes? What genes should we test for with regards to prostate cancer? And so when we think about that, we want to ask ourselves a few questions because there's a lot of genes out there. But just because we can test for it doesn't mean that it might be important. So one thing we think about is what is the risk of prostate cancer if I have a mutation in the gene? And we really want to be testing for things that have a higher moderate risk. If it just causes a low risk, not really sure at this point what to do with that information. We also might want to choose genes that by finding that mutation it would affect my family. And I just said that most of these do.

Another question we might want to ask for which genes we should test is do you having a mutation in that gene lead to more aggressive prostate cancer? Would I want to change treatment based on thinking about having a more aggressive disease? Or if unfortunately I were to develop widespread prostate cancer, could we target that genetic change for treatment? And so if the gene falls into hopefully all but some of these categories, that's what makes it the type of gene that we want to test for in patients with prostate cancer or at risk.

And I would say that right now there are basically nine genes that fit this category, the BRCA2 and BRCA1, the breast and ovarian genes. They also are linked to prostate and other cancers. So it's important to think about them. ATM and PALB2 are two genes that are pretty much definitively linked to prostate cancer. A little bit less information there, but they're important to test because of all the other implications they have. Lynch is a syndrome, can be due to mutations in one of four different genes. And then TP53 is very rare, but has very significant amplifications.

There are a few other genes that we talk about, HOXB13, NBN, and CHEK2. And if you've undergone germline testing, likely you would've had testing for these genes as well. The utility is still a little bit less clear, but that'll change as we get more data over time. But unfortunately, these genetic changes only are responsible for a pretty small proportion of prostate cancer that we see inherited in families. And so one of the things that I always tell my patients is it's more likely that we won't find a change than we do, but that doesn't mean that there might not be some risk. And so it's important to know that genetic testing will continue to change as the science advances.

So this is just a scheme of what we do when we find a germline genetic change and as really four buckets that we can think about. This is the BRCA1 and 2 example. There are a number of different screenings that we do for a variety of cancers. So you can see female siblings or say, daughters of a patient with prostate cancer. There would be implications for screening if a mutation were found. There's prevention that we can think about, both surgical and otherwise. Treatment is affected, as we talked about. And then family planning is also becoming a big piece that we talk about in cancer genetics. With patients considering if they were to have a BRCA mutation, for example, not passing that onto their offspring. So I thank you for your attention. I know that the biomarker space is getting more and more complicated, and I'd be happy to take any of your questions.

Dr. William Oh:

Thank you. That was a great overview. So I want to dig in a little bit to some of the questions we're getting and that we've gotten in advance of this webinar.

Dr. Kara Maxwell:

Of course.

Dr. William Oh:

So just you put a list of different genes. How does a patient get those genes?

Dr. Kara Maxwell:

Yeah.

Dr. William Oh:

Whether they give a blood sample or a saliva sample, do they go to their doctor? Do they send it to 23andMe? How do they get those genes tested?

Dr. Kara Maxwell:

Well, that's just such an important question, William, because one of the things that's difficult in the current spaces, there is a lot of marketing of genetic testing. We turn on the TV, we give our parents 23andMe for Christmas, et cetera. But it's really important that people talk to their doctor. So many of the companies that do direct to consumer advertising, they might not be testing for all those genes. 23andMe is a great company for what it does, but it's not testing for all of the mutations in BRCA1 and 2, for example. And so it's important to know that you didn't necessarily have genetic testing when you had that. And that your doctor, they know what they should be testing for, and that's really the person you should be talking to. And most programs now have good relationships with either a genetic testing company or a genetic counselor and services to help because it might not just be the prostate cancer. There may be other cancers in the family that we want to consider testing for at the same time.

Dr. William Oh:

So let's say a man on this webinar was diagnosed with prostate cancer. He's 50 years old and he has a cancer that's curable, treatable and curable. His mother had breast cancer when she was in her fifties, let's say, and he knows an aunt had ovarian cancer. How would you counsel somebody like that?

Dr. Kara Maxwell:

Absolutely. I think that it's really important to see whether or not there might be a BRCA mutation or another gene mutation in that family, especially with curable prostate cancer. There could be other screening that we begin. So for example, if they did have a BRCA mutation, we would do consider pancreatic cancer screening, male breast cancer screening, skin cancer screening. And so I would counsel that man that I think that considering that it's important. Not all patients know all their family history, and so that's another piece that we talk about as well. So absolutely, I think especially if there's breast ovarian in the family, we're considering it. I think the real challenge right now is for people who don't know their family history and what do we do there? I think that's really the next thing we're trying to figure out.

Dr. William Oh:

Some people have gotten these test results and they see this term VUS.

Dr. Kara Maxwell:

Yes.

Dr. William Oh:

Variants of undetermined or uncertain significance. Can you describe what that means and how a patient should understand that?

Dr. Kara Maxwell:

Yeah. That is such a challenge with genetic testing, and we are still so, so far, have so much to learn about the variants in our body. And all of us have thousands of changes as we talked about, and most of them don't really do anything. Even in a gene that's important, and when that's the hardest thing you see, I have a BRCA2 VUS, it must be related to what's going on. But there are just a wide variety of changes that don't make actually any impact on how that gene functions. And we just don't have the tools yet to have enough information to understand them.

And particularly given the fact that most of the research has been done in patients of European descent, we really don't have the tools in any non-European populations to understand a lot of these variants. But that doesn't mean they're bad. There have been studies in BRCA1 and 2 that suggest that 95% of the variants of uncertain significance are probably completely benign. But that's why it's again important to do this through a program that has genetic expertise because that genetic counselor and physicians that are trained like myself can help go through and say, "This variant I think we might be a little bit concerned about versus this one we really don't have to worry about." But I think it can be a very stressful component of doing genetic testing.

Dr. William Oh:

So if they see something like that, if we're trying to get a category, a dictionary for the future, but they shouldn't worry at this point and they might want to see a genetic counselor or a specialty clinic like yours.

Dr. Kara Maxwell:

I think so, yeah.

Dr. William Oh:

Yeah. What about insurance? Does insurance cover these tests?

Dr. Kara Maxwell:

That's a really good-

Dr. William Oh:

What's the out of pocket cost? Yeah.

Dr. Kara Maxwell:

This has changed so much, so quickly with Medicare getting on board for testing in many indications because of the significant treatment implications. Most insurances do cover genetic testing, particularly in advanced prostate cancer. We know that it impacts treatment. And so the vast majority of insurance companies cover. That said, with the advances of genetic testing, really the most that we will see people having to pay out of pocket, depending of course on their own individual insurances, but even if they just wanted to pay without going through insurance is about $250. That's still a lot of money for a lot of people, but it's certainly coming down and I think that the cost will continue to come down, but that's also why it's important to consider testing with a physician who's familiar so that they can make sure that the testing is covered in the right way by the way that they do the test order.

Dr. William Oh:

What about confidentiality? I know a few years back people were very worried they couldn't get health insurance and might be fired from their job. What are the rules around confidentiality about these results?

Dr. Kara Maxwell:

Right. Absolutely so important. So there's a Genetic Non-discriminatory Act in the United States that prevents you from being discriminated for health insurance and for jobs based on your genetic results. So that's a really good protection. The unfortunate place that we're still in though is that something like life insurance does not need to abide by this Genetic Non-discriminatory Act, which we also call GINA. And so we do actually have discussions with our patients on this that they're, say they'd find out that they have a genetic mutation because of their prostate cancer. They're thinking about advising their children on when to get tested. We do tell them that unfortunately a life insurance policy, for example, those companies can get that information and they could change rates. So it is something that we definitely talk about.

Dr. William Oh:

I know it's complicated by each person's situation, but let's say one of the patients with prostate cancer is found to have a BRCA mutation, a BRCA2 mutation. How should he approach his family? Let's say he has two daughters and one son. They're in their 30s. And-

Dr. Kara Maxwell:

Yeah.

Dr. William Oh:

Well, I realize again, every family's different, but when you talk to a patient like that and you tell him, you're giving him advice, how can you frame it in a way that helps him to know what to tell his children?

Dr. Kara Maxwell:

Yeah. I find this so many people, and I don't mean to generalize or stereotype, but especially for so many men, they can be take this very hard, and they feel that this is going to be such a difficult conversation. Their daughter now might have this really significant thing that could happen to her. And one of my favorite lines to tell people is that you don't get to take credit for how beautiful your child is. You also don't get to take credit for the bad things that happen either. So this is just chance. And at least we know about the mutation in your family, and that gives so much power for your children to be able to make choices that can protect them.

And again, though, we often say, "It's not your job to counsel. That's our job. Your job is just to present the information." And then that's that person's decision. For women, we do recommend that women get tested if there's a mutation in the family, say it's a BRCA mutation. We do recommend they get tested by age 25 because that's when we would start screening for breast cancer. For men, we would start screening for prostate cancer at say, around 35 to 40. Well, 40 for prostate, male breast at 35. But many, many, many young men are now increasingly using this for family planning. And so we see younger and younger men getting tested as well.

Dr. William Oh:

Yeah. There's one question in the chat about two men, two sons of a person who tested positive for BRCA, 36 and 33. So you directly answered his question. And I think genetic counseling is going to be really important for that person.

Dr. Kara Maxwell:

Yes.

Dr. William Oh:

Can you talk about a little bit about your work in the VA and how you're trying to get the word out to veterans? Both in Philadelphia but also around the country, around genetic testing?

Dr. Kara Maxwell:

Yeah. Our veteran population has even other specific challenges around genetic testing because there's a lot of fear regarding service connection and could the genetic testing change that? And luckily, we have not seen that happen. And so we really are getting that word out to veterans that it's really important that these genetic changes are also considered just like anybody else. Your cancer may have been connected to your service, but you also might have a genetic change, and those two might even have interacted together. So what we're trying to do through the National Precision Oncology Program is to really just make it easy for people to get tested. So you can go into the VA, no more referring outside to another provider, and then they're trying to find somebody. We really try to make it as easy as possible to either do genetic counseling or testing on the phone in telegenetics, or of course there's different sites doing it.

In Philadelphia, we do see patients onsite. And one of the things that we believe to be very important is that we want to, again, make it easy. And so if you're coming in for your treatment, just add that genetic testing on when you're coming in for your treatment instead of trying to make it go through a bunch of

hoops to get there. And we're really finding that when men and women, but when men with prostate cancer hear about that testing from their oncologist who they trust or their urologist who they trust, they understand that that's an important thing to do. And so the Prostate Cancer Foundation has been absolutely incredible at improving access to veterans for this type of testing.

Dr. William Oh:

So you talked about the likelihood of finding an abnormal gene.

Dr. Kara Maxwell:

Yeah.

Dr. William Oh:

And we talked about these VUSs, these uncertain genes. So there's one question. My father, my maternal uncle, and first cousin have all had prostate cancer in addition to the person writing the question. But my genetic testing at Penn did not find any mutations.

Dr. Kara Maxwell:

Yep.

Dr. William Oh:

Is this common with a familial cancer pattern?

Dr. Kara Maxwell:

Oh, it is still so common. So in any familial pattern of cancer, prostate, breast, ovarian, about 75% of people tested don't have a change, don't have a genetic change that we find. And it could be a combination of other factors. We don't test the vast majority of our genomes still. DNA is made up of millions and millions of bases, and we're testing maybe 0.1% of them because we just don't still understand. And so I think that that's important for patients to understand is that there might still be genetic risk. The other men in this individual's family should get tested, should undergo screening because there are clearly some sort of genetic risk going on, but we just don't know what it is right now. And that can be very disconcerting for patients. However, that's still the more common situation that we actually don't find something.

Dr. William Oh:

We're going to talk about in the somatic section. But I think there's still confusion about whether, for example, a toxic exposures, Agent Orange could damage your DNA. Can you just clarify again the difference between a germline?

Dr. Kara Maxwell:

Of course.

Dr. William Oh:

Can the DNA you inherit from your mother or father be damaged in such a way to cause cancer? And what are we testing for when we test germline versus somatic?

Dr. Kara Maxwell:

Well, it is. It's so confusing because aren't testing all the DNA in your body. We're only testing one set of cells. And even those cells, your blood cells, those can change over time due to your exposures as well. So what we look at is when we see all the DNA in your body, okay, is that change found in say, half of those pieces of DNA? And because we know we inherit half of the DNA from mom, half from dad, so that gives us an indication that something has been inherited. If the same change is found in you and your sibling and your parent and your child, then that's something that can be passed on. Any cell we test in the body, be it blood, be it your cancer, be it your skin could have genetic changes that were a result of some sort of toxic exposure or smoking or just living. As we age, we accumulate changes. So it's very complex. I hope, I don't know if that helps out at all.

Dr. William Oh:

Thank you. It is very complex. And just on the last note, Kara, thank you for all this great insight. What do you think the future holds for genetic testing for prostate cancer patients and for families in general?

Dr. Kara Maxwell:

Yeah. I think that we're going to rapidly go to a time where we're doing whole genome, every single base pair in the DNA is going to be tested. And we're going to have to reckon with that and what that means. Not just for cancer risk, but in general, and figure out how to use that information in the safest way possible. I still think it's a little far away that that will happen, but I think it's going to be pretty rapid that it does. And one of the immediately new things that I think is going to happen in genetic testing is looking not just at these rare, really high risk variants, but the broader types of more common variants that work together to affect risk. And that's something called a polygenic risk, for example. That's going to be clinically here probably in the next couple of years. So as an end statement, I always say to people, you don't just do genetic testing once. You think about it if there's a lot of risk in your family and it's going to be something that might change over time. For sure will change over time.

Dr. William Oh:

Well, thank you. On that note, Kara, thank you very much for spending the time and describing all this. Have a wonderful night.

Dr. Kara Maxwell:

Of course. Thank you for having me.