Becky Campbell: So, Dr. Heath serves as Associate Director of Translational Sciences and leads the GU Oncology Multidisciplinary Team at Barbara Ann Karmanos Cancer Institute in Detroit.

She has had a distinguished career as a prostate cancer researcher, serving as the Hartman Endowed Chair for Prostate Cancer Research. She's involved in prostate cancer committees of the American Society of Clinical Oncology, and is the Principal Investigator for a Department of Defense Grant in the nationally-recognized Prostate Cancer Clinical Trials Consortium.

So, welcome, Dr. Heath. I understand you have a few slides, and then we should have time for a bit of discussion.

Dr. Elisabeth Heath: Thank you so much. And, Alicia, that was a fantastic session. I'm often flabbergasted at how much we can talk about now these days when, if you really think about the timing, it hasn't been that long, and I think the topic I'm about to delve into is even shorter. And part of the value of these types of webinars and, sort of education sessions, is that we can share this knowledge that maybe began in earnest about ten years ago. As you've shown, Alicia, in some of your slides, part of that seminal work to understand genetics and everything else has been pretty recent. And so part of our struggle is to get the word out. And I think, events like this today is to share, globally, our understanding and that understanding continues to evolve. So whenever you're ready with the slides, I am ready. So next slide.

So the question always comes up with why do we even need to know about testing? Obviously one of them, Alicia mentioned, which is well, if you don't test, you won't know if you're a particular candidate for a particular study.

But then you say words like "this might impact the family," and this is the disease that we may have to think about what that risk is for others, and then sort of lots of words get garbled together. And then you say, "well, wait a minute. You know, this cancer business has always been something I've had to worry about, but now you're saying that I may have to consider other family members, and what does that mean?"

So significance of testing, especially in the advanced setting, is pretty broad. We use the words "molecular testing," "genetics," "genomics" pretty loosely. Probably because there's not that set terminology that's maybe globally accepted. I think we kind of all know what it means, because the top three things we tend to talk about, at least in our patient visits with you, is saying, "well, we're going to do some sort of testing. Now, we talked about those imaging tests, conventional tests, blood tests. We're okay with the testing issue, but what does it mean when you're doing these kinds of molecular or genetic or genomic testing?"

Well, the first one is to really understand is what you're talking about impacting something beyond yourself. "Is there a family risk? Are my children at risk?" And usually when I bring up topics like that, children and grandchildren, people's ears perk up and say, "well, wait a second, why is this now their problem? Obviously, I know I'm part of a cancer

family, or not at all. I'm the first one to have had cancer," so these topics can really face people quite differently. Sometimes when the first time or even the second time you're talking about it in clinic or in your office visit.

The second is to maybe understand, prognostically, you know, are we headed for a more aggressive course? Whether you're in the hormone sensitive area where we've heard about earlier or a lot of the newer drugs, or just what we've heard now in the castrate-resistant space, what do we have to do to maybe be prepared?

Are there signals, perhaps, that we should think about? And then the third one is what Alicia mentioned, which is should we have some biomarkers that would then enhance our menu to include other drugs like PARP inhibitors? And that list keeps growing. So talking about clinical trials, a lot of these things are being investigated right now in real time. Different markers that are maybe not just exclusive for prostate cancer, but other cancers where you have sort of a shared pathway that doesn't act right.

Next slide. So talking about the definitions, I know that when I say germline, a lot of my own patients would say "I have no idea what that means." And then you hear the word somatic, and they definitely don't know what that means.

So let's just deep dive a little bit. Germline testing is a test that really looks at your DNA but doesn't change over time. So a lot of folks would say, "yeah, no problem. My doc has tested my germline status multiple times," and that's probably not exactly correct. Repeat testing doesn't really change.

Now, where I put a little caution, is just to make sure that every test is very different. There are a lot of vendors, and if I think about five years ago to now, the number of companies that are offering this is growing. So one, you have to know what company the test is going to, or perhaps it's a university laboratory, wherever it is, as the question of, "well, what is actually being tested?" And number two, depends on what box you check. Sometimes you check 80 genes, sometimes you check two, which is that BRCA1 and BRCA2. So sometimes you'll say, "well, I need to repeat test this." It might be because your doctor only checked to ask for two genes and now you want to expand. So being empowered to know what it is that is being checked is really important.

And so we are. We're looking for heritable cancers, because those things, just like we know in breast cancer, information is knowledge and that's power. So knowing that if you have a particular gene, which--where we can call "pathogenic," which is another terminology, or "likely pathogenic," those kinds of instances, you don't have to figure it out yourself. There are true experts in the field known as "genetic counselors." So once we get that test result back and it shows, "well, wait a second. This needs more investigation." Sometimes your oncologist isn't the right person to really talk about this, especially when you have true experts in the field. Sometimes you get your report back and you see words like "variant of unknown significance or VUS," and you say, "well, wow, look at this. I have a BRCA2, but it's under a variant of unknown significance. Get me

that PARP inhibitor.” So again, additional discussions. But most of the time, at least right now in 2024, we don't utilize those kinds of testing outcomes to say, “okay, these drugs are now part of your treatment algorithm.”

The other question that comes up a lot is “how do we test?” So we know in germline or inherited testing, most of the time it's a blood test, but it's a special blood test. So there are usually kits that your doctor has to have in his or her or their office so that it can be properly drawn and then sent to the proper place.

You can also get it from buccal cells. So you'll sometimes see kits sent that you can scrape the inside of your mouth and that can then go on to be tested.

The other part is called “somatic.” So somatic has changes in the DNA that has both germline and some additional acquired mutations. So these ones are not inherited. So most of the time what you find, and I think Alicia showed a great slide with this, a lot of the cancers that we deal with are somatic in nature. As in, a person ages or is exposed or certain things. However that cancer pops up, it's not something that got passed down generation to generation.

In this instance, you can potentially have repeat testing. Because as the cancer mutates and it progresses, it can also change. And sometimes that change, it picks up more of the nasty friends that may be targetable. And so, sometimes it's worth repeating. In addition, not all somatic testing also report germline. So again, knowing what these reports are telling you is really important. So there's a sense of, if you have a BRCA2 mutation somatic there's probably a good likelihood you should at least check for germline. And then the other rules apply. Here, the testing can be done on tissue. Sometimes it's your biopsy materials. Sometimes it's your prostatectomy specimens. And then blood. Next slide.

So again, to just recap what Alicia has shown before, who should get tested? So metastatic, high, or very high risk. And then by family history or ancestry. Not that these are topics of conversation, but I often recommend that in family gatherings, such as Thanksgiving, is a nice time where you can ask these kinds of things. A lot of people don't know their family history. If you have a chance to find out whether you have a relative that had breast cancer early on at less than 50, or was a patient that's male with breast cancer, or pancreatic cancer at any age. That, in addition to the Ashkenazi Jewish ancestry, really is one of the indications that you should consider to do germline or inherited testing. Next slide.

And then getting deep into the weeds, if you also have a personal history of prostate cancer, but you don't fit the metastatic, high risk, or very high risk. You could be an intermediate-risk prostate patient and have that intraductal or cribriform histology and also qualify.

That certainly warrants a conversation. And also a personal history of prostate cancer and all of these other cancers listed here, you're also a candidate to be tested. Next slide.

So when you're looking at the inherited germline testing, what it really means is it uses a technology known as “Next Generation Sequencing.” And that's really looking at a large section of that DNA to find out are there any sort of squirrely genetic things that we can find and why is that important? Other than, of course, you might have a drug that could be helpful to you in your journey in treating prostate cancer, but it also can be linked to a bunch of other cancers, such as breast and colon. So depending on what you test, it really depends on what the actual results are. Next slide.

So sometimes the question is, “okay that's great, but I don't think my insurance is really going to cover this type of testing?” And that is a question I get a lot or they're really not comfortable having their insurance company know that I'm going to get genetic testing.

So here's an example of a free registry that all of our patients can try to enroll in as long as you have prostate cancer of any stage, a PSA over 100, or some imaging evidence that suggests that you have prostate cancer. And you get a survey as well as registry questions. You get your saliva tested and you can go on prostatecancerpromise.org and they're still available. At least now for this, for this next year, one hopes. Next slide.

The other big question you get is, the concern of, “well, I don't have a genetic counselor nearby. I'm in a small town in the United States. And, you know, the nearest medical center is two, three hours. How am I going to drive there to get whatever results?” There is a website called FindaGeneticCounselor.com. You can go on the NCI website. You can ask the cancer centers that are NCI designated all around the country to find out where is your nearest genetic counselor.

Sometimes the testing company that you use will also have an expert. So we want to make sure you know that you're not alone in being able to digest this information, because sometimes it's a little scary to know, “wait, is it up to me then to tell my son he's at risk?” And the answer is absolutely not. You are not alone. And there are guidelines and resources for you to be able to deal with the information. Next slide.

There's always a question about “what about 23AndMe? Isn't that just a genetic test that can tell me what's happening?” So again, 23AndMe is--I'm not picking on them--they're just a commonly used test that I know my own patients use. This is where you send in your saliva sample, and it's on this idea that human DNA is basically 99.5% identical from person to person. So this test looks at different “variants” that we call it, or small differences in the DNA sequence. So sometimes you'll know the as SNPs which stands for single nucleotide polymorphisms.

So they're tiny little changes in the genetic code at one single point in the DNA. So is this important to know what it is? Well sure, it's helpful in knowing that you have blue eyes or red hair or black hair. But depending on the test and in certain instances, this is very different than the inherited germline testing. That's really looking at a specific area that's concentrated on looking at cancer as a risk. So most of these

tests are for sort of the global community that are not really worried about cancer, but just knowing, “I just want to know where I got my green eyes from.” So be very careful that you know what it is that you're getting tested and what those results mean. Next slide.

The other ones that we talked about, somatic molecular testing, has now just blown up. Anywhere you go, the companies have now exploded in space using again this next generation sequencing. We're now, we're looking for most of these tests at your entire set of DNA. That's a lot of genes looking for a lot of mutations. And then they got fancier testing. So instead of just looking at DNA, we're now looking at RNA. And then there are a bunch of these other types of signatures that have also popped up.

So one that comes up a lot is MSI, which is really important to know if perhaps this status or this signature will allow a particular patient to get pembrolizumab, which is an immunotherapy. So sometimes these testings are also important to again expand the menu. As the world changes in drug development, it can also look at certain proteins, to look at perhaps other treatment options that would also expand your menu further. Next slide.

The concept of minimal residual disease is in a lot of other cancers. I know in bladder cancer this comes up in terms of “boy, do I get more treatment. Can I stop treatment? Can I predict?” But the question here is “do I have any cancer left?”

This happens a lot with you know, “I have oligometastatic disease, very small amount, I think we got it all. Do I have to worry that there's something else happening?”

This is still in flux. We're still all working on this, trying to find one cancer cell in 1 million healthy cells, and all of these fancy techniques. There isn't one FDA approved or FDA cleared test just yet, but I know that this field will take off. Next slide.

So this is the magical mystery ride of a lot of words, a lot of terminology. But I think it's just really important to know for those listening today, that prostate cancer patients with a family history of cancer or having advanced disease themselves should consider genetic testing. Know that there's a lot of resources available to explain the differences with germline somatic mutations and what that testing really means. But you should ask your physician when they're ordering, “what are we actually checking? How many genes? What will this tell me?”

Understanding this will really help us kind of figure out what's next for you in this journey. And then you're not alone here. So not only is your medical team there as a resource, you have genetic counselors to really help you understand how to figure out how to share this information, if you do test positive, to other family members, and figuring out what that impact is for inherited cancer. So I'll stop there and turn it back to you, Oliver.

Dr. Oliver Sartor: Thank you all, Elisabeth, this has been a really nice presentation. Now, one thing I want to give a perspective, if you will,

what percentage of patients will have a change in therapy because of germline or somatic testing? I think that's going to be important for our audience to hear.

Dr. Elisabeth Heath: Right. I think as, Alicia had just mentioned, you know, the germline is about 20%. So a lot of folks will say, “wow, my doctor was really just so not excited. You know, I'm negative again. And a lot of his or her patients are negative.” And I think a lot of that is exactly - many of the cancers are not inherited. Many of the cancers are, some are just, you know, somatic from environment. But I think to miss the, 10, 15, 20% chance is kind of a bummer because then you have that option of a PARP inhibitor, for example, that you didn't leverage.

Dr. Oliver Sartor: And just to be explicit on the somatic testing, what percentage of patients will have an actionable mutation today with FDA approved therapies? And again, I want the audience to kind of have perspective here.

Dr. Elisabeth Heath: Yeah, I think it's still quite low. And you know why --it’s a--if you say “am I looking at just BRCA? Do I look at MSI status?” You know, I think maybe 25%, I don't know in your experience if that's what you're seeing. I think that most of the time they're not actionable. So we didn't talk about that. It's more of, okay, BRCA 1 and 2, we have a medication. “What if I get a gene that I've never heard of and it says it doesn't function right?” It's pathogenic variant. And then you say, “uh oh, well, what do I do with that?” So you might have a positive result, but not one that you can do anything about right now. So I think there's a little bit of a difference with that too.