

New Recommendations for Genetic Testing: How Do I Make Sense Of It All?

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I. Introduction

June Mandeville: Good evening, everyone. I hope everyone is having a wonderful holiday season. I want to welcome all of you to Sharsheret's national webinar, *New Recommendations for Genetic Testing: How do I make sense of it all?* We're excited that so many of you have joined us tonight, and that so many states across the country are represented this evening. My name is June Mandeville-Kamins, and I am the Senior Support Program Coordinator for Sharsheret. I'm so happy to be here with you this evening, moderating tonight's webinar. We would like to thank Myriad Genetics, the Sigmund and Edith Blumenthal Memorial Fund, and the Cooperative Agreement, DP14-1408, from the Centers of Disease Control and Prevention, for their ongoing support and for sponsoring tonight's program.

We would also like to thank our partners in collaboration with tonight's event. Bright Pink, Cedars-Sinai Medical Center, Holy Name Medical Center, and FORCE, Facing Our Risk of Cancer Empowered. Sharsheret supports young Jewish women and families facing breast and ovarian cancer at every stage. We help you connect to our community, whatever your personal background, stage of life, genetic risk, diagnosis, or treatment. We receive many calls at Sharsheret from women and men who are trying to make sense of genetic testing. Is it something they need to do? Is it something they need to investigate? Most of the time, genetic testing is done through healthcare providers, such as physicians, nurse practitioners, and genetic counselors. But with the advent of direct-to-consumer genetic testing, providing people access to their genetic information without necessarily involving a healthcare provider or health insurance company, it can be a challenging time to determine which tests will be most informative and helpful to you.

Suppose you do genetic testing, and the results are positive for genetic mutation. What does that mean for you and your family? What decisions are you facing, and what are your options? This webinar will discuss the latest recommendations regarding genetic testing. We recognize that those of Ashkenazi Jewish descent, meaning those who have ancestors from Eastern Europe, can experience heightened concern about this information, because of an increased genetic risk. As many of you know, one in 500 individuals in the general population carry the BRCA mutation. For those individuals of Ashkenazi Jewish descent, that number is one in 40. Ashkenazi Jews are 10 times more likely to carry the BRCA mutation, resulting in as high as an 88% lifetime risk with being diagnosed with breast cancer, and as high as a 45% lifetime risk of being diagnosed with ovarian cancer. We at Sharsheret are always confronted with questions from our callers, asking for clarity in genetics in the news. Tonight's webinar is designed to help you make sense of the latest recommendations for genetic testing.

One last thing before I introduce our speakers for the evening. You can ask questions throughout the webinar by typing in the question box on your dashboard on the right side of the screen. Please keep your questions broad in nature so that everyone on the call can benefit from the discussion. We will try to get to as many questions as we can after the presentation. Those of you who are not joining us via computer, please know that you can call Sharsheret at any time with your questions, and we will be happy to discuss them with you.

Now it is my absolute pleasure to introduce our first speaker, Dr. Beth Karlan. Dr. Karlan is the Director of the Women's Cancer Program at the Samuel Oschin Comprehensive Cancer Institute, director of the Division of Gynecologic Oncology and the Gilda Radner Hereditary Cancer Program, and holds the Board of Governor's Chair in gynecologic oncology at Cedars-Sinai Medical Center. She is also a professor of obstetrics and gynecology at the David Geffen School of Medicine at the University of California in Los Angeles. She is a full-time faculty member at UCLA, where amongst other things, she is the Director of Cancer Population Genetics.

Dr. Karlan's research focuses on ovarian and other women's cancers, as well as inherited cancer susceptibility. She has authored over 300 research publications and is an American Cancer Society clinical research professor. She is the editor-in-chief of the scientific journals Gynecologic Oncology and Gynecology Reports. In 2012, Dr. Karlan was appointed by the White House to serve on the National Cancer Advisory Board, and in 2015, she was elected to membership in the National Academy of Medicine. Dr. Karlan, over to you.

II. New Guidelines and Research In Genetic Testing

Dr. Beth Karlan: Thanks so much, June. Welcome to everybody across the country. Again, I'll echo the happy holidays and congratulate you on taking this time to be empowered with new information to protect you and those who you love. June really set this up perfectly, and I'm going to go through some things that really you would do with the information. Then I know our next speaker is going to speak some more about the direct-to-consumer genetic testing and other genetic testing. We'll get right into it.

Just in this era of conflicts of interest, I do serve on a scientific advisory board for genetic testing company called Invitae, but that really does not influence any of my direct comments tonight. This is the agenda, just I'm going to go over a bit of hereditary cancer review. Again, not being able to see the audience, I want to make sure we're all on the same page. A brief update on the, on testing itself, but again we're going to hear more about that in the second half of the session. Then talk some about what you would do and how having this genetic information could really help you live longer or live better, if indeed you already have breast or ovarian cancer. Then look to the future about how we can bring the genetic testing into, really medical-grade genetic testing to everybody

across the country and around the world. It really just goes through the hereditary cancer, and then we can go onto the next slide.

Background. Cancer is the most common genetic disease. Most cancers happen a bit by bad luck, sporadic cancers, where we accumulate genetic alterations, or what we call mutations, in a specific tissue, a lung cancer, a breast cancer, prostate cancer. That, those mutations allow the tissue to grow uncontrollably, the disease we call cancer. It's often a disease of aging. As we go through life, we accumulate more of these mutations, and they have to do with environmental factors, such as smoking, alcohol, diet, asbestos, obesity, etc. They really play an important role.

Hereditary cancers are a bit different. Here the genetic mutation is actually in the sperm or egg, such that the risk of cancer occurs really at conception, as the mutation is in every cell in the body. Indeed the genes that lead to hereditary cancers actually predispose the cell to accumulate additional mutations. So not only does the cell have a head start, sort of, out of the gate of having one hit, it is also more susceptible to subsequent hits. Environmental factors still play an important role, but you often can see multiple cancers in one individual, or you'll see a family with multiple cancers in multiple generations. That's sort of how we began to understand that cancer is a genetic disease, can run in families, as many of the traits that you're more familiar with.

Some of the differences are that the hereditary predispositions are passed down in what we call an autosomal dominant pattern with incomplete penetrance. What that means, autosomal. These are not sex-linked genetic disorders, so they're not on the X or the Y chromosome. Men are just as likely as women to carry the risk, even though the cancer tissue affected may be more common, breast tissue in women versus men, prostate, ovary, again, men versus women, that the risk of those cancers is still carried equally in men and women, and then passed down. But not everybody inherits the disease. Who inherits the gene gets the disease. That's what we mean by incomplete penetrance.

Now the next part of the slide, you see here just these little, what we, these little dendrograms, with the red in the top group means that they have the gene. Here the square is a man and the circle is a woman. So the father or the grandfather here had this gene, passed it down to one daughter and one son, and that son and daughter, who were then married, passed it down again to a daughter. In the lower one, you see a woman, and these are just examples, again, the circle in purple is the woman who here had breast cancer, perhaps due to BRCA, as we're going to talk more about.

Now it's all statistics, so she passed the gene down to four of her six children. One child got ovary cancer, one child got ovarian cancer, but a son and a daughter carried the gene, as you see with that dot in the center, but didn't get

the disease. And were unknowing, they didn't realize they were really at risk at that time. Had children, and their families indeed, the unaffected son with the dot in the middle of that square passed it down to a daughter, who then got breast cancer, as did one of the other women. Again, you don't always know, and it's the importance of why we have family history.

As we already heard from June, when one has a BRCA mutation, you have a significantly increased risk of getting breast and ovarian cancer, as she went over. Men have a significantly increased risk of getting male breast cancer, still not high, but it is much increased, and even a higher risk of prostate cancer. There's also an increased risk for pancreatic cancers and melanomas. Now why is that? And we call this clustering of BRCA mutations, as June outlined, 10 times more common to be found in the Ashkenazi, of those of Ashkenazi Jewish heritage compared to the general population. It's generally what we call a founder effect. A founder mutation, or this founder effect occurs when a population is relatively isolated, either due to geographic or cultural factors. So it can be due to a geographic factor, as I have on the bottom here, that you can see specific BRCA founder mutations in Iceland, in Hispanic populations, in the Philippines, in any community that is relatively isolated. Amongst the Ashkenazi Jewish mutation, really dating back to the fall of the Temple and the diaspora, we were able to trace back three specific founder mutations in the Ashkenazi Jewish mutation. They account for almost all the BRCA mutations and cancer-associated mutations in this population.

As you are aware, there are many founder mutations in the Ashkenazi Jewish community. In fact, it's thought that about one in three Ashkenazi Jews carry one of these mutations. You can think about it, it's not just the Jewish population. We know sickle-cell anemia is more common in African Americans, or beta-thalassemia type of anemia in Asians, et cetera. These things do happen, but again, we've been able to map many of these amongst the Jewish population. With advocacy and information, we've actually been able to eliminate diseases, almost eliminate disease Tay-Sachs.

But testing for carrier status of some of these conditions on the last slide is different than BRCA testing. Most of these other traits, these founder mutations associated in the Ashkenazi Jewish mutation are what we call autosomal recessive. In that situation, again, it's not on an X or a Y chromosome, but recessive means, you need two copies of the gene to have the disease. For the example of Tay-Sachs, one in 30 Ashkenazi Jewish individuals is a carrier of Tay-Sachs, but carriers have no symptoms. They're otherwise healthy. It's only when two carriers have children together that they have a risk of one of their children getting the disease. So only one in 3,600 individuals would be affected with Tay-Sachs, thank goodness. Again, they need to have a father carrier and a mother carrier, as you see in the diagram on your left. And it's only when you get two copies, so only one in four children would then be affected.

However, with the BRCA testing, it's autosomal dominant, so even one copy, even one copy of the gene places you at risk for developing cancer. So one in 40, not one in 30, one in 40 individuals carry BRCA gene, but every one of them who carries the gene will be in increased risk. They may not all get the cancer, but they're all in increased risk, and can equally pass that along to their offspring. When we do genetic testing, and the importance of genetic counseling and testing, is that there's implications for the health of the person and for what they should be doing right then as they get the results, understand the results, and make the decisions that are personalized and best for them with their healthcare provider.

Going onto genetic testing, and this will be brief, since we're going to talk about it some more. The technology has gone gangbusters. You can get your genetic testing accurately done with really any cell, it could be blood, it could be saliva. I'm a gynecologic oncologist, I could even do it on a Pap smear. You actually analyze all the genes looking for these mutations that result in disease. As we said earlier, you can get three types of results that we'll hear about some more, either positive, negative, or a variant of undetermined significance that I'll touch bases on so that you'll understand that. Positive is that you carry mutation, and negative that you don't.

These are the guidelines, and I bring this up now, I'll just be brief, because it's been in the news a lot. This is from 2019, these are what's going to be proposed. Who should have testing? Anyone with breast cancer who is of Jewish ancestry, even one-quarter Jewish ancestry, you should have BRCA testing. Anyone at all who has ovarian cancer should have genetic testing. These will all be paid for, these are the national recommendations. Any male who has breast cancer, pancreatic cancer or metastatic prostate cancer should definitely have BRCA testing. Even those men with a higher grade prostate cancer and is of Ashkenazi Jewish ancestry, should have BRCA testing. This can impact their treatment and have importance for their families.

Cascade testing means the testing of other people, other relatives. In this time of families gathering, you can help save your relatives' lives. It's estimated more than 90% of people who carry a BRCA mutation don't know it until someone in their family gets cancer. Yet once you have a carrier, once you know someone in the family who has a BRCA mutation, the reality is, half of their blood relatives, or their first-degree relatives, are going to carry the mutation. So telling sisters, brothers, aunts, uncles, people related to you, that you are a carrier, can really help save their lives, too.

These days, most people do more than just BRCA testing. They do what we call panel testing. Different sizes of panels you can discuss with your doctor, whether you do 30 genes, 50 genes, 80 genes. The pros are, it's most cost-effective. Your insurance company will pay often for these panels. It's a more comprehensive approach. You can find genetic alterations beyond just the BRCA

genes, which we're seeing more and more of as we do these panel testing and are constantly surprised for me on a weekly basis in clinic. It really builds this large dataset for us to use in the future. However, when you test more genes, you get more of these variants of undetermined significance. We're not quite certain what to do about all of them, and it can get confusing and cause anxiety in patients and in their providers, I must say. We don't have a lot of recommendations for some of the genes that even have the mutation, because we're not sure exactly, we don't have enough data yet to know what to do.

A variant of undetermined significance is just that. It's an altered sequence in the DNA that may not change the function of the protein that results from the gene. We really don't know what it means. It's really of undetermined significance. As we accumulate more data, and in the last number of years, most of these VUS, as we call them, can have functional studies, have more patient data involved, and most of them are reclassified as benign, as not being a mutation at all. At the current time, if you get a result that says VUS, there's no specific clinical recommendation. One should not have prophylactic surgery due to a VUS, and the cascade testing for your family members is not recommended either. So these big panels getting a lot of VUS can lead to some anxiety, but please, you know, I think we take those data and move ahead. Do not act on them.

But when we get the information that someone carries a mutation, it's empowering. It can help you take action to not be victimized and to use this information as a way to save your health. But it needs to be personalized, what's right for you, at the right time in your life. Have you had your children? Are you married? What do you feel is best for you? What's your family history look like? You can consider things like different medicines, risk-reducing surgeries, et cetera.

These are just some of the actions you can take. Clearly for a BRCA mutation carrier, having earlier breast cancer screening, using MRI screening as well as mammography. You might consider prophylactic surgery, and if not, there are medications, such as Tamoxifen or Raloxifene, that can reduce your risk of cancer by up to 50%. For ovarian cancer, when you're childbearing, when you've finished your family, you might choose to have your tubes and ovaries removed. That's a salpingo-oophorectomy. So salpingo is tube, and oophorectomy is ovaries. More and more the biology is saying that many of these, what we call ovarian cancers, actually begin in the fallopian tube. So you may have your fallopian tubes out even at an earlier age, if you're going to consider or going to need things like IVF or other assisted reproductive technology.

We do recommend screening with transvaginal ultrasound and CA-125 blood tests. Although it's not a very effective screening for early disease, it still is the current recommendation. In terms of medications, birth control pills do reduce the risk of ovarian cancer, again, up to 50%, even in BRCA carriers. For men who

carry BRCA mutations, since they are at a higher risk of younger age and more aggressive prostate cancers, we would recommend PSA screening, prostate cancer screening. Pancreatic cancer screening can be considered, especially if there's pancreatic cancer in your family history. Really having complete skins checks and even eye exams because of the increased risk of melanoma, and clearly using more SPF and staying out of the sun.

Going onto what to do and what's the meaning of these PARP inhibitors that you've heard about in the news. Most of these data really refer to patients who already have the cancer. Going back to my guideline slide again, it says, "Regardless of family history, if you have the cancer already that's associated with BRCA, such as if you have ovarian cancer or breast cancer or pancreatic cancer or prostate cancer, you should definitely have BRCA testing, if you have not had it yet." That's because you may be eligible for a very effective targeted treatment, called PARP inhibitors.

PARP stands for poly adenosine ribose polymerase. That's why we call it PARP. What it is, it's a gene that's an enzyme, that helps repair DNA. BRCA proteins help repair DNA as well, and through evolution, our cells have multiple means to keep our cells intact. But when you take out two wheels of the car or whatever, it can't roll anywhere. If you're missing one, perhaps you can get along until you get to the next gas station, but if you miss two of them, your car is stuck, and the cells die. PARP inhibitors, on top of the cell that already has a BRCA mutation, causes cell death, and that's what we call synthetic lethality. It's a very effective targeted therapy.

There are many PARP inhibitors that are currently FDA approved. The initial approvals came in ovarian cancer, and there are currently three FDA approved PARP inhibitors. They're all been approved to use as maintenance therapy, so if someone's had ovarian cancer, had a recurrence, and now is back in remission, taking a PARP inhibitor can delay another recurrence of the ovarian cancer. Just today, the FDA approved using one of these PARP inhibitors for patients with a BRCA mutation even after they complete their first treatment with ovarian cancer and it's significantly delayed the time to having the ovarian cancer come back. It's seen as really a great breakthrough, from my point of view, as a GYN oncologist. Two of these PARP inhibitors can also be used as treatment for recurrent ovarian cancer.

For breast cancer, there's also PARP inhibitors, one the same as ovarian cancer and another new one, Talazoparib, that can be used to treat patients who have metastatic breast cancer, who also carry a BRCA mutation. Each of these approvals came to bear because they really improved the progression-free survival, how well women were living, how long they were living with their cancers.

Although PARP inhibitors are just a pill, there are still toxicities. It still is a cancer treatment. They cause anemia, they cause fatigue, they can cause nausea. All manageable, but you need to be aware, you know, this isn't Flintstone vitamins, this is something that will help kill cancer cells, keep cancer cells quiescent, so you can go on and live a very effective life. I've had patients on PARP inhibitors for over five years, and doing quite well. At the beginning, however, you do need to see how it works for you. There can be some PARP inhibitors that work well for one patient and not for another, and you can switch them off to get the one that's best for you. That's something to discuss with your physician.

Just lastly, before I hand this on, talking about some of the future. Currently, less than 20% of women with ovarian and breast cancer who meet the guidelines and would have the testing paid for, are getting testing. We really need to do better to identify the barriers, to get the genetic testing really out to the individuals at risk, to have cascade testing. As I said earlier, more than 90% of unaffected carriers have yet to be identified, which is tens of thousands of cancers that could be prevented if indeed they were tested and took action. So we really need to be doing better.

This study came out just this last week, and you may have heard about it, because it's been in the press, about really the need that we update many of the guidelines. The study was a large study using one of these, again, panel tests in the 80-gene panel, offered to any woman who had a diagnosis of breast cancer and has not had testing. They looked at genetic mutation. Pathogenic variants means a mutation, not a variant of undetermined significance. This is a real mutation, and really, the likelihood of having a mutation was independent of knowing if you have family history. It was the same whether or not, whether you did or did not meet the guidelines based on family history.

The conclusions of the study were that the guidelines are not accounting for all the variation, because family history with small families, incomplete family histories, are not as meaningful as in the earlier studies where we had very large families. We're missing an opportunity to identify the pathogenic variants and mutations, have risk management, personalized treatments, and the cascade testing. I think there's a lot of thought now being placed as a result of this study and others that we may need to upgrade, update the guidelines and expand the access to genetic testing.

So again, reaching out to both men and women, getting better education, better insurance coverage, and better discoveries. I'll just briefly mention a study I've been involved with that we call the BFOR study, or the BRCA Founder Outreach study, which is our attempt as a research study, to do this. Just briefly, the BFOR study is trying to use a new model to really democratize genetic testing, by getting it out into the hands of people who know they're at risk. It's looking at a high-risk population, those of Ashkenazi Jewish heritage, who have not yet been tested.

The testing is done, it's initiated by the patient, by, excuse me, the study participant, who says, "I want to know if I carry a BRCA gene." You can log on, do this yourself, do it on your computer or your cellphone, send in a medical model where you answer consents, and then you can go on and get your blood test drawn. Your result is given back to your own primary care doctor, so that you can decide and be followed where to go from there. So here's the website. B-F-O-R, bforstudy.com. You can register on your phone or on your computer. Watch your videos, learn about the implications, give consent, get tested, get your results and then have follow-up. I will be able to answer questions about any of this, or portions in the next, at the end of the webinar tonight. I'll give it back to June, and I think she'll introduce our next speaker. Thank you.

June Mandeville:

Thank you so much, Dr. Karlan. That was truly informative. I actually learned a lot, and you've really given us a lot to think about in light of the latest testing guidelines. I really appreciate that. I think it's so important to be in possession of as much genetic information as we can. It's definitely allowed us to walk away with a better understanding of how this information relates to us. I really do thank you for that. Now it is my pleasure to introduce our second speaker of the evening, Ms. Peggy Cottrell. Peggy is a graduate of the Sarah Lawrence College, Master of Science and Genetic Counseling program. Peggy has been counseling women at risk for hereditary cancer for over 16 years. In addition to working at Sharsheret, she currently works as a cancer genetic counselor at Holy Name Medical Center in Teaneck, New Jersey. At Sharsheret, Peggy consults with women and families and answers individual questions about their family history, BRCA mutations, and personal risks of hereditary breast and ovarian cancer, and contributes to the development and implementation of Sharsheret's hereditary cancer resources and programs. Now it's my pleasure to turn the floor over to you, Peggy.

III. Direct To Consumer Testing: How Does It Impact Me?

Peggy Cottrell:

Thanks so much, June. My role this evening is to talk a little bit about direct-to-consumer testing. I'm going to start out by giving you a little bit of brief history of direct-to-consumer testing. This was gleaned from an article that I have mentioned here at the bottom, in case you're interested in learning more. If we go back about 15 years, that was when the human genome project was first completed. That was when we really began to understand all of the sequences that made up the human DNA. After this was completed, genome-wide association studies were done, and these studies were trying to associate certain traits and diseases with findings within the genome.

It was some time after this, where the first direct-to-consumer companies became available. These companies were offering a mix of information. A little bit of information about health, along with paternity, ancestry, and some other interesting, nonmedical traits. At first, the growth of this was pretty slow, and that's because testing was still exceedingly expensive. As the cost of genetic

testing continued to go down significantly, the direct-to-consumer testing became more and more popular. The prices began to come down, so that more and more people were interested in testing.

As these companies became more popular and began offering more health information, the FDA got involved. Eventually, the FDA shut down some of the testing for health information, because they felt that the data was not there yet to really support that portion of the testing. What's been happening in the last couple of years is that the FDA is gradually giving back approval for certain tests, health tests, to the direct-to-consumer companies. That's where we are in terms of what we're talking about tonight.

So how do the direct-to-consumer companies do their testing? Is it the same technology that the medical-grade labs use? The technology is not the same. Most direct-to-consumer companies are using SNP testing to evaluate your DNA. They do this by a DNA microarray chip, and these chips assess hundreds of SNPs. What are SNPs? So SNPs stands for single-nucleotide polymorphism, as this illustration shows, here are three ordinary people. If we look at a section of their DNA, we see that some portion of the population at a particular location have the A. Other people have G, and other people have T. This variety may be meaningless, it just may be a normal difference between one person or another, but sometimes these small differences can have some kind of impact on health. When these labs, the direct-to-consumer labs, are doing their testing, it's not sequencing. So they're not going through and telling you the whole pattern of the chemicals that make up the gene. They're just looking at certain small locations.

In that regard, they're really accessing a much smaller amount of information than the medical-grade labs. How does medical-grade cancer genetic testing work? Instead of doing a SNP test on a chip, the testing is done by next generation sequencing. This is a cost-saving technology, that is part of the reason why genetic testing has become so much more affordable. It determines the full DNA sequence, so all of the chemicals that make up each of the genes that's being tested. The specific test that's chosen for a person to have done is targeted to the medical issues that are indicated in the family history. So people who have a strong pattern of cancer in their family would be offered a test that highlights genes that are associated with an increased risk for cancer. All of these medical-grade testing labs are under special regulation, not by the FDA, but a different federal agency called CLIA, which is an organization that provides important oversight in terms of how these labs do their testing.

So who should consider having a direct-to-consumer test done? We have a term in the genetics work called entertainment genetics. That sounds a little unusual, but entertainment genetics are things that you're curious about, that genetics could give you an answer to. One thing that many people are curious about, and especially this time of year, if you're shopping online, you'll see that a lot of

direct-to-consumer tests are on sale. People are very curious about their ancestry. Is it really what they've always been told, or is it something different? Paternity. Might people have long-lost relatives to discover? Is your father really your father, or is somebody else your father? People have curiosity about non-medical traits, things like how does your tongue curl, or how does your earlobe attach to the side your neck?

These are all very interesting things to learn about, and not surprisingly, these tests are popular. But if you're really concerned about the cancer in your family, then you really should consider a medical-grade test that's really going to be able to identify all of the genes that could be coming into play. So direct-to-consumer testing is really important for people with Ashkenazi ancestry to be aware of. That's because direct-to-consumer testing is able to identify the founder mutations that we were talking about earlier.

So the founder mutations are three changes that are common. They occur two in BRCA1, and one in BRCA2. They are present in all Jewish populations, because they originated in the Jewish population back more than 2,000 years ago. So we do find founder mutations, not just among Ashkenazi Jews, but among all Jewish populations. But again, in the Ashkenazi population, there were population factors that concentrated these mutations among Ashkenazi Jews, so that now we see the one in 40 frequency. Now testing for these three mutations can be done by the direct-to-consumer testing, because technically, these founder mutations are SNPs. They are small differences in the chemicals that make up the DNA that can be detected on a chip.

If you have decided to have direct-to-consumer testing because you're interested in finding out more about ancestry or relatives or one of these other reasons, how should you interpret the results that come back? If the results are positive, they need to be confirmed with a medical-grade test. This is not just my opinion, or the opinion of doctors, but actually the opinion that is listed on the direct-to-consumer sites. They don't want the responsibility for providing you with medical-grade information. Insurance companies very often now, in their guidelines include, if you have had a mutation identified through direct-to-consumer testing, insurance companies will often over having that kind of testing done. It's important, if you have a finding on a direct-to-consumer test, that you avoid making any medical management decisions until the result is confirmed. That's because we know of situations where somebody thought there was something inherited, and it turned out that the direct-to-consumer test was incorrect.

What about if you have direct-to-consumer testing and it checks for the BRCA1 and 2 founder mutations, and your results are negative? Your first thought may be, wow, amazing. There's not something inherited here. But it would be important for me to remind you that you could still have the mutation with BRCA1 or BRCA2 that's not one of those founder mutations. People with

Ashkenazi ancestry, while they are certainly more likely if they have the mutation that it's one of the founder mutations, they could carry a mutation elsewhere, and that could have been missed. It's also possible that a person could carry a mutation in a different cancer susceptibility gene that isn't covered on the direct-to-consumer test. Finally, there are many genes that predispose to cancer that scientists don't know yet how to look for. It's really important to realize that if you have a negative result on a direct-to-consumer test for a health issue, that that really leaves you at a point of uncertainty. That's because it's only looking at a very small portion of the possibility of inherited cancer.

What should you do if you're interested in finding out more about hereditary risk, or what should you do if you have direct-to-consumer testing, and you're wondering if that was enough test for you? So the best way to answer this question is to find a genetic counselor. Genetic counselors are uniquely trained to be able to provide important information about how to interpret the results of genetic testing and how to choose the correct genetic test. It is easy to find a genetic counselor on the Internet, and if you go to the webpage of the National Society of Genetic Counselors at the website that's indicated on the slide, you will find one of these hexagons that says "find a genetic counselor" on it. If you click there, you can put in your zipcode and choose a specialty like cancer and do a search for your locality and see if you can find a genetic counselor close to home. There are also remote genetic counselors, who can speak to people who may live in areas of the country that may not be well-served by the genetic counseling population.

Finally, the other option to consider, if you have questions about genetics, is to contact Sharsheret. I am able to set up an appointment to speak with people who have questions and concerns about genetics. If you're wondering how should I find out more about a possibility of cancer in my family, don't hesitate to give us a call, and I may be able to discuss with you the cancer that's in your family and help you figure out what's the best way for your risk to be evaluated.

June Mandeville:

Peggy, thank you so much. It was really interesting, because you gave us a lot to think about. You definitely gave us a lot to think about, so I really appreciate that, and sort of debunk so many of the common misconceptions. I know a lot of our participants tonight, including myself, are walking away with a greater knowledge and understanding of what's involved. As Peggy mentioned, the conversation doesn't have to stop here. Please do reach out to Sharsheret to continue the conversation with Peggy or with a member of our support team. Now it is my pleasure to introduce our last speaker of the evening, one of our amazing callers, Laura, who will now share her journey and experience navigating direct-to-consumer genetic testing. Over to you, Laura.

IV. Personal Story

Laura: Hi, June. Thank you so much for having me on the panel. I just wanted to share my story of how I found out that I was a BRCA1 carrier through direct-to-consumer testing. Earlier this year, curiosity of my ancestry spurred me to order a direct-to-consumer kit by mail. I thought maybe my blond hair was a result of some hidden Swedish genes. So when my kit arrived, I spit in the tube and sent it off. I didn't give any thought to the genetic and ancestry testing boxes I had checked off. I went through, I just had gone through a rigorous genetic testing process while pregnant with my third child less than two years, but I figured, why not pay the small price difference to add the genetic testing component.

Several weeks later, I was just drinking my morning coffee before heading out on a run, and it would change my future. I was scrolling on my iPhone and I clicked on my available testing report and first I saw my ancestry, which was 99.9% Ashkenazi Jewish. As I kept scrolling, my heart stopped. I saw "BRCA1 positive, consult with doctor." I thought, this is a mistake. No women in my family have had breast or ovarian cancer. I was shaken, and I was still hopeful that this was an error. So I called my OB-GYN and explained the situation, and by that afternoon, I was sitting in her office awaiting a medical-grade back-up test by blood, which is the gold standard in BRCA testing.

Seven days later, I received a call from my doctor that confirmed this nightmare that I was BRCA1 positive, and of course initially, I was shocked and angry. But then I was replaced with this fear that I had already developed a cancer, because women carrying this mutation begin advanced screening starting around age 20, and I was 37 and I never had had a mammogram or ovarian cancer screening. But then I realized that feeling sorry for myself and the fear was not productive. So I reached out and I spoke with the team at Sharsheret and felt comfort knowing I wasn't alone. When my breast and ovarian cancers came back clear, I breathed a sigh of relief, and then I developed an action plan.

As discussed, with BRCA1 mutation, I faced about an 88% risk of developing breast cancer and about a 50% lifetime risk of ovarian cancer. I always viewed my body healthy, strong. I was a former collegiate All-American runner. I never thought that I would test positive for this mutation. I realized that it was a ticking time bomb. Five weeks after receiving that initial email from my direct-to-consumer testing saying I was BRCA positive, I underwent my first surgery, and I was able to do that laparoscopically, tube and ovary removal with the amazing Dr. Andrew Li at Cedars. Eleven days after that, Dr. Li laughed, I showed up to my post-op, waiting to be cleared to go running. I was little hobbly and out of breath, but I was just so happy after that surgery that I had done what I could do to bring my cancer risk down.

Now next I had to tackle the surgery that obviously scared me the most, and that would be the double mastectomy. It's a very physically difficult surgery,

also emotionally difficult. But instead of ignoring all the fears I had and thoughts in my head, I had conversations about the emotions, the recovery, how it would change my body. I appreciate the tools and resources Sharsheret gave me before my surgery. I had a team of friends and family and Sharsheret all supporting me in this decision. Without regret, I chose to preventively remove both healthy breasts on July 26th of this year. I did a nipple-sparing bilateral mastectomy with immediate direct-to-implant reconstruction.

Although, you know, it was a hard surgery initially, each week I just got stronger and I had so much support and that really helped me, I believe, heal. Now I am completely back to myself. I'm chasing around my three kids, I feel strong, I'm running, I don't have any pain, and I'm just so thankful that I was able to catch this information. One other thing is that my surgeons, you don't have to sacrifice necessarily the cosmetic outcome, because there's such a fear with the word mastectomy. But with the surgical advances, I'm very happy with the results. My surgeons were so supportive that you don't have to sacrifice aesthetics to prevent cancer. That I think is important information to get out.

Now the final piece to my puzzle, as we talked about earlier, was this origin of my BRCA1 mutation, and it turned out my father was the one that carried the gene. Although he was at increased risk for prostate cancer, it went undetected. The greatest misconception is that women can't inherit the BRCA1 from their fathers. Because no women in my family had breast or ovarian cancer, the possibility I carried this completely flew under the radar. Finally, I just want to say, as we discussed, all Ashkenazi Jewish women carry a one in 40 risk of carrying the BRCA1 mutation, and we need to ask a lot more questions about family history on maternal and paternal sides.

Although it seems like a curse to have this mutation, I'm very lucky that randomly checking this box on the direct-to-consumer testing likely saved my life. We need to have a lot more conversations and raise awareness of how BRCA1 and other mutations are passed down from both parents. While I understand surgical prevention is not the right choice for every woman, we just have to know our risk, and we can take ownership of our bodies and be empowered to make informed decisions about our health. That's it. That's my story of how this direct-to-consumer testing likely saved my life.

June Mandeville: Laura, thank you so, so much. Really grateful that you shared your story with us. I think it's very meaningful to hear a firsthand account. I'm sure a lot of our participants were nodding along as you were talking, describing the fears and the relief also of being able to talk about it. I really do thank you for sharing that. Thank you very much.

V. Question & Answer

On that note, if you're looking for support or someone to connect with, as Laura mentioned, you can call Sharsheret at any time to speak with a member of our support team. Moving on, we are getting to our question and answer session. I just want you to let you know, we've had a lot of questions come in. The chances are, we will not get to all of them, unfortunately, this evening. But I want you all to know that we will have them all answered, and they will be available and posted along with the webinar. Please look out for them, if we don't get to your questions. I do apologize. Again, you can type your questions into the text box, located in the dashboard to the right of your screen. We will get started.

June Mandeville: Dr. Karlan, I have a question for you. "I participated in the BFOR BRCA testing, and my results were negative. I'm not a carrier, but I do have a strong family history. Can you share what the research advice is regarding elective ovarian removal?"

Dr. Beth Karlan: Thank you for the question. It's a very insightful question. For those individuals who've gone through BFOR, again, this is only testing for those three BRCA1, BRCA2 mutations, if indeed you have a strong family history, it's recommended that you have further genetic counseling, to have a panel test. Again, this study, we're just looking to see, can we implement this with this novel format to reach more people? If indeed you have a strong family history, the first step would be to have a full panel genetic counseling and genetic testing, to see if indeed you carry one of the other genes that may place you at an increased risk. Because that will give you some much clearer direct information, both in terms of whether you should have increased surveillance, whether you should have prophylactic surgery, whether you should take any medications to reduce that risk. I would say at this point, do follow-up, have further genetic counseling, so you can decide, for you, what is the best next step.

I'd add one other point to Laura's wonderful presentation. That's just as one in 40 women carry the mutation, one in 40 men do as well. So many times, as you saw and you heard so poignantly in Laura's study, we don't know, because you may not have never met your paternal grandmother, because she was already deceased. Or the family may be small. We need to get men to be tested as well, if we're going to have the full impact of saving lives from genetic testing.

June Mandeville: Thank you, Dr. Karlan. Next question, this one's for Peggy. What are the guidelines for testing children of a mother who is BRCA positive?

Peggy Cottrell: If someone has tested positive, then there would be a 50-50 chance whether her children would have inherited the mutation. Generally, when we test the children is going to depend on their age. We don't want to test children who are 18 or younger. We need them to be an adult when they have the test done. The

age when it makes the most sense is going to vary from family to family, but in general we say around 25 is a good age to consider having testing done. Most of the time, when a mutation has been identified in a family member, those close relatives are going to have an easy time getting that coverage from their insurance company to get that testing paid for.

June Mandeville: Thank you, Peggy. Laura, this question is for you. You had mentioned the idea of bringing up conversations, talking about these difficult subjects. Do you think doctors should be raising these issues with us? Have you found that's been a challenge? How have you approached these difficult conversations?

Laura: Well, I do think that doctors need to be more aware of the Ashkenazi Jewish risk for women, because I had been seeing doctors since a young age and never was flagged for needing testing because I did not have "breast cancer risk" in my family because none of the women in my family had had breast cancer. I do think there is this lack of awareness that you can get it equally from your father, which is what happened in my case. There does need to be, I think more of awareness for people to ask their doctor, women to ask their doctors, and also for the doctors to be aware of, you know, now that we have the availability of these tests, you know, ease of testing, that they should be recommending that their patients get tested for this.

June Mandeville: Right. Thank you, Laura. Dr. Karlan, my sister and I were diagnosed 22 years ago, at age 38 and 30. We had genetic testing done in 1996. Should we repeat the testing now? Are there differences?

Dr. Beth Karlan: Yes. That's the short answer. Again, it may be well beyond BRCA1 and BRCA2. The family history, the young age of diagnosis, assuming you and your sister have the same parents, it would be very, very important to have a full genetic test. Again, genetic counselors can provide great resources, help you sort out pieces of your family history that would be really be helpful for you, your next steps, that for your other family members as well. I would recommend additional testing at this time.

June Mandeville: Thank you. We only have time for one quick question. Peggy, why does BRCA1 and 2 receive more attention than other genetic mutations?

Peggy Cottrell: BRCA1 and 2 by themselves have the big implications for the development of cancer. They were studied early on and for that reason, and they are a little bit more common than some of the other genetic mutations that we identify. Some of the other things that we find now cause a more moderate risk of cancer, and so it may not be as straightforward what needs to be done. One of the main reasons that we at Sharsheret concentrate so much more on BRCA1 and 2 compared to some of the other genes that have been identified is because of how common they are amongst people with Ashkenazi ancestry. With that being our target population, that is often what we concentrate on. Again, we

encourage women, when it's appropriate, to have a larger test. We do know many Jewish women who have found inherited mutations in other genes besides BRCA1 and BRCA2.

VI. Conclusion

June Mandeville: Okay. Thank you, Peggy. For everyone participating, your feedback is important to us. You will be receiving an evaluation in your email box in the next couple of days. Please take a few minutes to complete the survey. We're committed to staying relevant by enhancing our programs to reflect the growing and changing needs of the women and families of our Sharsheret community. As mentioned before, there will be a video and transcript from tonight's presentation, and it will be available on Sharsheret's website. You can access it by going to www.sharsheret.org, and as I mentioned before, the questions will be answered also, so we have not forgotten. They're very important questions.

We would like to thank once again Myriad Genetics, the Sigmund and Edith Blumenthal Memorial Fund, and the Cooperative Agreement DP141408 from the Centers for Disease Control and Prevention for their ongoing support, and for sponsoring tonight's program. I want to also give a huge thank-you to Dr. Karlan for helping us make sense of genetic testing and what it means for us. To our genetics counselor Peggy Cottrell for masterfully helping us navigate genetics in the media, and to our caller Laura for sharing your story and for bringing these issues to life.

I hope that tonight's webinar was a helpful guide to decoding genetic testing, direct-to-consumer testing, and the value of genetic testing for you and your family. You can visit Sharsheret's website, at www.sharsheret.org, or call us, at 866-474-2774 to discuss tonight's topic or any other concerns you are facing. Thank you so much for joining us and have a great rest of your night.

VII. Speakers' Biographies

Beth Y. Karlan, M.D., is Director of the Women's Cancer Program at the Samuel Oschin Comprehensive Cancer Institute, Director of the Division of Gynecologic Oncology and the Gilda Radner Hereditary Cancer Program and holds the Board of Governors Chair in Gynecologic Oncology at Cedars-Sinai Medical Center. She is also Professor of Obstetrics and Gynecology at the David Geffen School of Medicine at the University of California at Los Angeles. Dr. Karlan's research focuses on ovarian and other women's cancers as well as inherited cancer susceptibility. She has authored over 300 research publications and is an American Cancer Society Clinical Research Professor. She is the editor-in-chief of the scientific journals Gynecologic Oncology and Gynecologic Oncology Reports. In 2012, Dr. Karlan was appointed by the White House to serve on the National Cancer Advisory Board, and, in 2015, she was elected to membership in the National Academy of Medicine.

Peggy Cottrell, MS, CGC, Genetics Program Coordinator, is a graduate of the Sarah Lawrence College Master of Science in Genetic Counseling program. Peggy has been counseling women at risk for hereditary cancer for over 16 years. In addition to working at Sharsheret, she currently works as a cancer genetic counselor at Holy Name Medical Center in Teaneck, New Jersey. At Sharsheret, Peggy consults with women and families and answers individual questions about their family histories, BRCA mutations, and personal risks of hereditary breast and ovarian cancer, and contributes to the development and implementation of Sharsheret's hereditary cancer resources and programs.

VIII. About Sharsheret

Sharsheret, Hebrew for chain, a national cancer organization with three offices (New Jersey, Florida, and California), serves 120,000 women, families, health care professionals, community leaders, and students, in all 50 states. Through 12 national programs, Sharsheret provides culturally relevant support and information to women and families facing breast and ovarian cancer. While our expertise is in young women and Jewish families, all Sharsheret programs serve all women and men of all backgrounds. In fact, more than 15% of the women who reach out to the organization for support are not Jewish.

Bringing our cause to the national platform, Sharsheret is a member of the Federal Advisory Committee on Breast Cancer in Young Women, has been awarded two multi-year grants to develop support programs from the Centers for Disease Control and Prevention (CDC) and participates in psychosocial research studies and evaluations in partnership with federal agencies and major cancer centers, including Georgetown Lombardi Cancer Center. Sharsheret is accredited by the Better Business Bureau and has earned a 4-star rating from Charity Navigator for four consecutive years.

WHAT WE DO - Sharsheret:

- Creates a safe community for women at every stage—before, during, and after diagnosis. We offer tailored resources, information, and support to caregivers, family members, and friends of women facing breast and ovarian cancer to guide them through the cancer journey.
- Services are free, confidential, and easily accessed online and by phone, email, text, and livechat. All services are individualized and provided one-to-one by skilled and trained professionals.
- Builds a strong community of “links in the chain” through education and outreach events for college students, healthcare professionals, and community organizations.

OUR NATIONAL PROGRAMS

Support Programs

- Peer Support Network, connecting women newly diagnosed or at high risk of developing cancer one-on-one with others who share similar diagnoses and experiences
- Embrace, supporting women living with advanced cancer
- Genetics for Life®, addressing hereditary breast and ovarian cancer
- Thriving Again®, providing individualized support, education, and survivorship plans for young breast cancer survivors
- Busy Box®, for young parents facing breast cancer
- Best Face Forward®, addressing the cosmetic side effects of treatment
- Family Focus®, providing resources and support for caregivers and family members
- Ovarian Cancer Program, tailored resources and support for young women and families facing ovarian cancer
- Sharsheret Supports, developing local support groups and programs

Education and Outreach Programs

- Health Care Symposia on issues unique to active women facing breast and ovarian cancer
- Beatrice Milberg Campus Program, outreach and education to students on campus and young professionals
- Florence and Joseph Appleman Educational Resource Booklet Series, educational and supportive publications for women and their families and healthcare professionals

IX. Disclaimer

The information contained in this document is presented in summary form only and is intended to provide broad understanding and knowledge of the topics. The information should not be considered complete and should not be used in place of a visit, call, consultation, or advice of your physician or other health care professional. The document does not recommend the self-management of health problems. Should you have any health care related questions, please call or see your physician or other health care provider promptly. You should never disregard medical advice or delay in seeking it because of something you have read here.

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