Understanding BRCA Gene Mutation

Scott Redding: Welcome to the 3Ps of Cancer Podcast, where we’ll discuss prevention, preparedness, and progress in cancer treatments and research, brought to you by the University of Michigan Rogel Cancer Center. I’m Scott Redding. We’re here with Michigan Medicine Genetic Counselor, Kara Milliron, of the Rogel Cancer Center’s Breast and Ovarian Cancer Risk Evaluation team, to discuss BRCA gene mutation and what to consider if you have a family history of breast or ovarian cancer. Welcome, Kara.

Kara Milliron: Thank you so much for having me, Scott. I really enjoy this podcast and I’m so proud and happy that you asked me to be a part of it.

Scott Redding: Can you tell us what exactly is BRCA1 or BRCA2 gene mutation?

Kara Milliron: Sure, absolutely. So we have about 20 to 30,000 genes that are the instructions for our growth and our development and we get one of each copy from our mom and one of each copy from our dad. And BRCA1 and BRCA2 are two genes that we all have and they are tumor suppressor genes, so their role in the body is to make sure that the cells grow at a very specific amount of time at a very specific rate, so they act like a brake on a car. When there is a change or a mutation in BRCA1 or BRCA2, those genes don't work properly, and that's where we see an increased risk for developing cancer.

Scott Redding: Obviously, this gene you said, part comes from mom, part comes from dad, so everyone potentially has this gene mutation in them or how is it determined on that?

Kara Milliron: Sure. Yeah, let me expand on that a little bit more, so we all have BRCA1 and BRCA2 genes. In most individuals they work just the way that they're supposed to and they work very hard to prevent cancer from developing in our body. In the general population, it's estimated that around one in 400 to one in 500 will carry a mutation in BRCA1 or BRCA2. And these individuals because they carry a mutation, that gene doesn't work properly and they have an increased risk for developing cancer. Now in certain populations, such as individuals of Ashkenazi Jewish descent or Jews from central and Eastern Europe, about one in 40 will carry a mutation in BRCA1 or BRCA2. So there is some population frequency differences, what we call carrier frequency differences, but most individuals have no mutations in either their BRCA1 or their BRCA2 genes.

Scott Redding: How do you know whether you have that mutation? Is there some sort of a test, should everyone be tested for this at some point or how is it determined?

Kara Milliron: I think that's the crux of the issue that we always talk about when we're talking about cancer. So we know that about five to 10% of breast cancer cases and probably upwards of 20% of ovarian cancer cases, are due to gene changes that are passed on in the family. So it is a small proportion, but there are some clues that we may be dealing with an inherited susceptibility in the family.
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So the first step is to know your family history. And when we say know your family history, try to go back three generations, so that goes back to your grandparents. And as a genetic counselor, some of the clues that we look for in the family history are one, a young age of diagnosis of cancer and so we define young as under the age of 50. We also look for rare types of cancer, so for example, ovarian cancer in a family, ovarian cancer is a rare cancer, one out of 70 women will develop ovarian cancer in their lifetime. Now, when I say ovarian cancer, I am lumping in also fallopian tube cancer, and primary peritoneal cancer. So more of what we call pelvis, CRS cancers, so cancers of the peritoneum, the ovary, and the fallopian tube, we sort of want those all together.

Male breast cancer is a very rare cancer and when we see that in a family history, it makes us be a little bit concerned about an inherited susceptibility. When we see pancreas cancer in a family, that again is a rare cancer, so that gives us some concern about inherited susceptibility. When we see breast and ovarian cancer in the same individual, when we see a rare type of melanoma called ocular melanoma, that makes us a little bit concerned about an inherited susceptibility. And so there are some clues that we see in the family history that make us a little bit more suspicious, that there may be a gene change that's being passed on in the family.

Certain types of breast cancer also may be associated with an inherited susceptibility to cancer. So when a woman is diagnosed with what we call triple-negative breast cancer or breast cancer that's not driven by estrogen, progesterone, or HER2/neu, so when they look at those three markers in the woman's breast cancer, they're all negative, so that's why it gets the name triple-negative. Anytime a woman is diagnosed with breast cancer under the age of 60 and that breast cancer is triple-negative, that woman should be offered genetic testing because there is a tendency towards triple-negative breast cancer in inherited susceptibility with BRCA1 and BRCA2.

Scott Redding: So, you've covered a lot of different cancers there, but lots of times when we hear BRCA1 and BRCA2 it's primarily breast and ovarian, but again, you rattled off pancreatic cancer. Are there other cancers that need to be aware of or is almost any cancer affected by this gene mutation?

Kara Milliron: I think that you hit on a very important topic, that we need to make sure that the public is aware of. So much of BRCA1 and BRCA2 we focus on breast and ovarian cancer, but these two genes have been linked to other cancers. And men in particular are somewhat forgotten with regards to these two genes because the cancer risks or the cancer burden is lower in men, but it does have significant consequences, if a man does carry a BRCA1 or BRCA2 gene mutation. And what I mean by that is that men who have a BRCA1 or BRCA2 gene mutation, they have a higher risk for developing prostate cancer and those prostate cancers may be more aggressive.
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I also look very closely in the family history to see if there’s any family history of prostate cancer, especially those aggressive prostate cancers with a Gleason score of seven or over. And in fact now, they’re recommending that any man who has a prostate cancer that’s over a Gleason score seven, that they consider genetic testing for BRCA1 and BRCA2. And of course, if any man has metastatic prostate cancer they also meet guidelines to offer BRCA1 and BRCA2 testing.

So I really think that we need to expand the focus beyond breast and ovarian cancer because if you have a family where there’s not a lot of women and the gene mutation is being passed on through the dad’s side of the family, sometimes those families can be missed because we’re focusing so much on breast and ovarian cancer that we don’t pick up the clues of the prostate cancer, or the uncle with pancreas cancer, or the uncle that had no cancer diagnosis, but their children may have had very aggressive prostate cancers. So we really need to make sure that we look at both sides of the family and that we look at three generations, so looking at grandparents, parents, aunts, and uncles, and also cousins.

Scott Redding: You mentioned metastatic cancer. If you initially get diagnosed with an advanced or metastatic cancer, is that an automatic that you should be considered for testing or does it depend on just because whatever reason that it was, maybe you ignored signs early on and you just let things go or so forth. How is it determined based off of the metastatic diagnosis to get the testing?

Kara Milliron: That’s a really good question. And so the national comprehensive cancer network guidelines, which the University of Michigan Rogel Cancer Center is part of the national comprehensive cancer network. The guidelines for offering BRCA1 and BRCA2 testing are for any individual who has a metastatic cancer that falls into BRCA1 and BRCA2 spectrum. So if a woman has metastatic breast cancer, if a man has metastatic breast cancer, it should be offered to them. If a woman has papillary serous, ovarian cancer, fallopian tube cancer, or primary peritoneal cancer, she should be offered testing. If a man has metastatic prostate cancer, if a man or a woman has pancreas cancer, it should be offered to that individual. And the reason behind that, is that BRCA1 and BRCA2 related cancers they tend to respond to a certain medication called PARP inhibitor.

And so in some instances, we use the genetic testing, not only to inform the family about potential cancer risks, but it also can drive treatment decisions. And I think that this is a really important point because so many times when individuals are diagnosed with cancer, the first thing that they say to me is, well, it’s a moot point, I already have cancer, why would I undergo genetic testing? And there’s two reasons to talk about that, actually three, now that I think about it. One is that, if they don’t have metastatic cancer, it potentially could give us information about future cancer risks and help us tailor a cancer screening plan that is better fit for them and make sure that we don’t miss anything. Also, if they have metastatic disease, it can potentially drive treatment decisions.
But three, and I think that this is the point that is somewhat lost in the general population when we talk about genetic testing for inherited susceptibility to cancer. So genetic testing, in some instances like Cystic fibrosis, Tay-Sachs disease, Down syndrome, those are genetic conditions where there's only one or two ways that an individual can be at risk for those genetic conditions and so we can test someone and we can say yes or no very, very quickly.

Cancer is really complex genetically, and there are genes that we know about and genes that we don't know about. And so when we're thinking about genetic testing for inherited susceptibility to cancer, we try to start testing with a cancer survivor. And the reason for that, is that we're trying to determine if any of the genes that we know about are contributing to that cancer that we see. And so we try to start with someone who has a cancer diagnosis, and that is something that is somewhat difficult for people to understand, because there's so much information out there about genetic testing being yes or no. And while in many cases that's true, it's not the same with inherited susceptibility to cancer, genetic testing.

Now that being said, sometimes the cancer survivor is not available to us, they may have passed away or they may not want to know. And of course the right to not know about genetic testing information is something that we as healthcare providers, we must respect. But in that situation, since we don't have that individual, we can test people who don't have a cancer diagnosis and we do that all the time. It's just that sometimes we have to be a little bit cautious in how we interpret those test results because we haven't been able to compare them to someone who has a cancer diagnosis.

Now, if we test someone who has a cancer diagnosis and we find a mutation in a gene, we can then test other family members specifically for that gene mutation and we can say very conclusively yes or no, who is at risk. And so that's another reason to start with someone who has a cancer diagnosis because if we find something, we can then do what we call Cascade testing, which is test other family members for that specific gene mutation. And in that situation, it's a very clear cut yes or no, because we know where to look, we know what is contributing to those cancer cases in the family.

And I think that's also a point that is somewhat lost about inherited susceptibility to cancer, genetic testing, is that if we find a mutation, yes, we can find individuals who are at increased risk who need increased screening, but we can also find people who are not at increased risk and we can save them from all of that additional screening, and so that is also a big public health win. We focus so much on increased screening, but we also can identify those that don't need it and so we can better use our healthcare dollars.

Scott Redding: Obviously high profile people have had the testing done for their own reasons. Can you talk more about why maybe some might go down the path of having
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preemptive surgeries as it relates to the diagnosis and is that necessary if a younger person, a family member does have the testing done and does find out that they have the mutations?

Kara Milliron: So it's very personal. And I think that is the number one thing that we try to share with patients when they come for an appointment is that there's no right or wrong answer, it's just whatever you feel is the most appropriate for you. So when we have someone who is, what we call unaffected or meaning that they don't have a cancer diagnosis, recommendations are different for men and for women. But let's say we have a woman who does not have a cancer diagnosis, but test positive for a BRCA1 or a BRCA2 gene mutation and they're wondering what are the appropriate next steps for them? So there are three main pathways that I think patients should know about, and again, just emphasizing that there's no right or wrong answer, it's just whatever feels the most appropriate for them.

One is increased screening. And so when a woman has a BRCA1 or a BRCA2 gene mutation, the increased screening for breast cancer is a mammogram and a breast MRI done yearly. Now some individuals they have those staggered every six months, some institutions do the mammogram and the breast MRI at the same time. There's no evidence that one way is better than the other, it's just really important to have the mammogram and the breast MRI done once a year, whether that's done at the same time or whether that's staggered every six months, is very institution dependent, but the most important thing again, is to have that screening done once a year. And then also a breast exam by a healthcare provider every six months. Now some women feel very comfortable with that, some women say, you know what, I'm not comfortable with that, I want to think about additional steps. And so they may consider breast cancer chemoprevention and that's taking a medication to reduce the risk of developing breast cancer.

And I think the word chemoprevention is a really bad word because women think, Oh my gosh, it's like taking chemotherapy, I'm going to lose my hair, I'm going to have all of these side effects, and that's not really the truth. It is a medication that you do take for several years, but it's very different from chemotherapy. And I think it's really important to have that discussion about the pros and cons and what to expect with a specialized healthcare provider. And when we look at breast cancer chemoprevention, you have to be at least age 35 and finished with family planning before you can consider taking a medication to reduce the risk of developing breast cancer. We typically offer Tamoxifen to women who are premenopausal, and Tamoxifen has been used for a long time to actively treat breast cancer and in fact, a lot of our advances in reducing mortality from breast cancer have been because of Tamoxifen. But since about 1998, we've used Tamoxifen in the preventative setting for high risk women and that includes women who have BRCA1 and BRCA2 gene mutations who do not have our breast cancer diagnosis.
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Now, there is a little bit of controversy regarding breast cancer chemoprevention for women who have a BRCA1 gene mutation. And the reason for that, is that when you look at the majority of breast cancers that are associated with BRCA1 the majority are not driven by estrogen, a small proportion are, but the majority are not, and Tamoxifen really reduces the risk of developing breast cancers that are driven by estrogen. So the BRCA1 mutation carriers, there is some controversy about the benefit of chemoprevention in those women, however, there are studies that have shown that there may be a benefit.

Now, BRCA2 breast cancer it's different, the majority of breast cancers associated with BRCA2 are driven by estrogen, and so breast cancer chemoprevention may reduce more breast cancers in the BRCA2 patient population.

Now, if someone is postmenopausal and has a BRCA1 or a BRCA2 gene mutation, we have other medications that we can consider for example, a drug cousin of Tamoxifen calledRaloxifene or an Aromatase inhibitors. So we have different options, but the most important thing to keep in mind is that, a woman has to be over the age of 35 and finished with family planning because these medications they do cause birth defects and so you have to make sure that you're finished with family planning. Of course, if your postmenopausal you're definitely finished with family planning, but if you're premenopausal that is something to consider.

Some women feel that is just not the road that they want to take and they really feel that prophylactic or risk reducing bilateral mastectomy and this is a very, very personal, personal choice. It has been shown to reduce the risk of developing breast cancer by about 90 to 95%, so it's a very significant risk reduction and it reduces the risk of developing breast cancer to below that of the general population. However, if you look at the statistics of the women who choose increased screening with mammogram and breast MRI, and the women who choose risk reducing or prophylactic bilateral mastectomy, there is no difference in the chance of passing away from breast cancer between those two groups. So that is something that I think is very important for patients to know and to understand.

Now, if the goal is to never develop breast cancer, then clearly having the risk reducing or prophylactic bilateral mastectomy, that is a very significant risk reduction, but if you look at the chance of passing away from breast cancer, there's no difference between the screening group and the surgical group. But a lot of times when we look at BRCA1 and BRCA2 gene mutations, they have devastated the family and they have seen relatives that have had to go through significant treatment, significant morbidity from their breast cancer diagnoses. And so, that plays a big role in decision-making, experience for cancer, family dynamics, cultural issues, religious issues and so it's a very, very personal, personal decision.
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When we look at ovarian cancer, we just don’t have good screening for ovarian cancer and I think that is something that is so frustrating. I’ve been a genetic counselor for 22 years, and that is the only thing that has not yet changed about my job, is that we still do not have a screening tool for ovarian cancer that works. We can use a CA 125 blood tests and a transvaginal ultrasound and we can do that yearly or every six months, but it has not been shown to find ovarian cancer at early more treatable stages. And so for a woman who has a BRCA1 gene mutation, we usually talk about having the ovaries and the fallopian tubes removed between 35 and 40. And then for a woman who has a BRCA2 gene mutation, we usually talk about having the ovaries and the fallopian tubes removed between 45 and 50. So there’s a little bit of an age difference about when that surgery is recommended between the two genes.

This surgery, depending on which research article that you look at, reduces the risk of developing ovarian cancer and fallopian tube cancer between 80 and 95% depending on which patient population you look at and which research article you look at, but the risk reduction is very significant. And I think that's something that is really important to talk about because when we look at the ovarian cancer risks, when a woman has a BRCA1 gene mutation, their lifetime risk for developing ovarian cancer is between 20 and 40% in some studies and between 20 and 60% in some studies, general population risk is about one to 2%, so it's a pretty significant jump in risk.

When you look at breast cancer risk with BRCA1 and BRCA2 again, depending on which study you look at the lifetime risk ranges anywhere from 55 to 85% over a woman's lifetime, general population risk is about 12%. So these are not options that women take lightly and I think that it's something that is very much misunderstood because if someone has not had a BRCA1 or BRCA2 gene mutation in their family, and they see some of the decisions that women are making, they may think that those are just very drastic and not appropriate. And unfortunately, given the risks for developing cancer, some women feel that this is their most appropriate decision, and again, it's very, very personal, and it's a decision that we must be respectful of.

When we look at ovarian cancer, we do have some prevention options. One of them is birth control pill use. We know that in high risk women birth control pill use for at least five years may aid in reducing the risk of developing ovarian cancer. So if a woman is under the age of 35 with a BRCA1 gene mutation, or under the age of 40 with a BRCA2 gene mutation and they haven't used birth control pills or they've only used birth control pills for a short time, and they are not wanting to pursue having their ovaries and the fallopian tubes removed, we can talk about birth control pill use. That of course has to be adjusted with their breast cancer risk, so that's a conversation that we have to have.

There’s some evidence in the general population that removing the tubes may help reduce the risk of developing fallopian tube cancer and ovarian cancer. However, in BRCA1 and BRCA2 mutation carriers it's still not known, if just
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removing the tubes and then having the ovaries removed at a later date, shows the same amount of risk reduction as if someone has ovaries and fallopian tubes removed at the same time. So there's a lot of data out there about, oh, just have your tubes removed and then have your ovaries removed at a later date. And I think it's really important to share with the listeners that, that is still something that is under investigation in clinical trials and we have no data in BRCA1 and BRCA2 mutation carriers that, that is safe. So hopefully that data will be available at some point, but we are several years away from that data being available.

For men who have a BRCA1 or BRCA2 gene mutation, they're at increased risk for prostate cancer. And so we do talk about prostate cancer screening, and there's a lot of debate in the general population that if we should be offering prostate cancer screening to men, but there's no debate with men who carry a BRCA1 or BRCA2 gene mutation. The prostate cancers associated with BRCA1 or BRCA2 can be more aggressive and we can see them at younger ages, so we do talk about prostate cancer screening with at least a PSA and a digital rectal exam yearly, starting between ages 40 and 45.

Now the University of Michigan Rogel Cancer Center is very lucky to have a prostate cancer risk assessment clinic and that is a very, very needed clinic, because again, so many times men are somewhat forgotten in the BRCA1, BRCA2 picture. This is a wonderful resource where we can refer men who have an increased risk for developing prostate cancer because they have either BRCA1, BRCA2 or another gene mutation and other genes that are associated with an inherited susceptibility to prostate cancer. Or they have a very strong family history where we have not been able to identify the gene that is contributing to that access of prostate cancer in that family? And this is a clinic that will follow these gentlemen and we'll also do the screening and there may be clinical trials for new types of imaging to detect prostate cancer at early more treatable stages and so this is a wonderful resource for us.

We also, for men and women who have a BRCA1 or a BRCA2 gene mutation, or another gene mutation that is associated with an increased risk for pancreas cancer. We do have the option of pancreas cancer screening, and that is very specialized and we refer to our colleagues in gastroenterology to discuss pancreas cancer screening, it is not considered standard of care, but it is something that we can offer and we want patients to have that discussion with a specialized physician, so that they can make the choice about whether or not that makes sense for them to pursue.

Sometimes patients will go and have the discussion with our colleagues in gastroenterology and say, you know what? This is not for me. And sometimes they'll go and have the discussion and I'll say, you know what? I feel really strongly that I want to consider the screening. And so I think that's a discussion that's really important to have. And then of course, with BRCA1 and BRCA2 there may be an increased risk for colon cancer and so we also refer to our
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colleagues in gastroenterology to modify the colon cancer screening regimen. Whether a colonoscopy should be done every five years as opposed to every 10 or if depending on findings from the colonoscopy, should we modify how often that colonoscopy is being done.

Scott Redding: Being that this is based off family history for the testing, if a younger patient male or female gets diagnosed with one of the BRCA gene mutations and they are in their late teens, early twenties, should there also be a conversation around fertility preservation and fertility options for those patients, due to some of these potential preventative measures could affect that family planning type aspect as they get older?

Kara Milliron: Absolutely, and that is something that is really, really important to discuss with these individuals. And I think in the past that was something that was very much ignored, it also possibly could be because we just didn’t have the technology that we have now, but that is something that is really important to discuss. Also, with BRCA2 and in certain mutations in BRCA1 there is a risk for having a child with a genetic condition called Fanconi anemia, if their partner has a BRCA2 gene mutation or a specific BRCA1 gene mutation in a specific area of the BRCA1 gene.

Fanconi anemia is a very serious genetic condition, individuals with Fanconi anemia they have short stature, they have a very small head size, what we call microcephaly, they may have thumb abnormalities, but more importantly, they have profound bone marrow problems, and these children are at risk for developing leukemia and lymphoma. And so if it would have an impact on their reproductive decision-making, either there is the option of prenatal genetic diagnosis, PGD and in vitro fertilization. And so we do have very wonderful colleagues in reproductive endocrinology that we refer these patients to, to talk about those options, whether or not they want to consider freezing [inaudible 00:29:51] or freezing embryos, or whether or not they want to consider preimplantation genetic diagnosis in the future, or whether or not they choose to not have children and build their family in a different way.

And I think the most important thing that we can say is that we are non-directive, we give the patient all of their options, and we certainly do not tell anybody whether or not they should have children, that is not our role in any way. What our role is, is to make sure that patients have all of the information in front of them, so that they can make the right choice for themselves.

Scott Redding: You touched on it a little bit when you were talking about the prostate cancer side of things with clinical trials. Are there clinical trials and or lab research that’s happening around BRCA gene mutations and ways to either come up with preventative or treatment options for patients that have cancers that have come from those mutations?
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Kara Milliron: Very much so. And I think that the University of Michigan Rogel Cancer Center is one of the leaders in the nation with regards to that research. And one of the things that we can also help patients is that if they are interested in that, we can help them identify clinical trials here at the University of Michigan that they may qualify for and so that's another reason why sometimes individuals will pursue genetic testing. And those clinical trials may not just be for individuals who have cancer, it may be individuals who participate in novel screening tools or they may participate in prevention trials. And so I think it's really important for people to understand that clinical trials are not just for people who have a cancer diagnosis, that there's a lot of trials that are looking at prevention and how to reduce cancer risk, but also how do I, screening trials? How to do identify cancer at its most early treatable stages? And we have all types of clinical trials here at the University of Michigan.

Scott Redding: Well, Kara, I really appreciate the time as we wrap up. If there is one key message you would like people to take away from this talk today, what would that be?

Kara Milliron: I think it's really important to know your family history. And if you have any questions about your family history, I think it's really important to talk to that matriarch or that patriarch in the family, to get that information down while they're still with us. One of the things that I profoundly regret in my own personal life is that, my paternal grandfather was one of 10 and he had 10 children, so my dad was one of 10 and his dad was one of 10, and my paternal grandfather passed away when he was 105. And I think we sort of got lulled into the sense that he was going to live forever because he literally was living forever and I miss him tremendously. He was an engineer on the railroad for Ann Arbor line and he saw so much of Michigan history and I really wish that I had taken the time to sit down with him and get his story and his family's story.

And so I would strongly encourage individuals to do that if they have, that individual available. Of course, sometimes people are adopted and they have no family history or their loved ones have passed away and they don't have that, and of course that happens. But if there is someone that you can talk up to that is in those elder generations to get that additional family history information it's so important for your healthcare and also really helpful for your primary care physician, your internist, any of your doctors to help guide your care.

I also think that it's really important to let people know that, there are state and federal laws that are in place for genetic testing that prevent this information from being used in a discriminatory manner. And so many times, one of the barriers to pursuing this information is fear of genetic discrimination. And the laws have been passed and have been in place for a long time, the first law was passed in 1996 under HIPAA, The Health Information Protection and Accountability Act. And then the second law was passed in 2008, GINA, The Genetic Information Nondiscrimination Act. And these are laws that are not part
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of the affordable healthcare act and so I think it's really important to get that information out.

I also think that, so many times patients are under the impression that genetic testing is very, very expensive and insurance companies won't cover the genetic testing, that's not true. The cost of genetic testing has dropped significantly. Just to kind of give you some points of comparison, when I first started at the University of Michigan Rogel Cancer Center in 1998, the cost of genetic testing for just BRCA1 and BRCA2 was around $2,700. When we look at genetic testing now, we are looking at multiple genes and the out of pocket cost, if someone had to pay out of pocket is $250, so a very significant drop in price. But most insurance companies do cover a large proportion if not all of the genetic testing and that is something that we can help patients understand before the sample is collected.

So I just want to make those points, understand your family history, there are laws preventing this information from being used in a genetic discrimination, and insurances are covering the cost of genetic testing and if you did have to pay out of pocket, the cost is much more affordable than in the past. I do realize that $250 is still a lot of money, but it's about 10% of what it costs previously and the costs will probably continue to drop. So those are the main points that I just want to share.

Scott Redding: Well, a wealth of information, really appreciate the time. Thank you.

Kara Milliron: Thanks so much for having me, Scott. It's a pleasure.

Scott Redding: Thank you for listening and tell us what you think of this podcast by rating and reviewing us. If you have suggestions for additional topics, you can send them to cancercenter@med.umich.edu or message us on Twitter @UMRogelCancer. You can continue to explore the 3Ps of Cancer by visiting RogelCancerCenter.org.