Beyond BRCA:

What Do These Results Mean For Me?

National Webinar Transcript

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Presented by:

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Melissa Rosen: Thank you for joining us tonight. We're going to get started in just a moment. I see a couple of people are just joining now. Perfect, thank you. Thank you for joining us tonight for an important conversation about hereditary cancer and mutations beyond BRCA. My name is Melissa Rosen, I'm the Director of Training and Education at Sharsheret. Before we begin, I have a few housekeeping details I would like to share. First, I want to thank our event sponsors. Without them, these programs would not be possible. So thank you to AstraZeneca, to The Max and Anna Baran, Ben and Sarah Baran, and Milton Baran Endowment Fund of the Jewish Community Foundation of Los Angeles. Thank you to The Basser Center for BRCA, The Edith and Siegmund Blumenthal Memorial Fund, the Cooperative Agreement DP 19-1906 from the Centers for Disease Control and Prevention, Eisai, GSK, The Marcus Foundation, Merck and Seagen. And I want to thank our two wonderful community partners on this program. Thank you to Share and to Jscreen.

This webinar is being recorded and will be posted on Sharsheret's website along with the transcript. As always, participants' faces and names will not be in the recording, and of course, you can choose to hide your video and even rename yourself on your Zoom square if you wish. All participants were muted upon entry. Please keep yourself on mute throughout the call. We received a wide variety of important questions ahead of today's program. Toward the end of the program, there will be an opportunity to get questions answered with a Q&A session, but if you have questions that arise during the presentation, please include them or type them into the chat box and we will add them to our list of Q&A questions. We'll answer as many as we can. Please note that no questions will be answered in the chat box itself.

As a reminder, Sharsheret has been providing telehealth services to the breast and ovarian cancer communities for 20 years. In addition to our many programs to help women and their families navigate different aspects of the cancer experience, our clinical social workers are available for one-on-one support. As we move into the webinar itself, I want to remind you that Sharsheret is a national not for profit cancer support and education organization and does not provide any medical advice or perform any medical procedures. The information provided by Sharsheret is not a substitute for medical advice or treatment for specific medical conditions. Of course you should always seek the advice of your physician or qualified medical health provider with any questions you might have regarding a specific situation.

As we begin the webinar, I want to introduce you to a wonderful Sharsheret caller, Marcy Wintrub. She's going to share her story which is so important for so many reasons and you'll hear those themes repeated when our main speaker speaks tonight. So Marcy, thank you so much and welcome to the webinar.

Marcy Wintrub: Thank you, and hi everyone. In my late 40s, I lost my father to brain cancer. My mom died in an accident a few years later and my brothers and I went down to

Florida, we were packing up their house, and one night, I began experiencing really awful abdominal pain. It was so bad my brothers took me to the emergency room. The doctor checked for all the obvious causes but found nothing. He actually told me it must be gas. So by then, I was feeling better and I kind of slinked away.

A few months later, I was on vacation with my family in Nova Scotia and it happened again, that abdominal pain. But I didn't go to the hospital because I didn't want to be told, "Oh, you have gas." But after a sleepless night and the pain just did not go away, I finally gave in and went and I have to say, I have to give full credit to the Canadian healthcare system. They are the ones who found a tumor in my ovary.

So within a few weeks, I was a patient at Dana-Farber and by then I had developed this really bad ascites, fluid built up in my abdomen and my imaging results seemed to indicate that there was a spread to other organs. The thing was though that they wouldn't know until I got through my surgery, and I remember praying right before surgery, "Oh please, just let it be stage three," because that was really the best outcome that I could even imagine at the time. But when I woke up, the unimaginable happened. It wasn't stage three, it wasn't even stage two, it was stage one, and they had found a simultaneous cancer, not a spread in my uterus, also stage one, and that was it.

So after surgery, I went in for genetic testing and because of the ovarian cancer and because of my Ashkenazi background, I was pretty sure that they'd find a BRCA mutation, but they didn't. And after a few rounds of chemo, I just went on with my life, very aware of how lucky I was. That was in 2009.

Last year, I didn't let the pandemic keep me from my annual mammogram, and that was a good thing too. Because they found what turned out to be invasive ductal carcinoma, also stage one. When my new oncologist suggested genetic testing, I said, "I already had it. They didn't find anything." She explained things had changed a lot in the last decade, and did they ever. My results came back with a big red pathogenic MSH6 mutation, Lynch syndrome. The term was new to me but I quickly got myself up to speed, and I just as quickly saw red flags in my history that could have and to me should have predicted this outcome. In 2009, gynecologic cancer was already known to be a sentinel cancer for women with Lynch syndrome, and a finding of two concurrent gynecological cancers was a near giveaway. Even my father's brain cancer was a known Lynch related clue. It was so obvious in retrospect I could not understand why I wasn't tested for Lynch in 2009, or in any of the 12 years since then, and I was furious that the only reason I had found out at all was that I've gotten another cancer.

Once I found out, several other members of my family, including my children, did too. My aunt says I saved her life because screening found early stage cancer in her kidney. My daughter found precancerous growths, a good 15 years before her first colonoscopy would normally be scheduled. Neither screening

would have happened without my breast cancer diagnosis and subsequent genetic testing.

People don't always understand when I say how lucky I am though I think this group might be the exception. I've had cancer, but I've never had to fight cancer, and that was pure luck in my case three times over. But my children won't have to rely on luck. They have knowledge and they're taking action. They're getting screened to find cancer before they have to fight it. Roughly one in 300 people are thought to have Lynch syndrome, but of these, fewer than 2% know it and get the screenings they need to find issues early. I'm so glad that Sharsheret is here to spread the word about this and similar conditions. I am so grateful to this organization and to Peggy for providing such wonderful life-saving support, and I thank you all for letting me share my story and my good luck and I hope it makes a difference. Thank you.

Melissa Rosen: Wow. Marcy already, I know it's made a difference. I know, listening to your story, so many of the things that Peggy's going to share tonight about the changes and about how people only think about BRCA and things like that, thank you. You've really clarified some of the issues and I know it will help people understand what Peggy's about to talk about. So thank you very much for being with us tonight.

Okay. Tonight's headliner is as you heard Peggy Cottrell. That's exciting to me for two reasons. First, I know Peggy well because as a certified genetic counselor, she coordinates Sharsheret's genetic program. And second, it's exciting to me that Sharsheret has such a valuable resource on staff. Peggy is a graduate of Sarah Lawrence College of ... She has a masters of science in their genetic counseling program. At Sharsheret, Peggy consults with women and families and answers individuals' questions about their family history, hereditary mutations including BRCA and many others, talks about personal risks of hereditary breast, ovarian cancers and other cancers. She also holds virtual family conference calls to address the concerns and questions of everyone in a family where there is a known mutation. And just like all Sharsheret's clinical support programs, every part of our genetics program is customized, confidential, and 100% free. Peggy, thank you so much for tonight's presentation and all of the work you do with the families of Sharsheret.

Peggy Cottrell: Melissa, thank you for that very kind introduction and thank you Marcy for sharing your story which was so amazing and while we're talking about sharing I'm going to share my screen and begin tonight's presentation. Okay, good.

Okay, so tonight, we're not going to spend most of the time talking about BRCA1 and 2, which is normally what we do, and that's not because they're not important, so we will certainly give them a few words. BRCA1 and 2 mutations occur in all populations around the world. I had a caller just last week who was Asian ask me, "Is it very unusual for someone Asian to have a BRCA mutation?" It's not unusual, it's not unusual around the world to see these mutations. But in the Ashkenazi Jewish population, there is a much higher risk, so it's one in 40

compared to one in 400, and as always, you want to remind people that men are just as likely as women to carry mutations in these genes.

So this is a chart that compares different types of risk, and I'm going to explain this very carefully. It looks like a bit of a confusing chart but it's actually pretty straightforward. If you start on the left hand side near the top, you see genes like TP53, BRCA1 and 2, PTEN, we're going to talk about these genes tonight, and they are rare to very rare, high risk alleles, and those are genes, alleles are genes that are predisposing to cancer. So they're rare but their risk is high. Then as we move over to the middle, we see rare moderate risk alleles. Now these are less rare, so these are some of the other things we're going to talk about tonight, BRIP1, ATM, PALB2, and CHEK2. And then as we move down, we see common low risk alleles and these are the changes that can occur very commonly amongst many, many people. But the risk that goes along with these mutations is very, very small. So having a change in one of these genes might only increase your risk for breast cancer by a quarter of a percent, very, very tiny risk.

But what can happen in many families is that a whole lot of these can accumulate and eventually, as many as hundreds can add up to enough risk that it can be as much as some of the moderate or high risk alleles. So we're going to talk about all these different kinds of testing and these different genes. So again, panel testing is going to look at the ones on the left, the very rare and high risk and more moderate risk, and then polygenic risk scores are going to look at the ones on the right. We're going to talk about all of those today.

So many genes and many cancers, so as I said, most current testing nowadays is done as a panel. There are multiple genes that predispose to multiple cancers. So here, first picture, these two pictures look a little bit like flowers. The one on the left we see breast cancer in the middle, and surrounding it, we see a whole bunch of different genes that can be predisposing to breast cancer, and I won't read through them all because you can read them and we're going to talk about them tonight. But what we see also in the second flower, we have a single gene, TP53, and we'll talk a little bit about this gene, and this gene can predispose to lots of different kinds of cancer, in this case, all of these cancers could be increased. And so we're going to talk about some of the other genes that are on the panel besides BRCA1 and 2, and what the implications are for those specific changes.

And one thing I'm going to mention right up front, this is a little family tree. Very often we look at family trees in genetics to try to figure out what's going on in the family, but the point here is that each of the genes we're going to talk about tonight, they will be ... If someone is a carrier of that mutation, there's going to be a 50% chance to pass that mutation to the next generation. I'm not going to mention that fact each time that I do a gene because I'm going to start out here by telling you that all the ones that we're talking about tonight are going to work in that same fashion.

So I mentioned TP53 and that's going to be the one that we start with, and when someone has a mutation in that gene, it's called Li Fraumeni syndrome, and one thing that's interesting in genetics, genetic physicians seem to like to name diseases after themselves, and that's just the nature of genetic doctors, I don't know why.

Okay. So fortunately TP53 is very rare as an inherited mutation. But in these days of tumor testing, we find that if the tumor is tested to look for mutations that could be targeted with therapy, TP53 is a very common change in a tumor, and that's because it's an incredibly important tumor suppressor. It helps to regulate how the cells divide and by regulating cell division it helps to prevent cancer and so it's very commonly a mistake that can happen in our body cells that can eventually lead to cancer, but again, most of the time, is not inherited.

When it is inherited, most commonly the cancers that are seen are female breast cancer, central nervous system tumors, specifically tumors in the brain or in the spinal cord, sarcomas which are a rare kind of cancer, or adrenal cortical tumors. That's a gland that sits on top of the kidney. Now one of the really terrible things about TP53 mutations is that they cannot only cause cancer in adults, but they also cause cancer in children. So in this case, I know I've told many, many people if they have a BRCA mutation, we're not going to test their children, we're going to wait until they're an adult. In this case, we do test children because children may need to have that cancer screening as much as adults do and the screening may include an annual full-body MRI. So fortunately this is rare because this is a very, very difficult inherited cancer syndrome.

So next we're going to talk about PTEN. PTEN is the name of the gene and the syndrome is called Cowden syndrome, and this is also rare. It's maybe a little bit less rare than TP53, but one of the interesting things about PTEN is that somewhere between 10 to as much as 50% of the time, it's de novo, and what de novo means in this situation is that someone has the mutation but it didn't come directly from their parents. So there was a mutation that occurred either in the egg or the sperm that formed that person and so they have the inherited condition and they can pass it to their children but it's not from their parents.

Now with PTEN, one of the most common cancers is breast cancer, but we also see thyroid cancer, uterine, kidney or colon cancer. And so people who have PTEN hereditary cancer need to have screenings for all of those kinds of cancer, and then finally sometimes in rare cases, there are mutations in PTEN that can cause either developmental delay, which is an intellectual disability, or autism. And so if there's a combination of those things as well with these cancers, that's something that can be also tested for.

So next I'm going to talk about Lynch syndrome and Marcy did a great job introducing Lynch syndrome to all of you. Lynch syndrome can be caused by five different genes and I won't read all of their names, they're at the top, and the risk for cancer is going to depend on which of the genes somebody carries. So there's a higher risk with MLH1, MSH2 and EPCAM. There is an in-between risk

with MSH6 and a lower risk with PMS2, and I think especially because there are five different genes that are involved, the risk is more like about roughly one in 300 people in the general population are carriers and I don't think ... I wasn't able to find any evidence of any population that's affected more by Lynch than any other population, so this is something that's common again throughout the world.

So the most common type of cancer that we see with Lynch is colon cancer, and the second two are uterine and ovarian cancer. More rarely, there can be stomach cancer, cancer of the small bowel, urinary cancers like kidney, brain cancer, biliary cancer which is the ducts related to the liver, pancreatic cancer and cancer of the sebaceous glands which are glands that are in the skin.

So the screening, when someone has Lynch syndrome, involves actually an annual colonoscopy. So those of you who have to have a colonoscopy every five years and complain about it, once a year is very difficult. But it's really important and that's because what happens with Lynch syndrome, people who have Lynch syndrome are not any more likely than the average person to get a colon polyp. But if they get a polyp, it can change very quickly from being a benign polyp to being cancer, and so the screening has to be done on that very regular basis in order to be able to catch the cancers before they become more serious.

Now with this, Lynch syndrome, women may consider having risk-reducing surgery. So if someone instead of having screening for uterine cancer and screening is not very good for ovarian cancer, those women may consider having a total hysterectomy. There isn't a specific age at which that's recommended but generally it doesn't have to be done at as young an age as it's recommended with BRCA2 or BRCA1.

So next we're going to talk about APC, and APC is another gene that's associated with colon cancer. And I'm telling two stories here of two syndromes. First I'm going to talk about what we typically see with APC typical mutations. And so typically, this is a rare colon cancer gene and what it causes differently than Lynch syndrome is hundreds to thousands of polyps. So people who have a typical APC mutation, if they have a colonoscopy and this is sort of a cartoon picture of a colonoscopy, where you see one polyp. Somebody might have hundreds of polyps. So many that it would be impossible to remove them one by one and very often people who have a mutation in this gene have to have their entire colon removed, which is very serious.

There are also risks for other cancers. Cancer of the small bowel, the stomach, the pancreas, the thyroid, and the brain, and this is another type of cancer where children can be affected, and so hepatoblastoma is a rare kind of liver cancer that can occur in children, and so children age six and under who have an APC mutation would have to have careful liver cancer screening, which generally involves I believe it's an ultrasound of the liver.

Okay, so that's the first syndrome we're talking about. The second one I'm going to talk about is the same gene, APC, but instead of a typical mutation, there's something called a risk allele in as many as 6 to 10% of Ashkenazi individuals. So this is a change that's in APC, but it doesn't cause the typical pattern with hundreds and thousands of polyps. It causes a subtle increased risk in colon cancer. Now the name of this risk allele, it's actually named for the change that happens in the protein and that's called I1307K. So most people would have the amino acid I at the 1,307th position, but people who have this change have the K amino acid instead. And people who have this change don't get small bowel, they don't get hundreds of polyps, they don't get stomach cancer, pancreatic cancer, all of those. But they do get an increased risk for colon cancer. That risk goes from about 5 or 6% which is the average risk for colon cancer up to about 10 to 12%.

So definitely an increased risk, but this is more subtle. Most people who have the I1307K mutation or change in APC will not get colon cancer, will not get any cancer. But this becomes one of the most common things that I talk about amongst callers because a lot of people with Ashkenazi ancestry are going to have this finding and it's really important to make sure that they understand that this is not the same thing as APC.

So next we're going to talk about PALB2, and PALB2 has an interesting name, it's sometimes fun to find out why genes are called a certain thing. PALB2 was named because it's the partner and localizer of BRCA2, and I kind of like to think about it that it's a pal, a buddy of BRCA, and that's why when we say the name PALB2, we don't say PALB-2, it's pronounced PAL-B2.

So this PALB2 is a more moderate gene but it has similar risks but slightly different than BRCA2 because it works with BRCA2 in the body to help maintain the integrity of our DNA. So most commonly people with PALB2 mutations have an increased risk of breast cancer. There's also an increased risk of pancreatic cancer and there may be an increased risk for ovarian cancer but if there is it's more subtle. It's not super clear whether or not there is a significant risk of ovarian cancer.

Now one of the things that can happen with more moderate risk genes is that you can inherit two copies of them. Now interestingly, I'm going to start off with an aside. If someone inherits two copies of BRCA1, they're probably not even going to be born because BRCA1 is so important that the embryo is not able to develop correctly if there's no BRCA1 working within the embryo, and so that would be an early miscarriage.

But it's possible if the child inherits two copies of BRCA2 that they will have Fanconi Anemia, and the same thing happens when a child inherits two copies of PALB2. And so it can be important when someone has a cancer gene to find out if there are reproductive risks as well, and there is some overlap between things that we think of in terms of carrier screenings and things that we think of in terms of risk for cancer, and PALB2 is an example of that.

Okay, so now we're going to move on to ATM, and this gene has nothing to do with getting money out of the bank. It's a moderate risk gene. Most commonly the risks for cancer are female breast cancer, pancreatic cancer, and prostate cancer. With ATM the risk is moderate enough that doctors don't routinely recommend a risk-reducing surgery so they're unlikely to recommend if you don't have cancer that you consider having a double mastectomy. When I learned about this gene when I was going to school, I learned about it first in terms of the disease that happens when you inherit two copies. So two copies of the ATM gene will lead to a disease called Ataxia Telengiectasia and this is a disorder which is sort of pointed out by the picture on the right. There are deficits in neuron development, deficits in the immune system. There can be cancer in children, radiosensitivity. So these are children who can't spend a lot of time outside because it damages their skin.

Now when I was going to school, we learned about Ataxia Telengiectasia and then we also learned by the way, people who are carriers for this disorder may have an increased risk of breast cancer, and that's what we now know and now testing is available for ATM and we find maybe about one in 100 people are carriers of ATM.

Next we're going to talk about CHEK2. This is another moderate risk, you see maybe about one in 100 people in the general population are carriers for a CHEK2 mutation. Mutations in CHEK2 most commonly increase the risk for breast cancer, colon cancer, and prostate cancer. There have been some documented risks for a couple other kinds of cancer, possibly thyroid, possibly kidney, but the main ones are breast, colon and prostate.

The thing that's interesting about CHEK2 is that there is variability amongst families. So sometimes a family will have a CHEK2 mutation identified, but there's very little cancer in the family. And it may be that those individuals are at significantly less risk than other families where we see lots of people in the family with breast, prostate or colon cancer. But the interesting thing is also with CHEK2 is that sometimes in those families where there is a lot of cancer, the cancer doesn't necessarily go along with people who are carrying the mutation. So in other words, there might be someone who has a CHEK2 mutation and they don't end up developing cancer, while a sibling let's say who did not have the mutation does end up developing breast cancer. So we know that other things that we don't know how to look for yet that may be carried in families could be having a significant implication with CHEK2.

Now the other thing that's interesting about CHEK2 is that different kinds of mutations can cause different risks, and so there's a founder mutation, one that's common in the Ashkenazi population. It has two names, sometimes gene mutation names come from the DNA, so at the 1,283rd position a C, one of the building blocks of DNA is changed to a T. Or the P name, S428F, that's named after the protein.

And with this particular change, the risk is much more moderate than mistakes where the protein product is significantly damaged. So with some mutations, there's a small difference and so here, as the protein is built which should be an S, it's an F instead, that's a more minor change than something that stops the finished form of the entire protein. And so depending on the mutation that's identified, some cause higher risk than others.

Now this particular one is very confusing because the major labs in the United States are not even in agreement on how to classify it. So some of the big labs will call this finding an uncertain variant, which means they're not sure if it's increasing risk or not. Others call it a reduced penetrance mutation, so something that does cause risk but maybe not as much as some other mutations. And others call it likely pathogenic, and so it can be very confusing in families when people say, "I got tested and I had something uncertain. I got tested and I had something that was a mutation," and it turns out that those are the same thing.

And so it's really important, especially with CHEK2 when you have a mutation, that you spend some time talking to a genetic counselor about the specific implications of the address of the mutation. Where it's located within the DNA and what that in particular might mean in your particular situation, and again, because this Ashkenazi founder mutation is common in people with Jewish ancestry, I end up talking to a lot of people about this particular one.

So next I'm going to talk about BRIP1. BRIP1 is a moderate risk gene that elevates the risk of ovarian cancer. Not as high as 10%, so not a huge risk. The general population risk for ovarian cancer is about 1 or 2%, so a significant increase but still not super high. It may not be increasing risk for breast cancer and women who have this can consider removing their ovaries and tubes somewhere between age 45 and 50. And when a child inherits two copies of BRIP1, they will have also Fanconi Anemia. Fanconi Anemia comes in a bunch of different versions and BRIP1 is one of them.

RAD51C and D are two other genes that cause a moderately elevated ovarian cancer risk, somewhere between 5 to 15%. There may also be a slightly increased risk for breast and prostate cancer with these genes and similarly to BRIP1, women may consider risk reducing removal of their ovaries and tubes somewhere around age 45 to 50. Now when a child inherits two copies of RAD51C, they will have Fanconi Anemia, but interestingly, no evidence that the same is true for RAD51D.

Okay, so we're done talking about genes outside of BRCA1 and 2. I'm just going to briefly talk a little bit about polygenic risk scores. So these are the genes that I mentioned early on that are common that only make a small difference in risk, and these are called SNPs, which stands for single nucleotide polymorphism. And what that means is that if we looked at the entire population at a particular location in a gene, there might be 40% of people who at that specific location would have A, and there might be another 20% that have G, and then another

40% that have T. And maybe it turns out that those people in the middle who have the G, they have a slightly, very slightly increased risk to develop certain kinds of cancer. Now that finding by itself doesn't mean anything, but if you look at hundreds of these SNPS, you can come up with a very sophisticated calculation that can try to determine what your risk for certain kinds of cancer are.

Now there are polygenic risk scores that are available out there for breast cancer and also for prostate cancer. There is evidence that they are useful and do work, but not strong enough evidence yet that insurance companies want to cover the cost of increased screening when those results are high. And so we based the need for high risk screening on the pattern of cancer in a family and that's why we always want to be extra careful about screening when there's cancer in a family, even if we don't find anything inherited, because we're concerned exactly about these SNPs, and that there's an increased risk related to things we don't know how to look for yet.

So perhaps you need an updated test. Maybe you had BRCA1 and 2 testing done a long time ago. You might have been tested only for founder mutations. You might have been tested with an older technology like PCR that might not have included duplication and deletion testing, and you might not have had a panel test that includes the other genes that we spoke about, and if you think about Marcy's story, you can understand why it might be a good idea for someone to have that updated testing done. And so very often that's going to be recommended.

Now if somebody had testing for BRCA1 and 2 in the past and tested positive, then there's less need for an updated test. The only time we recommend an updated test in that situation is if there is an additional pattern of cancer in the family that would not be explained by the BRCA1 or BRCA2 mutation. So for example, if I had a BRCA1 or 2 mutation that I perhaps inherited from my father's side but then somehow on my mother's side, there was a whole bunch of colon cancer that would not be explained by that, it was the other side of the family, then I might consider having additional testing done.

I want to take a moment here to just mention again about men. Now some of the syndromes that we spoke about tonight are just as much a risk for men as for women. The colon cancer genes that we talked about for example. But some of them really are more risk for women and not for men, so when we spoke about BRIP1 and RAD51C and D, I just want to remind everyone that men are just as likely as women to carry those mutations, even the ones that seem to mainly affect women, and that women who have any of those mutations that have been identified have the same chance ... Half of them would have inherited it from their father and half of them would have inherited it from their mother, and finally, that unaffected men or women can pass mutations to their sons and to their daughters. And so it's important for all of us to be educated about these genetic mutations.

So some people worry about testing and they're concerned that their insurance company might cancel their medical coverage if they test positive. Well thankfully, that doesn't happen, and there was a law passed in 2008 that's called GINA, the Genetic Information Non-Discrimination Act. And this law protects us from a genetic finding being called a preexisting condition. Now this law was passed well before the Affordable Care Act, and was signed by the second President George Bush. It is popular among Democrats and Republicans. So this is a strong law, a lot of its protections were confirmed in a stronger way by the Affordable Care Act. But what none of those laws protect are life, disability or long term care insurance, and so it's possible when you apply for these kinds of insurance, they're going to ask about your health and they're allowed to ask about it and they're going to ask about your genetic testing. And that's because if you know something that the insurance company doesn't know about your health, that can put the life insurance company or other insurance at a disadvantage.

Speaker 4: Whoops, sorry. It's not on mute, so why can't I hear anything?

Peggy Cottrell: So if you have questions about this law, there are some URLs here that can possibly help you. Or I'd always be happy to hear from you and answer more of those questions.

So I just want to point out again the importance of genetic counseling. Understanding the pros and cons is something that genetic counselors can help you with in terms of getting a test done. We can help make sure that the test that's ordered for you is the one that's appropriate for your personal risk and is also the appropriate one for your insurance risk so that it will end up being better. And then finally, if you do end up testing positive, we're the ones who can really do a good job explaining to you what the options are for people who are carriers.

Now I want to wind up by talking about at-home testing as we shift through an explosion of COVID again and people are more and more wanting to stay home. The good thing is that genetic testing is very easy to get done from home. So first you could find a genetic counselor online at the website of the National Society of Genetic Counselors, and a lot of genetic counselors now work for remote companies or if they work for a hospital maybe they see people in-person but also remotely.

Secondly, I want to talk about a great organization that offers cancer genetic testing online. That is JScreen. JScreen for years has been offering carrier screening for people who are having children and don't want to pass along things like Tay Sachs, but they now have a cancer test that's a big panel and right now we have a coupon with Sharsheret that gives 100%, excuse me $100.00 discount. But right now at the end of the year, we just found out from JScreen that they're having a special coupon which will expire at the end of the year, it's called CancerGenFreeScreen, and using that code, you can get a full

$199.00 off the cost of the test and that's when you include your insurance information.

So if you go to JScreen.org, you can find out information about the reproductive test, the cancer test, and if you use the special code before the end of the year or if you use our Sharsheret100 code even next year, you get a significant discount and this is a really great buy for a genetic test. So if you're somebody who needs an updated test, this can be a good way to get one done.

And I want to finish up by saying that I've talked about a lot of genes tonight and it could be a little bit confusing and I didn't tell you everything there is to know about each and every one of these, but if you have any questions about whether you need a test, about testing you had done and what it might mean, or where to get genetic testing done, I'd be happy to speak to you. You can reach me at genetics@sharsheret.org and also my personal email, pcottrell@sharsheret.org will be shared in the chat. So I'm going to stop my screen share. Melissa.

Melissa Rosen: Thank you so much. Every time I hear you, I learn something new and I learned a lot of something news tonight. So I appreciate that. We as I mentioned had a lot of questions come in during registration but we also had a bunch of them come in through the chat box. So I'm going to hit you with some participant questions. One that was of particular interest to me as well was, "You spoke a lot about if somebody inherits two of the same mutation, then there is a negative outcome for a child." But somebody asked, "Can a person carry two different mutations themself? Maybe a BRCA1 and CHEK2 or whatever they are, and what happens ... How do they interact with each other, what happens when something like that happens?"

Peggy Cottrell: So that's a very good question and early on when we were only looking at BRCA1 and BRCA2, we would find people who had one of each, and it turns out that with BRCA, having one of each is not much worse than having one or the other. You kind of have the risks of both but not increased from one to the other. So that's part of why we tell people who've already had a BRCA1 or 2 mutation identified on screening that they don't need an updated test. Because if it turns out they have BRCA1 and CHEK2, it's not going to be any different than just BRCA1. So if you have multiple mutations, there are different interpretations, depending on what two genes, what different genes you carry and if it's something like Lynch syndrome, the risks are very different than BRCA and then you could have a lot of risks and have to have a lot of screening. But again, if you're in that situation, you definitely want to talk to a genetic counselor and find out what exactly is the right thing to do.

Melissa Rosen: Thank you, thank you. Another question just came in in the chat as you were answering that one. So somebody noted that one of their doctors wanted just specifically BCRA screening while another one recommended a full panel. At this point, if somebody's getting medical grade testing, do any of them just do BRCA

screening or why would you choose to do just that when a full panel is so common these days?

Peggy Cottrell: So the main situation where I might think you could look at just BRCA1 or just BRCA2 is if you know there's a mutation in a family, and maybe you would just want to see if you inherited what was already there, and that could be significantly discounted. In fact you might get that kind of testing free in some labs. But I think more and more doctors are leaning towards saying, "Let's get a full panel and just make sure that there isn't something else there."

Now the chance of finding something else then is small, but if you find something for which there is actionability which means you would do something differently with that finding, then it can make sense to do. And so it's something you can discuss the pros and cons of that with a genetic counselor. But I think most of the time now testing is done as a panel.

Melissa Rosen: That's helpful, thank you. Somebody asked a question that led me to believe what they really wanted to know was about tumor or biomarker testing and how treatments might be targeted based on those results.

Peggy Cottrell: Okay, that's also a very good question and I'll just mention as an aside that I'm doing a webinar next month with Share that's going to specifically cover this topic. But there are ... When people develop cancer, it's a result of mutations that occur in our body cells that are not inherited. So when you can do a genetic test specifically on the tumor, and that's called biomarker test, the things that are identified are usually not something inherited, they are mistakes that have happened in the tumor, but when there are certain mistakes there, it allows doctors to know a specific medication that can treat that cancer. And so that's what they're looking for when they do biomarker or tumor genetics, and it can be very confusing to people because sometimes we're looking at the same thing. So there could be BRCA1 and BRCA2 inherited, but we also might look at those in the tumor in some cases, and so it can be very confusing, not only to patients but to some healthcare providers and a very important issue. So discuss that with your doctor.

Melissa Rosen: Can you explain why people of Ashkenazi Jewish descent have a higher risk than the average population?

Peggy Cottrell: So there are population factors that occurred over thousands of years and the founder mutations we see in BRCA1 and BRCA 2 that are common in the Jewish population occurred before there was a separation. They occurred more than 2,000 years ago. So we can see the founder mutations not just in Ashkenazi Jews but also in Mizrachi Jews from the Middle East or in Sephardic Jews who are from Spain, but there were specific population factors that occurred in Eastern Europe where the population got very, very small, and by chance, there were more people who carried that mutation and then when the population expanded again, they were concentrated. It's kind of a complex population reason, but that's what it has to do with.

And some of it is just a result of people who are Ashkenazi tended to marry other people who are also Ashkenazi. They didn't marry the other non-Jewish Europeans, and people were not marrying their close relatives but they were marrying people who were their third cousin, and this tends to ... In the same way, we see the same effect with people in Iceland because they are geographically isolated and in communities that have a religious isolation, like Ashkenazi Jews or like the Amish. We see the same problems, so ...

Melissa Rosen: Thank you, thank you. There were several versions of this question, but basically what goes into decision-making? What factors are considered when you're making ... Not treatment decisions but decisions about risk reduction?

Peggy Cottrell: Okay. So when you're deciding, sometimes if people have inherited cancer that's predisposing to breast cancer, they're going to want to have a double mastectomy even though they don't have cancer, and that's just to prevent having to go through cancer. They just want to have that surgery before. But that's always a choice. Even with BRCA1 and 2, there isn't that much difference in survival between having the double mastectomy or having careful screening that includes an annual breast MRI. And so each woman has to think about those decisions and what it means to her, and in my experience very often women who have lost relatives to cancer, who have relatives who have died, are much more likely to choose the preventive surgery because they're very frightened. Whereas other women who may have relatives who got cancer but survived it are a little bit more willing to take their chance on getting cancer and getting treated, but maybe having the chance to never end up having to have the surgery or the treatment.

So these are personal decisions that are made differently and it's one of the things that I often talk about with callers is how to think about this decision, and try to come to grips with what is the right thing for you to do.

Melissa Rosen: Of course. I know in other talks that you've given, that enhanced surveillance and healthy living behaviors also factor into that.

Peggy Cottrell: Oh absolutely. So you can really reduce your risk by eating a healthy diet, by exercising, by not drinking alcohol to excess, not smoking. All of those things make a difference. But the genetics are still powerful and even people who are very careful with lifestyle factors still get cancer.

Melissa Rosen: Thank you. Okay, we have time for one more question which is if someone has had a panel test in the past with no known mutations being identified, and the past could be five years ago, ten years ago, is it recommended to have a repeat screening at this point?

Peggy Cottrell: So that really is going to depend. I think that the panel tests started being offered more broadly in 2013 and that was the year that the patent that was held on BRCA1 and 2 was lost. There was some panel testing before that but the

panels didn't include BRCA1 and 2 so they weren't very popular. But those panels that were started right then in 2013, 2014, those were already excellent panels, and I think for most people, if they had a panel test six, seven years ago, that was probably enough of a test but it's going to depend on factors and so if you're not sure, maybe you had a small panel that was only a colon cancer panel. Because there are smaller panels that are also there. Breast panels and pancreatic panels. You may have had a small test.

The best thing is to be in touch with us at Sharsheret. I'd be happy to take a look at the test that you had done, and a look at your family history as well and figure out if what you had was adequate. Because it can absolutely be confusing to figure that out.

Melissa Rosen: Great advice. We unfortunately are coming to the end of this evening's program. Again thank you all for joining us and thank you to Marcy for sharing your story and of course thank you to our own Peggy Cottrell. The good news as Peggy just mentioned is if you have additional questions, you simply need to connect with Sharsheret and set up an appointment time to speak with Peggy. Which doesn't happen on all of our webinars, so that is the good news.

I also wanted to let you know that we recently launched a Facebook group for you. The Sharsheret Hereditary Cancer Community is for those who have tested positive for a mutation in a cancer predisposition gene or have a strong family history, and it's open to those who are dealing with increased risk and those who have been diagnosed with hereditary cancer. So that's a great source of support and even to get some questions answered it's monitored by Peggy so you might get some questions answered there as well. That link is in the chat box right now. Once again, I want to thank our generous sponsors, AstraZeneca, The Max and Anna, Ben and Sarah and Milton Baran Endowment Fund of The Jewish Community Foundation of Los Angeles, The Basser Center for BCRA, The Siegmund and Edith Blumenthal Memorial Fund, The Cooperative Agreement DP 19-1906 from the Centers for Disease Control and Prevention, Eisai, Seagen, and GSK. And of course, our amazing community partners for this event, JScreen and Share.

Sharsheret is here for you and your loved ones. We provide one-on-one support for those facing cancer, those caring for people facing cancer or those who are dealing with heightened risk. We have programs to help you navigate all parts of the cancer experience. As I mentioned all free, completely private. You can email us at clinicalstaff@sharsheret.org. Please take a moment to fill out a brief evaluation survey that is linked in the chat box right now. The evaluation provides you the opportunity to request additional support and other resources, and you can click the link now and still hear our final thoughts, and this is our final thought. I wanted to let you know that we have several exciting webinars on a wide range of topics planned for the start of 2022 including the one that Peggy mentioned, a second one that we're partnering with Share. We will post that link, it just got posted in the chat box and you can also access recordings

and transcripts of past webinars by clicking the same link. Thank you again and have a wonderful evening. Good night.