Uncertain About Variants of Uncertain Significance?

With Sharsheret's Genetic Counselor:

Peggy Cottrell, MS, CGC

National Webinar Transcript

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Presented by:

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Jenna Fields:

Welcome to “Uncertain About Variants of Uncertain Significance?” with Sharsheret's very own, Peggy Cottrell. I’m Jenna Fields, the California Regional Director of Sharsheret. Thank you so much for being here. I want you to know that this idea actually came from a volunteer that I personally get to work with who shared her own experience with variants of uncertain significance and asked if Sharsheret could choose this as our topic for our national genetics webinar this year. So thanks to her, we are having this conversation, and I'm really looking forward to learning more alongside all of you.

Before we begin, I have a few items to share. I want to thank our sponsors for this program whose generosity allows us to continue to provide support and education to you. AstraZeneca, the Basser Center for BRCA, The Max and Anna Baran, Ben and Sarah Baran, and Milton Baran Endowment Fund of the Jewish Community Foundation of Los Angeles, the Siegmund and Edith Blumenthal Memorial Fund, and Cooperative Agreement DP19-1906 from the Centers for Disease Control and Prevention.

This webinar is being recorded and it will be posted on Sharsheret's website along with the transcript. And as always, participant faces and names will not be in the recording. We did receive a number of questions tonight before today's program. Please know that we are going to have Q&A. And we'll be starting the Q&A with the questions submitted, and then we'll open it up to the questions that have come in into the chat. And feel free to submit a chat directly or a question directly to me at Sharsheret in the chat if you want to share and ask that question anonymously.

Now, Sharsheret has been providing telehealth services to the breast and ovarian cancer community for more than 20 years. If you're not familiar with us, we are a national nonprofit cancer support organization and we provide free mental health support, community education, and genetics conversations to people across the country. Please know that our services are completely free and available to you and your family should you be facing breast or ovarian cancer or increased hereditary risk for cancer. Now, the information we provide tonight does not substitute as medical advice and we are not performing any medical procedures. You should not use this information to diagnose or treat a health problem. Please always seek the advice of your physician or qualified health provider with any questions you may have regarding a medical condition.

So now before our wonderful genetic counselor, Peggy Cottrell begins, we've asked one of our volunteer leaders here in California to share her story. Sari has been a peer supporter for Sharsheret for over 20 years. She's one of our original peer supporters, and she sits on our California Community Advisory Committee. She's also the former co-chair of our committee. And if you participated in Pies for Prevention, you may have been lucky enough to taste one of Sari's pies here in Los Angeles, which are extremely delicious. So thank you, Sari, for sharing your story tonight. And I'm going to go ahead and spotlight you.

Sari:

Hi. Thank you, Jenna. And I am really honored to have been asked to share my genetic story, or perhaps we should say saga, with all of you today. When I was first diagnosed with breast cancer almost 30 years ago, nobody said anything about genetic testing because it wasn't something that was available or even really known. By the time I was diagnosed the second time almost four years later, testing was available for the three, quote, "Ashkenazi mutations" that have been found to be associated with breast cancer. And even though insurance did not yet cover the cost of that testing, that's how long ago it was, I did have the testing and found that I did not have any of those three mutations.

A number of years later, my oncologist began a discussion with me about having my ovaries removed prophylactically because of my elevated risk of having ovarian cancer with my history of breast cancer. By that time, genetic testing was more widely available and they were able to look at the entire BRCA1 and 2 genes from mutations, not just the three Ashkenazi sites. My doctor and I decided that I should get that more extensive testing done, and the result indicated that I had a variant of uncertain or unknown significance, which was probably the least helpful response I could have received. I had hoped to gain clarity about whether to get my ovaries removed, but the genetic testing did not shed any light on that decision.

After much agonizing and consulting with everyone I could find, and because I didn't intend to have any more children at that point, I did decide to have my ovaries removed. Over the next dozen or so years, my oncologist and geneticist would periodically check in with the lab to see if the variant had been reclassified, which it was not until about three years ago. At that time, the geneticist called me to tell me she had just been informed that my BRCA1 mutation had been reclassified as significant or pathogenic. This information did not really change anything for me as I had already had several prophylactic surgeries and had been undergoing regular screenings for other cancers that I am at risk for getting. However, it was now time for me to discuss with my siblings and my children the advisability of their getting tested for BRCA mutations. One of my children recently found out that he does have the same mutation as I do, and the genetic saga continues.

Jenna Fields:

Thank you so much, Sari, for sharing your personal story with us and sharing a little bit also about how this is now being passed on to your son. I mentioned that Sari is part of our peer support network, and you'll learn a little bit more about what Sharsheret offers in terms of our genetics program. But please know that our peer supporters are a wonderful resource for people who are impacted not only by breast or ovarian cancer, but also people facing hereditary risk who have not been diagnosed. So know that's a resource for you.

It's now my pleasure to introduce Peggy Cottrell, masters in science and a certified genetic counselor. She's the genetics program manager at Sharsheret. She's a graduate of Sarah Lawrence College, Master of Science in Genetic Counseling program, and has been a genetic counselor for over 20 years. She's available to speak one-on-one completely for free by phone, email, or texts to anyone in the country. This is a service that Sharsheret offers. She consults with women, men, and families about your family histories, genetic mutations, and personal risk for hereditary breast and ovarian cancer. This is a little known service that Sharsheret offers, so please don't hesitate to reach out to her. If you have a question that is specific to your own particular situation, our speaker, Peggy, can schedule a time to speak one-on-one with you, and my colleague Bonnie is putting that information in the chat. And now, it is my pleasure to welcome Peggy Cottrell.

Peggy Cottrell:

Hi. Welcome, everybody. I'm going to go ahead and share my screen. So I hope everybody can see that. And let me go to slideshow here. Okay, very good. I'm going to move right along and get started.

First, I just want to review our genetic fast facts. These are things that just in general are important to note about hereditary cancer and BRCA1 and 2. We'll start on the bottom left. 1 in 40 Ashkenazi Jews, both men and women, will carry a mutation in BRCA 1 and 2. And that's why it's so important, especially for our Jewish audience, to be aware of these mutations and aware of their family history and if the possibility is there that they could be at risk to carry one of these. Up one level, everyone who carries one of these mutations has a 50% chance to pass it to the next generation, and that includes men and

women. So when you're looking at the risk that you might have something in your family history that would indicate you might have something inherited related to cancer, you have to look not only on your mother's side but on your father's side as well.

Now, we know that there are other genes that we can look at. We can identify mutations in genes like ATM, CHEK2, Lynch, PALB2, and many others. And so if you had testing a long time ago, you might consider having a multi-gene panel. Although if you have tested positive for a big ticket item like BRCA1 or BRCA2, then an updated test makes less sense for you. Going down, individuals who carry these mutations have the opportunity to make choices about their care that could save their lives. There are opportunities for high risk screening, for prophylactic surgery. We heard Sari talk about having her ovaries removed when she was done having children. And these are really important procedures that can save your life. And then finally, if you have a strong pattern of cancer in your family and there's nothing identified, it's still possible that there's something inherited causing that cancer and you may need to continue to have careful screening.

Again, men just as likely as women to carry these mutations. If I had 100 women in a room who all had a BRCA 1 or 2 mutation, I would expect by chance half of them got it from their father and half got it from their mother. And even men who are unaffected with cancer can pass those mutations on to their daughters or to their sons. So important information to know.

Now, we're going to move on to the important topic of the night, which is variants of uncertain significance. Most people think that when you have a genetic test done, it's going to be yes or no. Yes, I have something inherited that's causing cancer, or no, I don't have anything inherited that's causing cancer. And unfortunately, there are these annoying in-between results that are called variants of uncertain significance. And variants, it's not uncertain whether the change they found is present in your DNA. That's absolutely certain. What's uncertain is what is the impact of that change in the DNA on the ability of the protein to perform its normal function. And scientists don't yet understand the implications of all of the variants that they're able to identify.

There is a gradual changing process by which we classify these. The variants can move along this chart. All the way on the left, the green is benign. And when we find things that are benign, they might even be different from what most people have, but we know they're not a problem, don't cause an increased risk for disease. Then there's likely benign, and these are almost never reported. These are ones that we're not 100% sure, but we're really 99% sure that these are not anything to worry about, and they are called likely benign. Uncertain in the middle are the ones that get called a VUS or a variant of uncertain significance on your report. Likely pathogenic and pathogenic, these are the two that will be called a positive result on your report. And even the ones that are likely pathogenic, we really overwhelmingly think that these are concerning, but there may just be some issue with the final proof. But we're confident that these are things to be worried about. And these are, the findings are usually classified in one of these five categories.

Now, years ago when Sari had her testing done and we were only looking at BRCA1 and 2, uncertain variants were somewhat less common. And part of that was because we were only looking at two genes. And I think when I first started working as a genetic counselor, I would tell people there was about a 10 to 15% percent chance of finding something uncertain. But nowadays, that's much smaller, probably about a 1 or 2% chance. But because the testing that we do nowadays involves a panel test where people may be having as many as 60 or 80 genes tested, the chance to find something uncertain is much, much higher. And that's because of the number of genes we are looking at.

And there is also a higher chance to find something uncertain if you are from a less common or at least less common among people who have been tested in the United States ethnic group. And so for people who have African, Asian, other ancestries, having uncertain variants are a little more common than they

are compared to non-Hispanic white people. And that just has to do with the people who have been tested in the country. And those have overwhelmingly been over the years Caucasian. More and more people of color are being tested, and so those uncertain variants are being reclassified as well.

How many variants are there? And so I took these numbers about a month ago, so they're probably different now if you looked on the webpage where I found these. There is a website called ClinVar, and ClinVar is a huge database filled with variants. And all kinds of genes are there, not just cancer genes, genes that are related to other conditions. And when labs find variations, they often deposit, make a deposit in essence in this database, so that other labs can see what variants have been found and how they have been classified by different labs. And so this is data from BRCA1 and BRCA2. I'm going to start at the bottom where you see pathogenic and likely pathogenic. These show you the hundreds to thousands of different unique mutations there are that are concerning. And then we're going to the middle where we see uncertain significance. We see thousands of variants of uncertain significance have been identified in these genes. Again, the likely benign still very high, benign.

And the most troubling category, the one that I always go to, to take a look, is conflicting interpretations. And this means that not every lab calls these variants exactly the same. And so what sometimes can happen in families is one family member goes and has a test with one lab and finds they have a likely pathogenic change, and another family member who has the exact same change is told that they have an uncertain variant. And that's because different labs are interpreting these results differently. And that's one of the problems that we can come to. Now, this is a public database. You're welcome to take a look at it. You can find it if you Google ClinVar. It's terribly complicated but public.

How do we interpret these uncertain variants, and how do we know what kind of advice to give people? The bottom line is I once had someone say to me when they had an uncertain variant and they said, "Well, I know you're telling me you don't know what this means, but my doctor is going to know what this means, right?" No. When these things are uncertain, it means that the smartest people out there don't know how to make this call and we're not sure. And so can I, a lowly genetic counselor, tell you what this means? No. The bottom line is that I'm going to have to tell you, "Yes, it's uncertain." But sometimes there are things that we can look at that can help us figure out if it's really something to worry about or maybe it's less likely to be something to worry about.

One of the most important things to do when I'm trying to figure out how important a variant is, is to take a look at someone's family tree. And what I want to look for is if you have an uncertain variant in BRCA1, do you have cancers in your family that go along with BRCA1? And is the variant perhaps tracking with those cancers? And in fact, that's one of the important ways that labs figure out if these variants are important or not. If they see that an uncertain variant is tracking with the cancer that's associated with that particular gene, then that begins to be evidence that it's something important. And when there's statistically enough evidence, that can be when the lab reclassifies it. So I want to look and see, is there evidence that this is something to be worried about?

Now, if you have an uncertain variant in a gene that causes a cancer that's not at all in your family, that doesn't prove that it isn't something to worry about, but it makes me less concerned than it would be otherwise. And the other thing, the important thing that I do also when someone tells me they have an uncertain variant is determine if there are any conflicting interpretations amongst different labs. I will go to ClinVar and just try to look and see. Are some of the labs calling this uncertain, but others are saying it's a mutation? Or perhaps some are saying it's uncertain, but others are calling it likely benign. And so if there are labs calling it likely benign, then they may have more evidence that it's less concerning and then I can be more reassuring to someone.

Again, I still can't say, "You don't have to worry about it at all." What I will tell you is that over time, variants do get reclassified. And overwhelmingly, the majority of them are going to be reclassified down,

which means less concerning. So more often, probably 80 to 85% of variants that are reclassified are determined to be benign, and it's a much smaller number that are determined to be actually mutations. And that's important to remember.

What should somebody do if they're just left with this uncertainty? What's the choice to consider? And so that's where again the family history is going to become important. We want people to pursue careful screening based on the family history regardless of whether there's a variant or not. And that's because there could even be something else inherited. Sometimes people will say to me, "Well, listen. There's so much cancer in my family, this variant has to be important." And that's not necessarily true. There may be other things that are predisposing to cancer in your family that are things we don't know how to look for yet. And so we don't want to blame the variant when that may actually have nothing to do with the cancer in the family.

It's really important when people have a mutation in their family that's pathogenic that other family members be tested and find that if they have it as well, and then we know how to take care of those family members. But it's not necessarily helpful to test family members who are unaffected when we're talking about an uncertain variant, because finding the uncertain variant doesn't help us know how to take care of people. It can make sense to look for the uncertain variant in family members who are affected but not necessarily in family members who are unaffected. It will not be helpful.

Sometimes, we recommend avoiding prophylactic surgery based on just something uncertain. But what I have to tell you is especially related to the story that Sari told us, because with ovarian cancer, there really isn't any good screening. Once someone is done having kids, and especially if they've already been through menopause, it's not a bad idea if you have an uncertain variant in something like especially BRCA1 to talk to your doctor to determine whether it might make sense for you to consider that prophylactic surgery.

But what we likely wouldn't recommend would be a prophylactic bilateral mastectomy just based on an uncertain variant. And that's because most people, if it turned out that you found out that your variant was not important, you would be very relieved. But then if you had done something drastic like a bilateral mastectomy, you might look back and say, "What was I thinking? I really shouldn't have done that." Whereas if you just had a bunch of extra breast MRIs, which is what this picture is showing, most people are not going to regret that they had a little bit of extra screening that didn't identify anything.

So these are important decisions to think carefully about, to discuss with your doctor. I've unfortunately over the years heard many stories of people who had what ended up being unnecessary surgery based on a variant that turned out to not be important. And again, these are hard decisions to make, but it's important to understand what you're making a decision on. And many people will make a decision, not so much on the variant, but on the family history. So if someone has a strong pattern of cancer in their family and all they find is a variant, they may decide to have a prophylactic bilateral mastectomy again based on the family history because there could be something else there that's causing the cancer in the family.

How does a variant get reclassified by the lab? There are further studies that are done all the times by labs. Labs have an interest in trying to give you the most accurate information. Obviously you saw the numbers of variants that there are, and it's very hard for there to be funding for thousands and thousands of variants that exist in the hundred or so genes that we know about that predispose to cancer. And so variants that are seen more commonly are more likely to be studied and eventually be reclassified because there is just going to be more information available.

Some variants are more rare, and you may find... Sometimes when I look up a variant, I can find out how common it is. And some of them are very, very rare. It might be the first time that that lab has seen that change, and that makes it a little bit less likely that it's going to be reclassified. But if you can provide the

lab, and this is something you can do yourself to help move science forward, if you have an uncertain variant in your family and there are several people with cancer who have been tested who also have the same variant, then you should let the lab that you had your testing with know this information. This is helpful information to them. And if you need help contacting them, you can speak to your doctor, to your genetic counselor, or call me at Sharsheret. That's something that I can absolutely help you get done. And then you are helping to move science forward.

There are a lot of other very fancy and sophisticated tools that labs are using to improve their ability to reclassify uncertain variants. And I watched a fascinating webinar this year about the use of artificial intelligence and machine learning that a certain lab is using in order to help reclassify variants. I will tell you that 90% of the webinar went totally over my head, but it was just very interesting what can be done. There are functional studies, and these are things where they try to produce a protein from the RNA of the variant and to see if it will work. Now, it's hard to follow in somebody's body, but in a lab they can try to do functional studies and determine if these variants seem to behave as the normal protein would. And finally, there are labs that do a specialized RNA testing to help find if there are variants somewhere in the non-coding region that can help to reduce the number of variants that are out there or to find mutations that might be harder to identify. So lots of good work is being done on reclassifying variants.

Now, if the variant has been reclassified, will your lab contact you? And the answer is no. They are going to contact your healthcare provider. And the reason for that is to make sure that you get the information explained to you in an appropriate fashion. And the great news in Sari's story is that she was contacted by her healthcare provider and was able to find out about this mutation and offer testing to other family members. However, not every healthcare professional is going to take the time to make these calls. Very often when doctor's offices order genetic testing, they will get these messages, but they might not understand the importance of calling out changes in uncertain variants. Sometimes, I had the experience over the years when I would try to contact people that their variant had been reclassified, the people had moved and changed phone numbers or could possibly have passed away. I wouldn't have known that because I just couldn't find them. And so sometimes it's hard to get this information out to people, especially if this is 10 or 15 years after the original testing.

And so it's really important, and this is another place where you can make a difference in terms of your own health. Find out who is the healthcare provider on your genetic test, and that should be written on the very top of the first page and that's the person who ordered your testing. And that's the person who's going to be notified when your variant is reclassified, and make sure that that person knows how to reach out to you. And ask the office if it's a doctor's office or if it's a genetic counselor, "If my genetic variant is reclassified, will you be in touch with me?" It's an important question to ask. Sometimes in busy genetic departments, they only contact people if the change would affect the medical management. So a story like Sari where this now is something important might be called out. Whereas something else that's changed from uncertain to benign, that's not necessarily going to change anything and you might not get a call. So this is important information to find out.

And before we go on to the next topic, again, we did get questions in advance about people's specific uncertain variants. And I really cannot answer people's personal questions about their own personal variants of uncertain significance on the webinar tonight, but I can absolutely talk to any of you who have any questions about either your uncertain variant or your actual genetic mutation that you're not sure if it's being managed correctly. So if you have any questions at all about uncertain variants, don't hesitate to reach out. You can set up an appointment with me. I usually talk with people for about half an hour. Sometimes it doesn't even take that long. I can look up your variant and find out if it's something to be very concerned about or if it's something less worrisome.

Okay, so you remember I showed you those five categories that variants usually fall into? Here's one that's a little bit different, and I really added this. I'll tell you I added this slide at the last minute because I got a question about this. And I said, "You know what? This is really important to cover." There are some variants that are considered to be mutations, they're considered to be pathogenic, but they're called low penetrance pathogenic. And what that means that for whatever reason, something about the type of mutation that it is means that it's less severe than a typical mutation. And usually when the result comes back from the lab, it'll say something like low penetrance variant. It might say low penetrance allele. There's one lab that writes, "See below." And the first time I got one of those back I thought, "What are they talking about?" But this was something that was not typical and they wanted to make an explanation. And below was the big explanation of why they thought this was not as bad as most changes that are present in that particular gene.

And there are two of these low penetrance variants that are particularly common in our population, people who have Ashkenazi Jewish ancestry, and I'm going to mention these two briefly. One is in CHEK2, which is a gene that can be associated with breast, prostate, and colon cancer. And this CHEK2 low penetrance variant has two names. Variants always have two names. One describes the change in the DNA and the other describes the change in the protein. The two names of this CHEK2 are 1283 C changed to T or S428F. And this particular change, some labs call this uncertain. Other labs call it a low penetrance variant. We see significantly less risk than might be present in other families with more typical CHEK2 mutations. And so if you have one of these, you do want to be more careful about your breast cancer screening. And it may be a good idea to get a breast MRI, but it's probably overkill to have a bilateral mastectomy unless you have a strong family history that goes along with this. And then it could be something that you might consider.

And the second one I want to talk about is APC. And this is either 3920 T changed to A, which is the DNA name, or I1307K, which is the protein name. And typical changes in the gene APC, we don't see more commonly in people with Ashkenazi ancestry, but this particular change is very common in people who are Ashkenazi. I think about 5 to 6% of all Ashkenazi Jews will have this change. It's very common. And while a true APC mutation causes a very severe pattern where people get hundreds to thousands of colon polyps, this low penetrance I1307K just causes a somewhat increased chance of colon cancer. If the average person's chance to get colon cancer is about 5 or maybe 6%, a person with this change has about a 10 to 12% chance. So higher, higher than the average person, but not gigantic. And the recommendations if you have this low penetrance allele is to have colonoscopy every five years starting at age 40.

Updated testing. People who may have been tested in the past while you're looking at your results to see if you had a variant in BRCA 1 and 2 or anything else, if you had testing more than 10-12 years ago, you may benefit from having an updated panel test. And if you have any questions about whether this does or doesn't make sense for you, again, you can talk to your doctor, your genetic counselor, or be in touch with me at Sharsheret and I'll be happy to take a look at your result and let you know. And I'll look at your family history and let you know if I think an updated test makes sense for you. And we have options for low-cost testing. And so generally, it's not exceedingly expensive to get an updated test done.

A story from the news last year, and I think it was about a year ago that this story came out. And this is really a story about an uncertain variant. And I will tell you that in some ways, this story could remind us of Sari's story, but a twist here made this a little more dangerous. This is a famous person. For those of you who are a lot younger than me, the name Chris Evert might not mean anything, but I as a young person watched Chris Evert play tennis and watched her continue to report on the sport. She's still a broadcaster. Chris's sister, Jeannie, who is in this picture with her, was diagnosed with ovarian cancer a number of years ago now, and she had genetic testing and had an uncertain variant in BRCA1. And

unfortunately, Jeannie passed away from that ovarian cancer. And a couple years after she died, her uncertain variant was reclassified and Jeannie's physician was notified and let the family know about the change in the classification, that it was now considered to be pathogenic.

So once the result was reclassified, Chris was tested. She tested positive for the same variant. Now, she's in her, I want to say, mid to late sixties. I don't remember her exact age, but not a youngster. But decided right away when she tested positive, she had seen what her sister went through and she decided that she would have the risk-reducing removal of her ovaries and tubes. And during that procedure, was found to have ovarian cancer. Now fortunately, the ovarian cancer was at an early stage. She didn't have any symptoms before the surgery. And this year, she's undergone treatment and is doing very well. It's been fabulous of her to be public about this story.

I will tell you that the first story that came out via ESPN last year around this time talked about the uncertain variant. Other stories have somehow said that originally her sister tested negative, but then it turned out it was positive. That wouldn't have made sense, but the uncertain variant aspect of it absolutely makes sense. Obviously, I didn't call Chris and confirm the story with her, but I think this makes more sense and was the way the story was reported originally by ESPN in the first story that came out.

You have to think about, for Chris, this turned out well regardless, but she had to go through treatment for ovarian cancer. And you just have to think about, I don't know whether anyone ever talked to her about whether given that this was an uncertain variant in BRCA1, and she was certainly at the time her sister died in her late fifties or early sixties, past having children, past menopause, certainly could have thought about having her ovaries taken out regardless. So again, one of the reasons to think about these things. Now, we have two stories here where variants were upgraded to something serious. But again, I want to remind you, most of the time variants are downgraded.

And then finally, another thing about variants in the news. This past year, Myriad Genetic Labs, which was the first lab that did testing for BRCA1 and 2, they used to hold a patent that they were the only lab that was allowed to do testing. They lost that patent by virtue of the Supreme Court in 2013. And after they lost the patent, they felt that they had an advantage in the marketplace because they had tested so many more people for BRCA1 and BRCA2 than any of the other labs. And so they had better information about the uncertain variants and they decided not to share with anyone else. They never put their variant data into the ClinVar database which I spoke about earlier. And up until this time, Myriad has never put any data into the ClinVar database. And whether you think that's a right thing or a wrong thing, I think a lot of genetic counselors over the years really thought that wasn't the right thing. It looks like a business decision.

But they have decided this year that they are going to be, this year 2023 during this year, they will be entering their variant data into ClinVar after finally, after so much time. And I think this is also going to improve cooperation amongst labs and should reduce some of the uncertain variants as well.

One more piece of news which has nothing to do with uncertain variants but which I could not help myself from sharing, is that there is starting to be evidence that pancreatic cancer screening can have a benefit for people at an increased risk to develop pancreatic cancer. There is an increased risk for pancreatic cancer with BRCA1 and 2 and a number of other hereditary cancer genes that I mentioned here on the screen. Screening is still best performed through a pancreatic cancer screening study. And if you're looking for studies, we have information on our website or you can be in touch with me and I can help you find a place that may be somewhat near to your home if that's something you're interested in. The screening is not straightforward. It's not a simple blood test. It involves an MRCP, which is a MRI of the pancreas and its ducts, as well as an EUS, which is an endoscopic ultrasound which uses an

ultrasound camera which takes pictures of the pancreas which is behind the stomach. So important news. And again, if you have questions about that, I would love to hear from you.

So a perk for my profession, genetic counselors understand the pros and cons of testing. We'll order the correct test for you based on your personal risk and your insurance. I've spoken to people who told me, "Oh, no. My insurance won't cover testing." And it turns out that the lab that was chosen for them was out of network. So really important to have somebody who understands those nuances, and we are really in the best position to explain carefully the pros and cons and what makes most sense for people who are carriers in terms of pursuing in the future.

And the great thing about speaking to me, I do not give medical advice. I'm not your physician, but I can tell you what the variety of options are and help you think about the pros and cons of each one. So in essence, helping you make that decision without necessarily telling you what to do. It's never our job at Sharsheret to tell you what to do. That's between you and your doctor. But we want to make sure you have all the information you need to make the best decision.

If you're interested in having testing done, there are lots of ways to get testing now. You can find a genetic counselor online. I can help guide you. The national site of genetic counselor has a database of genetic counselors. We partner with JScreen and they have at-home testing where you order the test online and it's sent to your home. We have a coupon code, Sharsheret100, that reduces the cost of the testing by $100. If you have insurance, whether or not the test is covered by your insurance, the bottom line cost of the test to you will be $99, and that is an excellent and amazing buy. Another lab that has testing is Color, and they also have good prices and you can buy the test online.

I've come to the end of what I want to say in terms of my presentation. I'm going to leave this slide up while I answer some of the questions that came in ahead of time. I'm available to chat with people one-on-one over the phone. Generally, we set up an appointment by email or by text and then I'll give you a call. And your questions, I'm there to listen to you and to try to help you with the facts you need to make the correct decisions. If you want to talk with your whole family on a call or a couple of family members, that's absolutely doable. And I do Zoom calls. I'm also able to do Zoom calls if people are outside of the US. I've spoken to people in Europe, in Israel, in Australia over the past couple years. But unfortunately, only in English. I don't speak anything else. And my email address and my direct line, which can be texted.

So questions. A couple of people ask questions about specific genes. And a couple of these genes include BARD1, NBN, RAD51C, and FANCC. These are a bunch of genes that all have something in common in the sense that they do slightly increase breast cancer risk, but not as much as most of the genes that we talk about. So if someone has a mutation in one of these genes, it does increase their risk for breast cancer, but not by a whole lot and maybe not even enough to recommend a breast MRI for screening unless there was also a strong family history going along with those specific changes. Therefore, if someone had an uncertain variant in one of those genes, because even with a mutation the risk is very low with an uncertain variant, the risk is even less concerning. Again, it's really important to look at the family history because if there's a strong pattern, then even in the absence of any finding, we want to recommend careful screening and you might consider doing prophylactic surgery.

And I want to recommend, in fact if Bonnie, if you can put it in the chat for me. The webinar we did last December 2021, we spoke a lot about the different genes outside of BRCA1 and 2. And so if you have an interest in some of these other genes, you can take a look at that webinar from last December. It's still on our website, and Bonnie's going to put in a link so that it's a little easier for you to find.

What's the impact on sons of people who are carriers? Or in other words, what do mutations in BRCA1 and 2 have to do with men? And so it's really important to realize that men do get cancer related to BRCA1 and 2, but their risk to get cancer is lower than a woman's risk to get cancer. The risks for cancer

include prostate cancer, pancreatic cancer, male breast cancer, and sometimes melanoma. And men can pass mutations to the next generation. And again, I'm going to reference a webinar that we just did in November that was about the implications of BRCA1 and 2 and other hereditary cancers on men. And Bonnie is also going to put a copy of that link into the chat so that you can easily find that webinar. But again, it's on our webpage.

Someone asked a question about ctDNA testing, which is testing that looks to see if there is tumor DNA in the blood, and wondering if these are things that we recommend that our callers consider doing. And I will tell you that these tests are relatively new. They haven't been approved enough to be covered by insurance yet, and they can be expensive. There are benefits possibly to finding cancer early, but there are also false positives. And so in making a decision about whether you want to have a test like this, it's really important to talk to your doctor about your specific situation and how much a test like this would be helpful. But we're going to be cautious about making any recommendation on those.

There was a question about a connection between MSH6 or PMS2 mutations. These are mutations that are associated with Lynch syndrome and there has been some thought that with these two particular Lynch syndrome mutations, there might be an association with breast cancer. But unfortunately, the evidence is still very mixed. And so what I would recommend to people who have this, again, it's MSH6 and PMS2. If someone has one of those Lynch mutations, then if you have a strong pattern of breast cancer in your family, absolutely consider a better screening. But otherwise, probably the regular breast cancer screening that's typically recommended is probably going to be enough.

And then finally, what about somebody who has a close family member who has ovarian cancer who died of ovarian cancer, and you yourself have a negative result? What does that mean? And this, again, is really hard. We know that there are things that predispose to cancer that we don't know how to look for. And so scientists estimate that people with a close relative who's had ovarian cancer may have a little bit of a higher risk to develop ovarian cancer than people in the general population. But that risk is probably not high enough to consider recommending prophylactic surgery. And we still don't have a good screening test.

We really, really need a good screening test for ovarian cancer. It's still not something that we have. So this is a hard question to answer. And the bottom line is it's important to have a conversation with your doctor and discuss. There are pros and cons of having the ovaries and tubes taken out, and you can weigh those with your doctor and figure out if this is something that makes sense for you to do or not. But there really is not going to be one answer that fits all. This is going to be something that people will approach differently.

I'm going to stop sharing, and we'll see if... It looks like there are questions in the chat. Do you want to-

Jenna Fields:

Yes, Peggy. So thorough, and I learned so much. Let's go to the chat. Peggy, can you tell us if JScreen or Color go to Canada? It's a very simple question to start with.

Peggy Cottrell:

Yeah. I know that JScreen does not test people in other countries, and that's because their system is set up where you need a US physician order to get the testing done. You don't need to have insurance. If you don't have insurance, you will have to pay more at JScreen, but you can still get the testing done without insurance. If you are looking to have the test done and you are in Canada or another country, you may be able to get testing at Invitae, and that's another lab. And if that's something you want to do, then you can set up an appointment with me and I can give you more details about how you can pursue that.

Jenna Fields:

Great. My VUS downgraded. Shared, I worry it'll be upgraded in the future.

Peggy Cottrell:

So certainly anything is possible, but I think once evidence starts to add up that is leading towards the VUS to be downgraded, they don't do that just on a whim or on a shred of evidence or one family. Or there's usually significant evidence when they take the step to reclassify. I would say you can feel pretty comfortable not worrying about it, especially because ongoing people who have that thing that was reported to you as uncertain are not going to get any report at all. So again, I think you can feel if your variant has been reclassified to not being of concern, I think you can take that as meaningful. But what you... Again, we'll remind you if you have a strong family history, you may still have to be concerned about an increased risk.

Jenna Fields:

We have a few minutes left. Interesting question. If you have both BRCA2 plus a low penetrance other mutation and a VUS, does the BRCA2 risk overwhelm significantly any other mutations?

Peggy Cottrell:

Usually with BRCA1 and 2, the risk from those is so high that it tends to outweigh other things. So even if someone has, let's say someone has BRCA1 and CHEK2 or BRCA1 and ATM, because the risks are similar, they don't add up. It's just that the risk that's higher is the one that you follow. And that usually means BRCA1 and 2. Sometimes people will even have a BRCA1 and a BRCA2 mutation, and you might think, "Oh my goodness, their risk must be 10 times as high." But actually, it's similar to the worst of both BRCA1 and 2, but they don't add up.

So for things that the risk is higher with BRCA1 one ovarian cancer, that would be higher. But then things where BRCA2, the risk of pancreatic cancer is higher. So that person would have the higher risk of both, but not necessarily anything additive. If you have an uncertain variant and a big ticket mutation, then you could feel more comfortable ignoring the variant unless it's associated with totally different kind of cancer. And then you may want to pay attention. So for example, if it's an uncertain variant that predisposes to colon cancer, then maybe be cautious about colonoscopies.

Jenna Fields:

Because colon cancer is not associated with BRCA?

Peggy Cottrell:

Because colon cancer is not increased with BRCA1 and 2 to any significant extent.

Jenna Fields:

So a follow-up question from someone was, if you tested for BRCA1 but it was 14 years ago, is there a reason to be retested for other mutations?

Peggy Cottrell:

If your results were negative, then it absolutely makes sense to be retested because there could be something else that we identify. But if your result is positive, then the only time I would recommend being retested is if there was evidence that there was some other pattern of cancer in your family that's

not described by the BRCA mutation. So if you had a BRCA mutation, but then on the other side of the family there was a lot of colon cancer, endometrial cancer, and ovarian cancer, then that could be Lynch syndrome. And it could be that you also inherited a Lynch syndrome mutation, and that would be important to know. That's not super likely, but that would be a case where even if you had previously tested positive, you may want to consider an upgraded test.

Jenna Fields:

Okay. So we are over time. I'm going to ask you a few more questions, but I'm going to ask the ones that are a little bit more general. Anyone who's asking more specific questions, again, Peggy is available to answer questions one-on-one and we'll keep putting her information in the chat so you have it. How often should you be following up with your provider to check on updated VUS classifications?

Peggy Cottrell:

It probably makes sense to check in with them, I would say, once a year. Now, if you speak to your provider and they tell you, "I will notify you if your result is reclassified," then you don't need to keep calling them and checking in because they will let you know. But if you either suspect they won't let you know or if they have told you that they don't generally recontact people when results are reclassified, then it's on you. And I think calling once a year is reasonable.

Jenna Fields:

This person wrote that they had tested negative for a particular gene on one test. It was found to be okay. But on another test, it was found as uncertain. So should someone in that kind of scenario get tested for a third time? And how do they manage conflicting information?

Peggy Cottrell:

That would be that in a situation like that, you want a genetic counselor to look at those results and try to understand why they are different. So is it a case of labs that have a conflicting interpretation but it was the same thing that was found? Or was something found by one lab that was missed by another lab? And that's a complex question where you really need somebody to take a look at all of those results and try to put together exactly what's going on.

Jenna Fields:

Can you explain why it would have been missed and the importance of lab quality?

Peggy Cottrell:

Yeah. So even amongst the very high quality labs that do most of the testing in the United States, there can be certain labs that will find something that other labs can miss. There are labs, for example, that do RNA testing. And so when you have your sample drawn, and this kind of testing is not done with saliva and you can't get RNA out of saliva, but if you get an RNA test done, there are two different kinds of tubes that blood is drawn into. And one does a better job of preserving the RNA, and that test can sometimes find things that other labs miss.

Now, that's not a case where the other labs are not doing a good job or making a mistake. This is a lab that has an add-on that's able to find a few things that may be missed at other labs. But it's certainly really important if you're interested in finding out important information about your health that you not go with a fly by night or direct to consumer, but go with one of the top several labs that do most of the

testing in the country. I generally tell people, and again, I don't want to criticize Labcorp or Quest because they are fantastic labs for what they do, but they're generally not good at genetic testing. Their genetic tests are not great. Some insurances will only cover testing through Quest or Labcorp and that's not ideal, and that can be a case of poor quality.

And obviously, things that are ancestry-related are not done in any way that are going to really be able to find the majority of mutations that are predisposing to disease. Those are really in a totally different category and are great for finding missing relatives and finding out if you actually have Native American ancestry or are you really 99.9% Ashkenazi and all those kind of interesting things. But if you're concerned about disease, make sure you talk to a genetics professional about the right place to have your testing done.

Jenna Fields:

Okay, Peggy. Well, thank you so much for this presentation. I know that like I mentioned, there were some more personal questions in the chat, so please reach out to Peggy. This is what she does at Sharsheret, and it is a privilege to be able to provide this free service by phone and email for our community across the United States and Canada and Israel and UK and all the other places where we know that you've answered questions from.

So again, as we're wrapping up, we're going to put her contact information in the chat one more time. Email genetics@sharsheret.org. And as a reminder, our peer support program is also available to you if you're interested in connecting with other people who are facing hereditary risk for breast or ovarian cancer. And our genetics program website has really robust information and access to all of our previous national webinars, including the one targeting men that we put in the chat earlier.

We have some upcoming webinars this month, including Ask Beller Nutrition - Answers to Your Burning Nutrition Questions. And I know that Rachel is particularly skilled at addressing questions related to people who have increased hereditary risk for breast cancer, not just people who have been diagnosed with breast cancer. So that is a great webinar to participate in among other webinars coming up, including Navigating a Gynecologic Cancer Diagnosis on January 24th.

I want to thank Sari Abrams again for sharing her story. And I want to thank our sponsors for this webinar, AstraZeneca, the Basser Center for BRCA, The Max and Anna Baran, Ben and Sarah Baran, and Milton Baran Endowment Fund of the Jewish Community Foundation of Los Angeles, the Siegmund and Edith Blumenthal Memorial Fund, and Cooperative Agreement DP19-1906 from the Centers for Disease Control and Prevention.

Please take a moment to fill out the survey from tonight's webinar. We're putting that survey link into the chat, and it'll allow us to learn a little bit about your experience and what you might be interested in for future webinar topics. We look forward to continuing this conversation with you. We'll always be updating. Every year, we do an annual genetics webinar, so please stay on our list. Contact us if you have any questions. And Sharsheret is also here to provide emotional support for you along your cancer journey. We know that this is not an easy topic, and we are here to hold your hand and provide support. Please don't hesitate to be in touch with our clinical team, and my colleague Bonnie will be putting our clinical contact information in the chat box as well.

And finally, as a reminder, the information provided tonight by Sharsheret and tonight's speaker is not a substitute for medical advice or treatment for specific medical conditions. Always seek the advice of your physician or qualified healthcare provider with any questions you may have regarding a medical condition. Thank you again and have a wonderful evening.