PCF Webinar 6/30/25: Genetic & Biomarker Testing

Becky Campbell [00:00:03] Good afternoon and welcome to this afternoon's webinar on how genetic and biomarker testing can help guide your care. My name is Becky Campbell, and I lead medical content here at PCF. And we really appreciate everyone taking the time out of your day to join us for this webinar and this really important topic. It's because of your interest and your support that we produce these webinars. So, thank you once again for joining.

Just a few housekeeping points before we get started. So, this is being recorded. So, if you have to drop off for some reason, no worries. We'll send you a link to view the webinar in a few days when it's posted on our website. You can type questions using the Q&A icon at the bottom of your screen. And we received a number of excellent questions in advance that helped us guide some of this content. So, we'll answer as many as we can towards the end of the webinar. Please make sure to consult your own healthcare provider for individualized recommendations. And if you have other questions, we have a lot of resources available on our website that I'll talk about in a few minutes.

I'd like to thank Pfizer for their support of this webinar and note that all views expressed represent those of the speakers. So, thank you, Pfizer, for your support in making this possible.

Just a quick roadmap on what we'll be talking about in the next hour. We're going to start out with some definitions. There can be a lot of confusing terms and maybe new terminology, so we're going to get that out of the way at first. Talking about why testing is important, who should consider talking about testing with their doctor, what the results mean, and then how to advocate for yourself and how to start these discussions with your providers should you be identified on this webinar as maybe someone who should consider these types of testing.

Here's a brief overview of PCF in case you're not familiar with our work. So, the organization was founded in 1993 with the aim of reducing death and suffering from prostate cancer. And we do that largely through funding research over 2,000 projects and counting. Many of the therapies used today, maybe some that folks on the webinar are listening to now maybe are taking themselves were funded with early-stage research funded by PCF. As well as other diagnostics, imaging, other types of important components to the care of prostate cancer patients.

So, in particular, the topics we're discussing today, I just wanted to spend a couple extra minutes talking about PCF's role in the funding of this research. So, in 2012, PCF funded two large scale research teams to really dive into identifying key gene changes in patients with metastatic prostate cancer. And this really hadn't been done before on such a large scale. We'll go into more details during the webinar about mutations and this type of terminology. But this research really was key into ultimately identifying new targets for treatment for patients with advanced disease. So, it's really a phenomenal example of how research is so important in ultimately leading to novel treatments for patients and making a difference in extending lives.

So, the other component of PCF is ensuring that people have access to this knowledge to help them make decisions about their care. So, you can go to our website, find a number of resources, join online support groups, make sure to register for our next webinar coming up on July 21st. We'll be talking with. Dr. Zach Klaassen about the latest updates from the

ASCO conference, which is the largest medical conference in the world or cancer conference in world. So, make sure to join that for the latest updates in prostate cancer.

I'd also like to encourage you to go to prostate cancer patient voices where you can listen to patients and caregivers tell their stories in their own words.

And so finally, our speakers tonight, we have Dr. Andrew Hahn from MD Anderson. He is an expert in prostate and kidney cancer, among others. He has an active research program in addition to his clinical focus, and he's the recipient of a PCF Young Investigator Award studying the impact of obesity on treatment response in patients with localized prostate cancer. Dr. Helfand represents our urologist perspective. He is also an active clinician and researcher at North Shore University Health System in Illinois. His research actually focuses on genetic and biomarker testing for patients with prostate cancer and has received multiple research grants and published a number of manuscripts during his career. And then I'm also pleased to welcome Mr. Justin Lorentz for the genetic counseling perspective. He's very experienced in articulating these complex concepts to patients as part of his clinical practice. And he is also an academic researcher in male breast cancer and prostate cancer genetics. So, I'd like to now welcome our host, Dr. Phil Koo, PCF Chief Medical Officer, and then take it away, Dr. Koo. Thanks again.

Dr. Phillip Koo [00:05:48] Thank you very much, Becky, appreciate that. And really, thank you for showing that one slide that talks about, that shows how the research dollars used leads to clinical impact at the bedside. And it's really nice to see that project that was funded lead to so many new drugs that are benefiting our patients. And also thank you to Pfizer for making this webinar possible.

You know, when we talked about various programs, this topic specifically was very, very exciting, just because it's confusing. Even for someone like myself who practices in the space of prostate cancer, there are a lot of questions and there's always some confusion around terminology and whatnot. And today we have a wonderful group of panelists who are going to help demystify and teach all of us about what biomarker and genetic testing means. So, thank you, the three you for being so generous with your time and expertise tonight. So, you guys could go ahead and turn on your cameras and your microphones.

Just to be clear, tonight we're going to be focusing on genetic testing. We're not going to be talking about the RNA testing or the gene expression testing like Decipher, Prolaris, things of that. We're going be focused more on, again, just the genetic testing and sort of to kick things off, we're going to turn it over to Justin who's going to level set for all of us with regards to the topic today. So, Justin, thank you.

Mr. Justin Lorentz [00:07:13] Yeah, no problem. Thank you for the introduction. I am going to see if we can share screen here. Can you confirm that you can see that okay? Brilliant, okay, good. All right, so we'll go through some definitions. Instead of kind of just putting out a sheet with a chart, talk about what terms are, I figured I'd go through some pictures and maybe do a little bit of storytelling. What we have here is just a typical image of a person. People are made up of billions and billions of cells. In our cells, we have our genetic information wound up into these things called chromosomes. When you unwind those, you get these very long pieces of DNA. And sections of DNA are called genes. And genes basically have instructions. They tell a body how to grow, how to function. Genes create proteins that do jobs. Genes come in pairs. We get one copy of our gene pair from the egg. The second copy of gene pair we get from the sperm. Sperm fertilized egg and we get two copies of our genes. When it comes to genetics, we typically expect that

people will have two copies of each gene that work just fine. Humans have about 20,000 genes that each have their own job. And the lens with which we'll be looking at that are the genes that have the job of protecting from cancer, we call these cancer protecting genes. They have more kind of complex names, but generally that's what they do. Most people's cancer-protecting genes are working just fine. Some people have mutations, alterations, gene changes, mistakes. Really, the technical term for this is a variant. And if someone has a variant in their gene, in one of their copies of their gene that's causing a problem, that's really insightful for us in the medical community. It can help us kind of get insight into how to manage somebody in terms of treatment or manage people who maybe don't have cancer. And screen them more carefully. I make the analogy of genes being like books. We have kind of two copies of a book, of each book, and a variant in a gene is synonymous with a spelling mistake in a book. When we do genetic testing, there's two main things that the person in the lab doing the genetic testing is trying to do. The first thing is to identify all of the variants that are present in the genes that they're testing. So, some genetic tests will be 20 genes, some genetic test will be 80 genes, some genetic testing will be four or five genes, maybe some are just one. Really what the scientists are doing is they're reading through the gene like a book, line by line, page by page, they're looking for spelling mistakes or mutations, and sometimes they find one. Sometimes they find multiple different variants or mutations within that one gene, that one book. When they do genetic testing, they're finding multiple variants in many different genes that they're testing for a lot of different genes. People have genetic testing done. Oftentimes you don't see that there's 80 different variants that were identified. And that's because the scientists have a second job. That's classifying those variants. And there's three kinds of main classifications of the variants that are identified. Most variants are benign or likely benign. This means that they're not problematic. These are variants that account for normal human variation. Why people have blue eyes, brown eyes. It doesn't mean that their eyes work any better or worse. They're just different and that's fine. These variants are not reported and so someone could have a negative genetic test result and have 80 benign or likely benign variants and we don't care about those. Sometimes people do genetic testing, and they have a variant of uncertain significance. This is called VUSs or VUS (Variant of Uncertain Significance). These oftentimes do not have much of a clinical implication. Sometimes these variants of uncertain significance can get reclassified as scientists learn more and they can get upgraded, but most of the time they actually get downgraded to being benign or likely benign. Oftentimes these are reported, but we don't do too much with them. We like to see that they're there. But they oftentimes don't change clinical decision-making and oftentimes, family members don't get tested for these variants of uncertain significance. It's the pathogenic variants. These are what we refer to when we say that there's a mutation or a gene change. We're focusing on the variants that are pathogenic or likely pathogenic. This means that they are disease-causing or they increase risk for a health outcome. And in the case of this conversation, the health outcome is a hereditary cancer risk. The word hereditary cancer comes up quite a bit, and I want to narrow in on this a little bit. Hereditary Cancer Risk is focusing on cancer risk that's caused by genes we inherit from the egg or the sperm. The gene that we inherit from the eggs and the sperm, we have two copies of those. Those are genes that are present in every single cell in our body, our eye cells, our skin cells, our prostate cells, breast cells. And if there's a mistake or mutation in those genes, that's present in every cell in the body. Germline variants is what we call those. And it's not a really commonly used phrase, but genetic tests will report it. And nowadays it's important to differentiate between different types of genetic tests. And so, I want to lean into this a little bit. Germline refers to germ, which if you look at like wheat germ or germ from like a corn, these are the origin cells that make the wheat, that make the corn. It's the same thing with humans. Our sex cells create the fertilized egg is the origin of what makes a person a person. So, these are genes that

are present in every cell. And if there's a mistake or a mutation, they're present in everything cell as well. If someone has a germline genetic mutation that they inherited from the egg or the sperm, means that they can pass it on to the next generation. There's a 50-50 chance that the genetic mutations passed on to the next generation. So, family members are involved when we find a genetic mutation that's germline or variant that's germline. What's really common with all cancers actually is that we will find mutations in the cancer cells themselves. We call this somatic testing or a tumor test. And this causes what's called sporadic cancer, which happens by chance, by bad luck, by environmental factors. Cancer happens when a normal cell accumulates mistakes or mutations. And if a normal cell accumulates enough mistakes or mutations in cancer-protecting genes, that cell can go rogue, start dividing uncontrollably, taking up resources. It forgets that it was a prostate cell, and instead it becomes a selfish cell that just wants to do its own thing. Mutations in cancers continue to accumulate. And if you take a cancerous tumor and you look at the cells on the left side, the mutation patterns will be different than the cells on the right side of that tumor. So, there's lots of diversity that's going on there. Testing of the tumor is done when you take a biopsy of the tumor. Testing of the germline is done accessing any cell. You could use toenail clippings; you could use eyelashes. The reason why we oftentimes do germline genetic testing with blood or saliva is just because it's really easy to access. If I take a skin biopsy it'll leave a scar. And so, it's easy for us to distribute blood and saliva samples. And so, lots of labs use that to do the testing. A genetic test result, that's germline testing, will give us insight into hereditary risk. Mutations that are identified through germline genetic testing. It's really rare for us to find a pathogenic variant. And again, germline-testing, egg and sperm looking for mutations in those genes or variants in those genes that are pathogenic. Tumor testing, tumor biopsy or a liquid biopsy. We take a blood sample, and we look at the DNA floating from cancer. To see what the mutations are that are present. And knowing what those gene mutations are can help us with management and treatment. This is a generic way of how cancers happen. Big chunk of cancers are sporadic, happen by chance, which we talked about. Another smaller chunk are due to hereditary known genes that happen in the egg or sperm that are passed on from generation to generation and present in every cell in our body. But a big chunk of prostate cancer genetic risk is actually familial. And familial talks about the genes that we don't know, all the stuff in between, where we know that there's something going on in a family, but it's not an obvious hereditary gene like BRCA1, BRCA2, ATM, CHEK2. It's something else that's not really well established. And we know that this exists by doing studies like twin studies. Now, this is my only technical kind of slide, and this is my last slide. MZ stands for Identical Twins, Monozygotic Twins. And DZ stands for non-identical twins, fraternal twins. And one way that you can really look to see how genetic a condition is, is by looking at two identical twin boys, two non- identical twin boy, following them for a long period of time and say, hey, if any of those men who are identical twins, if one twin gets cancer, what's the chance the second identical twin is going to get cancer? If that's a high chance, then there's probably something strongly genetic. Whereas the non-identical twins if one gets prostate cancer and the other one doesn't, then we start thinking, maybe their shared genetics isn't the big thing because they have some shared genes but they're not identical. And so, by understanding the cancer differences between these two groups of twins, we can get a lot of insight into how familial or the term for that is heritable a cancer is. That's why sometimes we see people who have a strong family history of prostate cancer, we do genetic testing, we find nothing. It doesn't mean there's nothing genetic. It just means that there's no gene that's hereditary like BRCA1, BRCA2 on our radar, but there could still be something genetic that's not on our radars. So, we still have to respect the family history, even if there's a negative genetic test within the family. Okay, that's it for me for definitions.

Dr. Phillip Koo [00:17:34] Great, thank you very much, Justin. So, you know, big takeaways, germline, those that you inherit from the mother and father, and then you have somatic, those that sort of occur as you go throughout life. And prostate cancer has a component that could be hereditary, and a lot of these are going to be sporadic. So, before we get into the weeds and the details, Andrew, maybe I'll start with you. Why is it so important that we test?

Dr. Andrew Hahn [00:18:04] Yeah, thanks Phil and Justin. Wonderful overview to make this an easier discussion for all of us. So why is it so important that we test? So first is that we can add more tools to our toolbox as medical oncologists treating advanced or metastatic prostate cancer when we identify certain pathogenic variants or certain mutations that can be passed on or acquired within the cancer. These are things that are mutations within a group of genes called homologous recombination repair, specifically referencing oftentimes BRCA2 and BRCA1. So, if we find those, we get to add another tool to the toolbox of our treatments. And that's really important. So, I think that's the most actionable component as a medical oncologist treating advanced disease. The other I think there's two other really important ones of why we're testing either primarily for germline on this one is we can start to understand what the risk is that this mutation could be passed on to children. I know it's a question that my patients always ask me and I think it's something that weighs heavy on a lot of patients with prostate cancer. So, we can start to answer some of that, Justin also explained why there's components we can't answer with the testing we have. And then the third one, and this is the most nuanced of them all and the one I think you'll get the most debate over, is it can start to inform prognoses. I mean there's the easy ones of prognosis of if you find a BRCA2 mutation you have certain expectations for outcomes with treatment and survival than compared to somebody who does not have those. And then there's even kind of further layers onto that as well of how we maybe choose the first group of treatments that we're going to choose and then the second group of treatments. Um, so I think overall that can influence prognosis as well.

Dr. Phillip Koo [00:19:50] Great. So, Brian, from your perspective as a urologist, how does it help? And can you also talk a little bit about clinical trials? I know we're learning a lot more about these genetic mutations and how that might influence how patients are managed.

Dr. Brian Helfand [00:20:06] Yeah, so again, just so that everyone's on the same pages, there often is, the prostate cancer journey is truly a journey. And so, at various aspects, you'll need a urologist. Those are people like myself who helped diagnose the cancer and to work you up in that initial diagnosis and then hopefully your disease doesn't progress or even you don't present necessarily with advanced disease, but that's when you see, Andrew and colleagues in the medical oncology world. And so, the utility of genetic testing is variable and has different meanings along that journey. And so certainly at the earlier part where most urologists interact and lie, is that it's really important to help initially when you should start screening, right. Because we need to understand that a lot of that risk, that heritability of prostate cancer, it is not an absolute. Often patients will come to me and say, well, this is Pandora's box, and I don't want to know. And the truth of the matter is it's going to be there. So, whether you like it or not, but certainly even if you have a mutation, it does not mean that you are going to get prostate cancer or other cancers, but rather this information is used to help screen you in better and more informed ways. And so, if you have a mutation, generally a lot of those mutations portend that you would be more likely diagnosed earlier. And some of them, not all of them may even portend that you may more be likely to have aggressive disease. So, because of that, starting screening at earlier ages is generally recommended. So, most of our guidelines will say that if you have a

mutation that we should start screening you at least about 10 years earlier than the current recommendations, or at least 10 years earlier than the earliest diagnosis of a relative. And I'll leave Justin to help me describe who may or may not be indicated to get genetic testing if you're unaffected, meaning you don't have prostate cancer. But certainly, understanding that initially to help guide your prostate cancer screening is important. Not only if you have a mutation, it is going to help guide your prostate-cancer screening initiation, but it's also going to inform us if you need screening for other cancers that you may be at risk for. So, a lot of these mutations are not prostate cancer specific. There's really only one gene, HOXB13, that really promotes prostate cancer, but most of the other mutations that we know about, BRCA1, BRCA2, et cetera, also increase your risk of other cancers. So, it's important for you to understand that you should also be screened if you have one of these mutations and get in programs that you may benefit for colon cancer screening or pancreatic cancer screening, et cetera. Of course, if you're diagnosed with prostate cancer and you have one of those mutations, it also can influence how we treat you. So again, I think Andrew got into the concept that there is some prognostic value of this. So, if we have, you know, some of these mutations, BRCA2, ATM in particular, that do seemingly promote more aggressive disease, we may need to treat you more aggressively. And things like active surveillance may not be strongly recommended just because of the natural history of a lot of these types of mutations. And then of course, along that prostate cancer journey, if you have metastatic disease, again, the prognosis in terms of responsiveness to different chemotherapies, you now certainly is there. So again, that journey and the involvement of germline testing is really a lot more important when we're talking about screening, but certainly as we move on, the importance of somatic tumor testing for DNA is also very important. And the only other thing, sorry to kind of hog up all this, is that it's also very important not only for the patient, but I think as Andrew alluded to, it's also very important for your family as well. So, there are things that we call cascade testing, which is just a fancy way to say that if you are found to have a mutation, then certainly your family members should also consider testing because it has a lot of impact on their ability to get screened for many of the cancers that you could be at risk of. Again, very related to germline, not somatic testing in that regard. I think, again, we have learned a lot about genetic testing overall, but I think there's still a lot to be had, and a lot of this is still under clinical trials. So, there are many clinical trials and an increasing number on a seemingly monthly basis now that have recognized the impact of if you have a certain mutation and its potential response prognosis to chemotherapies. So again, those settings, whether we do it, let's say before surgery, or if you have metastatic disease and you've been followed and we want to test a new drug, there are many different trials that are currently available and out there.

Dr. Phillip Koo [00:25:19] Great, thank you. So, you know, genetic testing clearly helps inform how you get managed if you have a diagnosis of prostate cancer, and then it's obviously going to help inform how family members might need to be managed and again as you alluded to not just prostate cancer but other cancers as well. I do want to clarify you know we've used the term screening. This type of screening is separate from PSA screening for prostate cancer. So, I just want to make sure you know the listeners there are aware that this is separate. That being said if you do have family risk, a higher risk, for certain cancers, your screening recommendations might be different compared to someone who did not have those types of mutations. So just wanted to clarify that. So, let's move on to the who should get tested. And before we get into the details, Justin, can you talk to us a little bit about how does insurance coverage work for genetic testing?

Mr. Justin Lorentz [00:26:20] Yeah, so it's funny, I'm from the Canadian perspective, I'm based out of Toronto. And so, to be perfectly honest, I'm probably not the best person to

be talking about the insurance component of genetic testing. But typically, if there is insurance coverage, sometimes a plan will be able to dictate that. If people don't have insurance coverage sometimes there are clinical trials that people can access for genetic testing. For example, I work with the PROMISE Registry. Where any individual with a prostate who's diagnosed with prostate cancer, they at no cost can get genetic testing, germline, and genetic counseling by being enrolled into that study. And so, when it comes to the story of genetics, I think an important thing to kind of reflect on is we're talking a lot about people who have gene mutations. But the vast majority of people who do genetic testing have a negative genetic test result, or they have a variant of uncertain significance. And one thing I think that's really important about this is that if someone does do genetic testing and we find that they don't have a gene mutation, that's also really informative. It means that we can rule out that risk for them, but for other family members. And there are still lots of great treatment options. It just means that for that small percentage that do have these gene mutations, there might be a few other clinical trials available. So, I feel like we're talking a lot about genetics, but most people who do genetic testing are going to fall into this bucket of, ah, man, we didn't find anything in me. I have no explanation for why I got cancer.

Dr. Phillip Koo [00:28:12] Great. So, Brian, let's start with you. Someone gets an abnormal PSA test, they get, let's say an MRI, they a get a biopsy, they have a diagnosis of prostate cancer. From your perspective as a urologist, who should get genetic testing?

Dr. Brian Helfand [00:28:24] Yeah, so right now, if you follow the guidelines, certainly I usually follow mostly NCCN. What they would dictate is to say that the people who are most eligible for genetic testing, and again, at this stage, and really referring to germline genetic testing, is going to be those who have a high-grade disease. So that is with a grade group three or higher. Those who have intraductal features, so those tend to be a little bit more aggressive. And then certainly those who have a family history. Family history meaning it's not just your father, it is certainly what we define as hereditary prostate cancer, so those are three or more first-degree relatives diagnosed at earlier age points if you use the strict Hopkins criteria. Those who have Ashkenazi Jewish history, again, just because of the higher prevalence of having a lot more BRCA and these DNA repair type mutations, Ashkenazi is recommended. Those who have a strong family history of other cancers that are related. So, we often call these BRCA cancers. So, if you have especially diagnosed at earlier time points but three or more family members who have either breast, ovarian, colorectal, pancreatic, endometrial, melanoma, those types of cancers that they will also qualify. So those are the current recommendations and I'm going to put an asterisk there as to say that this is still a moving target. We still have made huge strides over the past decade regarding the inclusion of more and more patients in this definition. But unfortunately, they're still not perfect, and if we use strict criteria, we'll still miss about half to 60% of men who carry mutations. So, you know, I just put an asterisk there to say that, you now, be on the lookout because I hopefully, and we're pushing for this, is that more patients will be included for genetic testing because our current definitions are good, but they're still insufficient to pick out who carries those germline mutations.

Dr. Phillip Koo [00:30:40] Great. So, Brian, you talked about the high-risk patients at diagnosis who should get germline testing. Any role for genetic testing in someone who might be low or intermediate risk who's thinking about active surveillance.

Dr. Brian Helfand [00:30:53] You know, I think I would say yes, but I know that I'm biased and that's my personal anecdotal kind of thing because I'm someone who likes to gather as much information to really help with that decision making about the appropriateness of

active surveillance. Certainly, there is data from ourselves and Hopkins. Who have really shown, and we just revisited it and redemonstrated that if you have a mutation, and it's only a handful of these types of mutations that do promote more aggressive disease, that your chance of success, meaning not upgrading on active surveillance are a lot lower. So, it is just one of those where, you know, I think certainly if you're considering active surveillance, you know we do offer genetic testing. It may not currently be covered and so it is a discussion that I have is to say that they may not meet criteria. In the U.S. that general expense could be about $249 if you are paying out of pocket and don't meet that criteria. So again, it's a risk benefit discussion that I have with the patients. But when we consider a lot of the other expenses that we have, this seems to be a one-time testing that is beneficial. And many patients are happy to consider doing it.

Dr. Phillip Koo [00:32:16] Great, so Andrew, oftentimes you see patients when the disease might get out of the prostate and spreads to other parts of the body. At that point when they come to you, let's say they haven't had germline testing, do you recommend it? And at what point do you start getting somatic testing either from the tissue itself or from the blood?

Dr. Andrew Hahn [00:32:38] Yeah, so my light might turn off here in a second. Okay, happy to take this one on. So, it's very simple for me as a medical oncologist. When someone comes in with metastatic prostate cancer in the germline space. And by metastatic, I'm referring to, we can see a cancer spot on a scan, not just a PSA rising, but we can something on a scan. In that situation, everybody is going to get germline DNA testing in my clinic. And that's pretty much, that's guideline driven, the same NCCN guidelines that Brian was referring to clearly list metastatic disease, even if it's only including lymph nodes as well. Um, everybody qualifies in that one. My workflow that works as well for us so we're not chasing things all the time is within the first two visits of seeing us, we're going to discuss germline testing and then internally we're a big institution. We have a simple workflow to get that done for people. So, within the 1st 2 visits, we talked about germline, testing, you went down to get your blood drawn and now we're waiting for the results to come back. Now moving on to somatic. This one's a bit more complicated. The simplest answer. So, if we kind of break the metastatic prostate cancer into two groups, and let's just focus on after the cancer has become resistant to hormone therapy, which we call metastatic castrate-resistant prostate cancer. So, when someone makes, when their cancer makes that transition. I recommend doing somatic DNA testing on tumor tissue, if available, in everybody. And ideally, if you can, that's contemporary tumor tissue testing. So, if there is a lymph node that's easy to get a biopsy of, your doctor might recommend that you do a biopsy or if there's something in the lungs or the liver, places that it's easier to place a needle and get tissue to do DNA testing on. If your cancer is only in your bones in this situation, it's not as easy to do a biopsy, and this is where we'll think more of doing these liquid somatic DNA test. So, the same asking the same question, but saying, can we find these cancer cells in blood. And we can dive into that more details, but just to say metastatic castrate-resistant prostate cancer, somatic testing at least once early on in that, because again, I'm looking to add a tool to my toolbox. And if I find, um, especially kind of, I really think a BRCA mutation is driving your cancer, I'm going to be recommending that we use a medicine as the first treatment for your metastatic CRPC, not waiting till after chemo or after Pluvicto or after other things. Now, if we go into metastatic hormone-sensitive prostate cancer, so this is, again, right when you're being diagnosed with metastatic prostate cancer and you're starting hormone therapy, that one is a little more complex. You'll see a lot of heterogeneity and how people go about getting somatic DNA testing. My recommendation, if you have tumor tissue that was recently obtained from a prostate biopsy, a lymph node biopsy, something like that

and it was recently done and it's already sitting there, it's very easy to do and it informs prognosis. And I think in the ASCO presentation that Dr. Koo and team are going to be going over next week, you'll start to see kind of where we're moving and where these mutations are going to start informing treatment for metastatic hormone-sensitive prostate cancer. So, if you can do it, do it there as well and then do it again at Metastatic CRPC. If it's hard to do, hold off on doing it in metastatic hormone-sensitive prostate cancer, just do germline and then wait till you develop castrate-resistant prostate cancer

Dr. Phillip Koo [00:36:16] Great, so then from the somatic testing perspective, is it safe to say that the preference is for tissue, so the actual tumor that's gotten out of the prostate, and then if you can't, such as like when it's in the bone and it's harder to get a good sample, you would lean towards, you know, blood?

Dr. Andrew Hahn [00:36:36] Yes, that's my preference.

Dr. Phillip Koo [00:36:39] All right, and can you tell us in those instances, let's say you do tissue, Sometimes the results will come back inconclusive. Sort of, how do you handle those situations?

Dr. Andrew Hahn [00:36:50] Yeah, I mean, I think it depends on, you know, what is your negative result? Is it that you had tumor tissue and that ultimately you're not finding any actionable alterations? Okay, then you just move on to whatever your other informed next treatment strategy is going to be. If it's inconclusive due to a technical failure, then I will, you know I will look at the scans, try to figure out how much cancer we're talking about in total. If you have a lot of cancer, that's where those liquid DNA tests can be really helpful, these blood-based somatic tests. These are things called, I'm just throwing one company out here, but like Guardant, would be an example of this, who does it. But it can be helpful then. Now, if you have a very small amount of cancer and your tumor tissue was not helpful, that can be tricky. You may not be able to get informative results from your DNA testing.

Dr. Phillip Koo [00:37:46] You know, this was an interesting question. So, can you do germline testing on a metastatic sample, a tissue sample?

Dr. Andrew Hahn [00:37:55] So I, well, I'll take first step, but then I want to open this to the other two too, because this can get a very kind of heated conversation even within this space. So just for everyone listening to know that there's still a lot of kind of debate and nuance to how to do both germline and somatic testing. In my experience, you need a normal control in order to do germline testing, and then you need a biopsy of the tumor tissue. So, some companies, when you go to do your somatic DNA testing, they will request both the tumor tissue, but they'll also have you go down to the lab and give some blood for normal control. In that situation, they have the capability of reporting both germline and somatic to you. It's very much on your oncologist to understand the tests, or your urologists, to understand the tests that they're ordering and what they're getting back. I will say internally with our own test, we do not get the germline results read out to us. They get filtered off from our somatic test. So, you would actually just need to order a separate test. And I think that's pretty common in most places. And I would say the safest approach would still be to do both.

Dr. Phillip Koo [00:39:08] Great. So, it seems like it's a hot topic. Justin or Brian, anything to add here?

Dr. Brian Helfand [00:39:12] No, I think the point there because I think a lot of people bring up that point is to say that if you have a, you find that there is a mutation in your tumor and then people say, well, why do you want to, what's the need to do germline? And again, the point of doing and going back to doing germline is to understand that what is your risk of passing it along, and certainly for your family members. Because again, that we're looking at the whole picture and we want to make sure that number one for the patient itself, you're going to be around. That's our plan. So, we want to make sure you're getting screened appropriately for other things you could be at risk of. And certainly, for your family members who we also take into account. We want to make sure that if they have that possibility of getting affected, we're also prepared to address that as well.

Dr. Phillip Koo [00:40:03] Great. So, Justin, let's start with you. For germline testing, you know, there's a lot of what we call maybe retail genetic testing out there. You know, there used to be 23andMe, I think Color, some other companies out there, what are your, sort of, are they the same as what you would get through your doctor or how are they different?

Mr. Justin Lorentz [00:40:21] Yeah, yeah, it's a good question. So, I mean, 23andMe is a bit of its own entity. I mean 23andMe will tell you about your ancestry, your eye color, like how thick or thin your hair follicles are. And so, it's kind of lots of peripheral information and it's more like a hobby genetic test, right? You do it out of interest. But 23andMe stepped into a bit of a clinical space. And so, Dr. Helfand kind of mentioned a little bit about the Ashkenazi Jewish variants. And so 23andMe did, at one point in time, just report the three common variants in the gene BRCA1 and BRCA2, and so 23andMe dipped their toes into a very clinical space. Now when we do genetic testing, the people who are identifying the variants and then classifying those variants, there's a standard for which we do that, and there's certain lab accreditations, and one of the big ones is called CLIA certification. And so, it typically results that come out of a CLIA-certified lab, you believe. But when 23andMe does a test, it's not actually a medical test. It doesn't become part of your medical record. And so oftentimes when 23AndMe reports something, you want to validate it through a medical lab so it does become part of your medical record and has all the appropriate demographic information connected to it and so that healthcare providers can use that information. 23AndMe went on to expand. They did more, you know, looked at different types of variants within the genes BRCA1 and BRCA2. So, you want to do a test within a CLIA certified lab that's providing a medical result. It's companies like, you know, Color, Invitae, GeneDx, Myriad Genetics. There's so many of them out there. These are kind of tools that are really a good lab that do a really good job at identifying variants. And the more important thing nowadays is how well these labs classify variants and whether or not If a variant is identified in 2022 as being a variant of uncertain significance, if it got reclassified and upgraded to being a likely pathogenic variant, that's really important information. And certain labs are better at kind of recontacting and saying that there's been a variant reclassification. And oftentimes it's the center, the oncologist who orders the test or the genetic counselor who orders the test that will be notified of these updates and may reach back out about that. And so, if you find yourself doing testing through what's called a direct-to-consumer route, like 23andMe, the other kind of downside to this is that they oftentimes aren't as comprehensive. They're not reading through the gene like a book, line by line, page by page. They are just picking and choosing certain pages to look at. And so, it's, you know, if in doubt, consult with a genetic counselor, consult with your oncologist. Your urologist says, hey, I did this, is this good? And you can get a lot of good insight into whether or not you might need retesting or whether the test that you did do is fine.

Dr. Phillip Koo [00:43:28] You know, there's some discussions about, like, the gene panels and, you know, broad panel versus limited. Brian, you, know, what advice do you

have for patients when they go and request or they're asked to get one? How do we make sure they get the right one?

Dr. Brian Helfand [00:43:43] Right, so this is really a contentious point, because if you would take your entire book, if you will, you sequence your DNA from the top to the bottom, all 23 chromosomes, that you would, everyone would have mutations, right, in something, and you can report all of that out and you can really kind of scare people. Not that it's bad information, it's just we don't know what to do with a lot of that information. So, when we do a what we call multi-gene panel, we order a genetic test that incorporates looking at certain genes. So which chapter are we actually looking at? We want to make sure that that is a relevant genes, things that would actually impact prostate cancer because even though we can do really large panels and a lot of people choose to do this, we have to also be able to filter that information and say, well, this is impactful because if you have this mutation, that it has some type of increased risk or susceptibility to prostate cancer or some type of prognostic information in terms of response to a drug. But if I test for a drug related to melanoma, as an example, skin cancer, and I say, well, you have that mutation. Well, that's really good if we're going to go screen you for skin cancer but may not be relevant for prostate cancer. So, I think when you choose to partner with a company and you have that conversation with your physician, just make sure that you're doing one that's relevant to the question that you are trying to answer. Because again, it can become overwhelming with the amount of information if you do your entire genome, you will get a lot of information back, but very limited amounts of that is actually related to prostate cancer.

Dr. Phillip Koo [00:45:39] Alright, so it sounds like it's a discussion that needs to be had. You don't want to have it too limited, yet you don't want to have it to it to be too broad, so there's kind of like a sweet spot to make sure you get everything in that test that's needed to make the right decisions. So, no, go ahead.

Dr. Brian Helfand [00:45:56] I was going to say most of the companies that, you know, I think Justin alluded to really have set panels really in this space that will really kind of help answer those questions. Even then, it's still important to have that discussion with your physician and include genetic counselors, et cetera, especially if you have a positive result to really kind make sure and focus in on what is actionable and how that should be acted upon.

Dr. Phillip Koo [00:46:25] Great. So, Andrew, you mentioned this a couple times, you know, one of the benefits is it helps give you more tools in the toolbox. So, you go through this, you get your germline testing done, and then you get your somatic testing done if it's spread outside of the prostate. Tell us a little bit about the tools. Yeah, we'll start there.

Dr. Andrew Hahn [00:46:46] Yeah, so two main classes of tools, the first one are a group of drugs called PARP inhibitors. These are oral pills that you can take that depend upon in most patients having a specific vulnerability in the way DNA is repaired. And when that vulnerability exists, the medicine can be remarkably effective. And so, it's been a total game changer for patients with BRCA2 mutations. I mean, that's the biggest one. You almost get like, to some degree you get excited as a medical oncologist. When you see that come across because you're like, man, I have a really exciting option to offer my patients. So BRCA2 mutations, BRCA1, PALB2. If you look at some of the approvals for these drugs, they'll be broader in the genes that are listed, but those are the three main ones right off the top of my head. And then PARP inhibitors, Phil's going to, I think, go over this next week, but they are moving forward. You know, we're currently using these for

metastatic castrate-resistant or hormone-resistant prostate cancer. They're moving forward, it's happening, they're going to be coming forward. The second group of drugs and, oh, sorry, one more thing. The number of patients in theory who should qualify or be eligible for a PARP inhibitor is somewhere between 20 to 30% of patients. So that's kind of the odds of your oncologist finding something, you know, not looking at your family history and such. Now, the other one is less common. So, the other is you're looking for kind of two things. It's either called microsatellite instability or tumor mutation burden high cancers. This is like two to 3% of men with advanced prostate cancer. And in this situation, we can use two specific immunotherapies, but just one class of drugs for those patients. And these are the immunotherapies that you see advertised on TV heavily, like Keytruda or Pembrolizumab, used for many other cancers, like kidney cancer or melanoma, but much less common that we find these mutations, two to 3% in total.

Dr. Phillip Koo [00:48:48] Great. So, you know, Brian, from your perspective as a urologist, urologic oncologist, do you change your approach? Do you maybe increase the type of treatment or do you counsel patients maybe to do surgery as opposed to radiation based on some of the findings you get from germline testing?

Dr. Brian Helfand [00:49:06] Yeah, I mean, so certainly we know prognostically that certain mutations, as I alluded to, just predispose to more aggressive cancer, right? So, these are really still a limited panel, but these are going to be BRCA2, these are going to be ATM. These are potentially going to be CHEK2, PALB2, MSH1. There is a newer mutation really described within the past several months known as MSSL22 [MMS22L] that seemingly is following the same path and influences the same path as BRCA2. So, another gene to just kind of be aware of that may also influence our decision is appropriateness for active surveillance. When we talk about responsiveness to treatment, whether we're talking about surgery or radiation, I still think that's somewhat of a moving target. Although certainly there is some bias, I suppose, but I think that certainly removing the prostate in those situations is potentially safer because we're not introducing a toxicity. And as I have one of the experts sitting right in front of me who probably has stronger opinions here. Is to say that either responsiveness to radiation may not be as robust as if you didn't have that mutation. And certainly, there is some limited but emerging evidence to say that certain mutations may have somewhat resistance or predisposed to resistance. So based on that, I think we have those kinds of discussions there in that regard. But I think that some of that data will be still forthcoming.

Dr. Phillip Koo [00:50:58] Great. So, we're going to shift gears a little, and hopefully everyone listening sort of walks away with knowing that genetic testing, whether it be germline and somatic, is very, very important in your prostate cancer journey. What we noticed though in the real world is a lot of patients are not getting these tests performed. And one of the current concerns that we hear about is sort of privacy or you might get this test and then themselves or their kids might not be able to get insurance later on because they might be identified as higher risk. So, Justin, I'm sure you hear these concerns very often. What can you tell our listeners today to reassure them that this is not the case?

Mr. Justin Lorentz [00:51:38] Yeah, so in the U.S. there's legislation called the Genetic Non-Discrimination Act, or the Genetic Information Non-discrimination act called GINA. And what this does is it protects from health insurance discrimination based off of genetic findings. And there's website called the NSGC, the National Society for Genetic Counselors that really goes into detail explaining what the GINA act does, how it protects. And if people have concerns about this, which I think is very valid to have that question and to get some more insight. Genetic counselors can provide a lot of insight into your

circumstance, but also an insurance broker, knowing that these people are available to consult with to kind of give you that detailed information if this is a strong concern for you.

Dr. Phillip Koo [00:52:40] Great. Brian, Andrew, your thoughts? You see a lot of these patients come in, I'm sure not everyone goes and gets the testing done. What advice do you give patients in your office?

Dr. Brian Helfand [00:52:51] You know, I think, again, we review GINA and just they're protected medically. I think that the biggest concern is really life insurance. And ironically, most of the life insurance companies really don't ask directly about a mutation. Most of the questions are still directed at family history. So again, I always bring that up to patients to say that if you're filling out a life insurance plan, you know, you should be aware that that's what they're also monitoring as well. And again, that does not apply to medical insurance. That does not apply to medical insurance that is life insurance companies in general. So, certainly, I will let you all interpret that for whatever that is worth. But it is one of those where know that distinction between medical insurance and life insurance that they cannot hold this against you medically.

Dr. Phillip Koo [00:53:49] Great, Andrew?

Dr. Andrew Hahn [00:53:50] I would just add in that I agree with both of them. I would just add in that disability insurance, but if you're younger, probably also falls within that same space of life insurance and is different than medical insurance. So, things just to think about, I know that as you guys are thinking through this as patients, you're thinking about your children and you're kind of trying to have all these thoughts going through your head in the clinic. The one other follow-up is. I made it sound like all these things are really easy to do in an advanced prostate cancer clinic and everything is perfect, and we do it so quickly. I mean it is easy to do but we get really busy as well. Like we're all very busy in clinic and sometimes it's simply that we do it all the time and we forgot our systems are not perfect. So please, please remind your oncologists and give them nudges. If you've had your testing done you know sometimes things it gets lost in the medical record, give nudges Give reminders. It's really helpful. It does not hurt our feelings. We just need that reminder occasionally.

Dr. Phillip Koo [00:54:48] I love that vulnerability and an informed patient is an empowered patient and an empowered patient I think you know will get better results. I appreciate you highlighting that important piece. You know we have five minutes left. It's such an important topic, complicated topic. I do want to give each of you a chance to sort of leave with some key takeaway messages for our listeners today. So, Justin, let me start with you, then I'll go to Brian and then Andrew.

Mr. Justin Lorentz [00:55:13] Yeah, I mean, the germline testing versus somatic testing. People sometimes, one misconception that I think I want to clear up is that people worry about whether a blood sample or a saliva sample are any different, it's the same thing. To address further what Brian mentioned about criteria, family history of prostate cancer is one thing that's really on people's radar. Family history of ovarian cancer, very predictive of a germline mutation. Family history of pancreatic cancer, very predictive. Metastatic prostate cancer, quite predictive. Late-onset breast cancer, not as much. Late-onset prostate cancer, not as much. And so, there are some key things. Men, male breast cancer. Big predictor. And so, there are some key factors that sometimes get highlighted, sorry, that are important in the medical community for us to kind of factor but aren't as obvious to a patient when they're just looking at the prostate cancer story. Ovarian,

pancreas, male breast, these are important. And early-onset breast cancer in women are all important factors as well when it comes to thinking about germline testing.

Dr. Phillip Koo [00:56:22] Great, Brian?

Dr. Brian Helfand [00:56:24] So I think genetic testing is really the epitome of personalized medicine testing. And what I mean by that is that it's really our job to really kind of guide patients of the screening and our treatments that they need throughout their life. And I think that we've made just such large advances in genetic testing that it really allows us to help and we still have a long way to go, but it's certainly the first step is to say, hey, we have information that can empower you. It can empower you to get screened with PSA and other tests at the right time. It can inform us of how would you best respond to a certain treatment? Which should you get? Should you watch this? Should you get surgery? Should you consider radiation? How are you going to respond to hormone therapy? Certainly, if you develop advanced cancer, what is the best therapy that we can offer you? What is the timing of that? That is the information that we're really starting to get at with this genetic testing. So, if we don't include this, again it's usually an oversight, but it is one of those where we understand that we are really using this to help you and help guide your decisions so that along that journey you are most empowered and making that the most informed.

Dr. Phillip Koo [00:57:49] Great, thank you. Andy?

Dr. Andrew Hahn [00:57:51] Yeah, if you have metastatic prostate cancer, get germline DNA testing very early in your journey. That one's simple. Again, if have metastatic prostate cancer, you should absolutely have somatic tumor testing done at the time of developing resistance to hormone therapy and likely multiple times thereafter. And it's also even helpful when you're first diagnosed with metastatic prostate cancer. There's value to both of these tools and very supportive of everything Brian and Justin both said as well.

Dr. Phillip Koo [00:58:24] Great, so, I think what we're hearing also is, have this conversation with your doctors about genetic testing and have it early. Don't be scared to bring this up. I think it's a really, really important topic and we are only scratching the surface and, as you alluded to, each meeting that comes up, we're learning more and more about how this is driving better care for patients. So please, please have those conversations. There have been several questions asking about, you know, the RNA expression tests. Again, those biomarker tests, RNA expression, gene expression-type tools, they'll be discussed on a different webinar, but appreciate the many listeners asking questions about that today. So, I want to thank you guys very, very much. It was a wonderful discussion. Hopefully the listeners walk away with a better understanding, and at least, you know, the courage to speak with your providers about this important tool for patients with prostate cancers. So, thank you all, and good evening.