Program Title: Updates in Genetic Testing for Hereditary Breast and Ovarian Cancer
Presented by: Support Connection, Inc.
Moderator: Robin Perlmutter, Support Connection Peer Counselor
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Guest speaker: Wendy Chung, M.D., Ph.D.: Dr. Chung is a medical and molecular geneticist, and the Kennedy Family Professor of Pediatrics and Medicine at Columbia University. She received her B.A. in biochemistry and economics from Cornell University, her M.D. from Cornell University Medical College, and her Ph.D. from The Rockefeller University in genetics.

Dr. Chung directs NIH funded research programs in human genetics of breast cancer, heart disease, and birth defects. She leads the Precision Medicine Resource in the Irving Institute At Columbia University. She has authored over 300 peer reviewed papers and 50 reviews and chapters in medical texts. She was the recipient of the American Academy of Pediatrics Young Investigator Award, the Medical Achievement Award from Bonei Olam, and a career development award from Doris Duke.

Dr. Chung enjoys the challenges of genetics as a rapidly changing field of medicine and strives to facilitate the integration of genetic medicine into all areas of health care in a medically, scientifically, and ethically sound, accessible, and cost effective manner.

Topics:

- Who should get genetic testing for cancer genes?
- What's new in genetic testing for breast and ovarian cancer?
- What if I had cancer genetic testing before? Should I do it again?
- How can I use the most up to date genetic information for myself and my family?
- What do my results mean for my daughter, sister, or niece?

Robin Perlmutter: Please remember that Dr. Chung is sharing her expertise, and any information from tonight or questions pertaining to individual concerns should be discussed with your doctor. It is with my great pleasure that we have Dr. Wendy Chung, a medical and molecular geneticist and the Kennedy Family Professor of Pediatrics in Medicine at Columbia University. She directs NIH-funded research programs in human genetics of breast cancer, heart disease and birth defects, and leads the Precision Medicine Resource in the Irving Institute at Columbia University. Thank you, Dr. Chung, for sharing your time and expertise with us tonight.

Wendy Chung: Thank you, Robin, for having me. It's my real pleasure to be here. We're going to go through some material tonight that is aimed at especially women with either a personal or family history of breast cancer, and I hope it will give you some updates, because there have been some changes over time, really great improvements, actually. And even for some of you who may have had genetic testing in the past, it may be time to revisit this again.

So, when we think about cancer, and this could actually be breast cancer or even if any of you have other cancers in your family, it could be other cancers as well. But we often ask ourselves the question why? Why did this happen? How did this happen? And although I am a geneticist, I will say that it's not all genetics in the sense of something that you're born with or something that is coming down in the genes of your family. However, for about 30% of women who have breast cancer, they will have had some family history of breast cancer. That also means there are 70% of people who don't have any history of breast cancer -- 30% do, 70% don't. Within that 30%, and I

know this is very confusing terminology. It's actually not the best terminology. But of that, of all of the women with breast cancer, about 5% to 10% will have what we call heredity breast cancer. And what we mean by that when we say it is -- that there is a single powerful gene, and we'll get into examples of this, the BRCA1 or BRCA2 -- but single powerful genes are responsible for the breast cancer. There is also, as you can see in blue, another slice of the pie, 15% to 20% of women who have a family history of breast cancer, but it's not necessarily one of the genes we know about at this point. And that could be theoretically either shared genes or shared exposure, but there is some familial clustering to that. So, I know it's difficult to understand the difference between that pink and the blue slot, but, again, the pink slot meaning a single gene, blue spot meaning some other, ill-defined or undefined genes, or other exposures at this point.

So, if you take that pink piece of the pie and you look and you say what's accountable for those hereditary aspects, about half of those cases, or half of those women have their cancers due to mutations in the gene BRCA1, or B-R-C-A-1. Another -- and, again, in that pink slice of the pie on the left, about a third of those individuals will have mutations of the gene BRCA2, or B-R-C-A-2. And then as you can see, there is still a little bit of the pie that's left, you know, another 25% or so that's due to other, and those are individuals -- actually, I should say more like 20%, due to some other genes that we're going to talk about later tonight. Next slide.

So, as you're thinking about this, which individuals out there should be thinking about being in that pink slice of the pie, that hereditary aspect, where there might be a single powerful gene? And there are some red flags or things that we think about either in your personal history or in your family history. And I've listed these actually in order of importance in terms of what they are signaling potentially being in that pink slice of the pie.

So, the first is maybe not intuitive, but it's not just breast cancer but ovarian cancer. And ovarian cancer is not nearly as common as breast cancer. And when we see those two together, it's definitely indicative of a possible BRCA1 or BRCA2 mutation. The other thing you can imagine is that women who get cancer at a younger age, there is a greater likelihood that it's heredity, not always, but there is greater chance. And we'll define 50 as being at a younger age. I hate to say that anymore, because that makes me not younger, but still we'll say it's less than 50.

In addition, women who have had two breast cancers or even essentially a breast cancer and some other cancer are at greater risk for having one of these hereditary factors. And if there is a man with breast cancer -- it doesn't happen very often, thankfully, but men with breast cancer may get an increased chance of being in that pink slice.

Many of you know that when we look at breast cancers, we actually look at them under the microscope, and we look at things like estrogen, progesterone status, HER2/neu status. And when you're negative for all of those, that is, that you don't see estrogen, progesterone or HER2/neu, then we call that triple negative, negative for each one of those. And seeing that is actually associated with BRCA1.

And then just a couple other factors, not nearly as important, but they still do increase the risk. If you see pancreatic cancer, that's, again, not a very common cancer, thankfully, but that increases the risk. Individuals who are of Jewish ancestry and, of course, not surprisingly, if there is already a mutation identified in the family, then it increases the risk that the person with cancer might have a mutation in that family. Next slide.

So, I've shown a schematic here for almost all of these cancer predisposition genes. And this is true, actually, whether it's breast cancer, ovarian cancer, colon cancer, pancreatic cancer, almost all of them are what we call autosomal dominantly inherited. And so what I mean by that is that you can see -- and one important thing to remember about this is, these genes can be passed down from fathers or from mothers. And so one important thing to remember is that even though breast cancer might be something that we see most commonly in women, your father's side of the family, your father's family history still matters. Because a father or a man could pass down the gene even if that man did not have breast cancer.

So, so that point, on the left here, what I'm showing is two chromosomes, these two stick figures to the left of the gray man. These two chromosomes have two different copies of the gene. This little white box is meant to show the copy of the gene that has some genetic typo that increases the risk of cancer. The blue box here is meant to be the normal version or the normal copy of that gene. In this particular case the mother is the one that has the blue boxes, so she doesn't have any change in the cancer gene, but the father here has two copies of the gene -- the white one with the genetic typo, and the blue one that's normal.

Now, when we have our children, we give our children half of our genes and our children get half of the genes from our partners, our husbands or our wives. And when that happens we take one of our two copies of our gene and we pass it down to the child. And it's like flipping a coin which one of those two copies it is. We have no control over this. There is nothing we can do to prevent it or make it happen, but just like flipping a coin, it could be either version A or version B. And about half of the time you will transfer to a child that white square, or the one that has the genetic typo in it. And if that should be, in this particular case that we're talking about, one of these hereditary breast cancer genes, if that should get passed down to a girl, then it would increase -- or a woman -- that would increase her chance of breast cancer. Next slide.

So, let's take a look at another way of looking at this. So, lots of time genetic counselors and I will actually make a visual picture, a visual representation of what your family looks like. And you could do this yourself. Lots of genealogists do this, lots of people do it to trace their family roots. But when we do this we simplify it, and we make men into symbols that are squares, and we make women into symbols that are circles, and so that's what you're seeing here.

So, if we look at the family on the left, this is an example of one of these families with the hereditary cancer. So, a gene that might be passed down from generation-to-generation. So, as an example, if you look way at the top, the top line of that hereditary family on the left, there is a woman on the right who is colored in gray and it says underneath her, OC 46, and for us that's a shorthand that stands for ovarian cancer diagnosed at the age of 46. And that woman, you'll see, has two daughters. Those are those two, if you sort of follow that line down, she's got two circles colored in blue underneath her, and those are her two daughters. And she had one daughter with BC, breast cancer, at the age of 35, and a second daughter, BC, breast cancer, at the age of 40. Her daughter with the breast cancer at the age of 5, she went on to have three daughters herself. One daughter had breast cancer, BC, at 56, one ovarian cancer, colored in gray, OC at 43, and one daughter who didn't have cancer.

So, when you look at this, and this is what we sometimes see in these hereditary families, you see it generation after generation. Again, you see breast and ovarian cancer, and you're seeing cancers at a particularly young age, even 35, and that's for us the hallmark. This is sort of a classic family history of a hereditary breast cancer case, not surprisingly.

Now, on the right is, thankfully, what's much more common, that is, women that have, we call it sporadic, but it looks like there is no family history of cancer. So, that woman on the -- the family on the right, all the way on the lower right, is a woman with breast cancer, BC, at the age of 56; she is colored in in blue. And if you look back, she doesn't have any family history of cancer. Her sister didn't have cancer, her mom didn't have cancer, her father's sisters, her paternal aunts didn't have cancer, so we're not seeing much cancer history here. And that's what we see, as I was saying before, that 70% of the time. But one of the issues is that family histories sometimes don't tell us everything. So, in some cases, as I said, there might be a family -- there might not be very many women in the family, maybe that's why we don't see the pattern. Sometimes we have people who are adopted and they just don't know their family history, so that may be a limitation. In some cases families have been, unfortunately, bad things have happened to them. Someone might have died in an accident, in a car accident, in a fire; people have died in the holocaust so we may not know the family history. They may not have lived long enough to have developed cancer. So, there are lots of reasons why the family history may not be helpful. But when we do see a family history of cancer, it is something that we take seriously. Next slide.

So, when we think about that, what's happening at the level of the individual cell? How do cancers actually start and how do those genes that we talked about, how can that relate to the process that's going on in terms of what forms a cancer? So, when you think about this, for the most part, for the majority of individuals, you're not born with a cancer. Cancer happens over time. And, in fact, when you look in the general population, we don't usually see babies with cancer; we're much more likely to see someone who is in their sixties or seventies or eighties with cancer. Cancer is just generally the older you get the more common cancer is. And that's because there's a time element in this. It takes time to develop the changes that happen with cancer. So, when this happens, what I'm showing on the top line here is that most individuals are born with two normal genes. These particular genes are genes that prevent cancer. So, many of the cancer susceptibility genes, when they're functioning normally, actually prevent cancer. And when they are missing or they are not doing their job, they allow cancer to progress. Cancer starts growing, cells start growing out of control when they are not doing their job.

So, most people are born with two of those normal genes that are doing their job. I think of them like brakes on a car. They are slowing down cells from growing; they are actually keeping cells from growing out of control. It's a brake to stop things. That's their normal job. Now, most people are born with two normal copies of the gene, or I think of it in the car, it's like two brakes. You've got your brake that's your foot pedal, and you've got your emergency brake. And if either one of those brakes are working, it's okay, you can stop your car. For most people, when they're born, they've got both of those two brakes working -- the foot pedal brake and the emergency brake. But over time, and that period of time could be 50, 60, 70 years -- over time, something happens to one of those brakes. Something happens to one copy of the gene and there's a mistake. There is something that happens to it. Someone cuts that brake line or the brake pads are malfunctioning and you can't necessarily stop those cells from growing out of control. When something happens to both of those brakes -- so, what's happening in that top line there is not just one gene that has a problem, but both genes have the problem. If something happens to both of those genes in one cell, that cell can start growing out of control, and that's when a tumor develops. And so, again, for most normal people it takes not just one change but two of those changes before that tumor starts growing.

Now, on the bottom what I'm showing is people who are actually born with a hereditary predisposition. And what happens in that case is you're already halfway there. You're born with

one of your brakes missing -- either your emergency brake or your foot brake, and so it takes just one less step to go to the process of developing cancer. Next slide.

So, when we think about this, there can be many different contributing factors to breast cancer. I've shown on the left some of the genetic factors, BRCA mutations, and I'm trying to show you the relative contributions. For people who have, for instance, BRCA1 or BRCA2, that's about a tenfold increased risk. It's a very powerful risk factor. But it's not the only factor. You'll see in the middle of the slide, family history increases your risk by 1.7, or about twofold increased risk, and there are other factors as well. If you're on hormone replacement, if you have early menarche, or start your period early, those are factors, but they are relatively modest factors. Next slide.

So, now we're going to switch gears in terms of now describing what it looks like for individuals who have hereditary breast/ovarian cancer syndrome, or in other words BRCA1 or BRCA2 mutation. Next slide.

So, I'm going to go relatively quickly through this next part, because I want to save plenty of time to talk about some of the new developments. But for women who go through the process of genetic testing and they do find out that they've got either one of these BRCA1 or BRCA2 changes, they have a much higher risk of breast cancer and ovarian cancer. And, in fact, one of the most compelling reasons for women with breast cancer to get this type of genetic testing is to figure out if they're at increased risk for ovarian cancer, because that's a difficult cancer to screen for. We really need to be more aggressive about mitigating that risk by even removing the ovaries.

So, if you look at this by age, for women that, again, have one of these BRCA changes, BRCA1, BRCA2 by age 50, the risk is about 37% of developing breast cancer; by age 70 it's about 66%, and for ovarian cancer by the age of 70 it's about 31%. And I've shown in pink here just what the general population is by that same age. As you can see, those blue bars are much, much bigger than those pink bars. Next slide.

The other part of this is for women who have already had a breast cancer diagnosis, can they get another cancer? And by another cancer, I don't mean the cancer recurring. I don't mean that same breast cancer coming back; I'm talking about a second, brand-new cancer. So, as an example, if you had breast cancer on the left, I'm now talking about getting your breast cancer on the right, brand-new cancer. And, again, for women who have had cancer, many times, been there, done that, don't want to go back again. One of the reasons to think about this type of testing is to decide whether or not to do something more aggressive in terms of either surgery, like a mastectomy or tamoxifen, or something to reduce the risk. And, again, within the first five years after diagnosis, with a BRCA mutation, that risk is 16% having a second cancer, and by age 70 it's up to 36%. And, again, to compare the ovarian cancer risk, up to 13% risk of ovarian cancer within the first 10 years after having a breast cancer. And, so, again, compared to those pink bars, significantly increased relative to just any woman who has had breast cancer. Next slide.

So, in addition, for any of the men listening in or any of your loved ones -- I didn't want to leave them out of this -- BRCA1, BRCA2, much less risk compared to women, but not to say that it's zero with risk. There is still some risk associated with it. BRCA2 in particular is associated with a breast cancer risk in men, and that breast cancer risk can be as high as 8%. And one of the other things that some people haven't recognized is that the risk can also be for prostate cancer. It's not a huge risk, because compared, prostate cancer is relatively common in men, so it's slightly increased compared to the general population, but it is real. It's something that we have seen consistently. Next slide.

The other part of this is, even though these risks are not very high, and I want to emphasize, the absolute risks are not very high for BRCA1, BRCA2, we can see an increased risk of pancreas cancer as well as the skin cancer melanoma. And there are some ways to screen for pancreas cancer. We can do things like what's called an endoscopic ultrasound or even MRI to look at the pancreas, and for melanoma, obviously, we can use lots of sunscreen, stay out of the sun. Those are both risk factors for that type of skin cancer. Next slide.

So, finding out that you're at increased risk isn't much fun if there is not anything you can do about it. So, what can we do about it for the women or men that find out they're at increased risk because of their genetic factors, what can we do? Next slide.

So, I like thinking that early diagnosis is a way to be able to catch something, nip it in the bud, take care of it, and hopefully do it without nearly as much rigmarole. So, we focus a lot in terms of early diagnosis, and to do that we increase the surveillance. So, in other words, we look more carefully, we look more frequently, we start earlier. We do it in greater detail, and we do that all to be able to catch something very early before it becomes metastatic, or in other words, as it's gone around the body.

So, as an example, for breast cancer we will do regular mammography. I think all of us are used to that. But in addition we'll do MRI, so being able to look at the breast using very, very detailed ways of getting greater resolution. And we'll do both of those once a year. So, what I like to do is stagger them -- a mammogram in January, an MRI in July. But do something every six months so that we're constantly looking. For ovarian cancer we can screen. There is a blood test we can use called a CA-125; we can do an ultrasound. But I'll be honest, we usually don't catch ovarian cancer early enough to be able to save someone's life. So, once we get to the point that we're finished having children, we know that we don't need them for that reason, if women are at high risk, my recommendation is to remove the ovaries. And this can be done very safely, relatively quick recovery as well. Okay, next slide.

So, if we're thinking about this, are there other things that we can do? And one that you may not have thought about but is birth control pills. The birth control pills can actually decrease the risk of ovarian cancer by as much as 50%, and I think that's a pretty good thing. Tamoxifen is another medication that you may have heard about. A lot of people think about it as treatment for breast cancer, which it certainly is, but it can also be used in a preventative way to prevent breast cancer in the first place. And, again, some women, especially the BRCA2 women, can reduce the risk significantly, almost 60%, or a little over 60% risk reduction for breast cancer. So, that's a very good option for some women. Next slide.

I think a lot of people, you know, obviously are familiar with this. Angelina Jolie decided to do both of these, but surgically you can decide to nip -- you know, to be really aggressive in terms of reducing the risk. And none of these is 100%, but they do significantly, significantly reduce the risk. So, a mastectomy, taking off healthy breast tissue will reduce the risk by as much as 90%, or oophorectomy, or taking out the ovaries. And I may warn you, it is not just the ovaries, but it's actually the tubes and the ovaries, so the fallopian tubes and the ovaries. Those can reduce the risk very significantly by over 80% for ovarian cancer. And if you remove the ovaries before menopause, you can get sort of a double benefit -- you can also reduce the risk of breast cancer. So, those are some good options in terms of risk reduction.

Okay, let's get into, next slide, some of the nitty-gritty now. There is something you can use this information for. It might make a difference. You might have a personal or family history that smells like one of these. What are your genetic testing options? And let me emphasize that for the appropriate people, these are covered by insurance. There shouldn't be a huge out-of-pocket cost. So, if you think this is the right thing for you, talk to your doctor about it. Next slide.

So, for genetic testing options, and I'm going to try and catch people up, because you may have had testing already. You may have never had testing, but I'll try and speak to both audiences. So, for BRCA1 and BRCA2, many people had testing at some point. It could have been two years ago, 10 years ago, 20 years ago, but the test has evolved. The test has gotten better and better over time. So, in the old days people would read out BRCA1 and BRCA2, and by old days I mean even eight years ago, this is all that people were doing. They were looking at those two genes and they were not looking at anything beyond that. So, I'm going to talk about beyond BRCA1, BRCA2 later, but this was the heart of testing for over a decade.

When they did that, they did not necessarily detect some very complex rearrangements that I'm showing over here on the right. And so many people, when they got their first BRCA test, it did not include BART or these rearrangements. If you still have your genetic test, you can actually pull it out and check. If they say BART on there, then it was tested, and if it doesn't, then you weren't tested for these rearrangements. Most of the answers came out from this comprehensive, what we call sequence analysis. So, most people got most of the answers, but there were about 5% of genetic changes that got missed that were picked up by BART.

Now, for certain individuals, you may have had a very specific test that was a very good test for you but it was because of certain circumstances. So, as an example, if there was a known mutation, a known BRCA1 or BRCA2 mutation in your family, you didn't necessarily have to have the whole comprehensive test, you must needed to have the very one specific spot in your family, so we would call that single site, single place that was being tested. For some people of Jewish ancestry, we know that there are three spots in the two genes -- two in BRCA1, one in BRCA2, and those three spots altogether account for over 95% of individuals who are Jewish that have mutations in BRCA1 or BRCA2. So, some people had what we call multisite-3 at the time. But at this point I'm going to blow your mind. We're going to go way beyond BRCA1 and BRCA2. Next slide.

When I talk about the results here in terms of possible test results, these are true of either BRCA1 or BRCA2, but it's also true of all the other tests, all the other genes that we'll talk about in a second. So, if the test comes out positive, and I know we have very confusing terminology. But if the test becomes positive, that doesn't necessarily mean positive, great news, woo! What it does mean, though, is that there is a change in the gene. So, we did find a change in the gene that is associated with increased cancer risk. If the test comes back negative, that doesn't mean, you know, oh, what a negative sort of day it is; it means that we did not find a genetic change associated with an increased cancer risk. But there are two times, two different circumstances when you can get a negative test, and they have slightly different implications.

So, imagine the scenario where you know there is a BRCA1 mutation in your family. Maybe your sister had testing, she found that she had the BRCA1 mutation, and you got tested for BRCA1 and you don't have any mutations, you don't have any changes. In that particular case, that is really great news, because we know what's causing the increased risk of cancer in your family and you don't have it. You got lucky. And in that particular case, I can now significantly reduce your future risk of cancer. I can never say it's zero, but I can significantly reduce your risk of cancer to what we say is the general population.

There is another circumstance, though, where you say you have had breast cancer and you now go through this test and you get a negative result, or you are told that there is no gene that they've been able to identify to account for your breast cancer, that's good news in the sense that we would think you don't have BRCA1, you don't have BRCA2, but we can't define what caused your breast cancer in the first place. And it is possible that there is a BRCA12 or a BRCA25 that we haven't yet identified, and maybe you have one of those genes that we just don't know about yet. So, I can't take you or your family totally, totally off the hook. I can reduce some of those risks, but I can't make them zero. I can't even make them population risk, because you have a history of breast cancer.

And then, finally, and this is one of the ones that is more complicated, sometimes you can get a result which is what we call uncertain. That is that when we read out your genetic code, your genetic alphabet, we see a genetic change but we're not sure what it means. And I have to admit, I'm very humble about this, that happens for me when I do testing of what I'm going to tell you about in a few minutes. When we do testing of a large number of genes, that can happen to us about 20% of the time. Now, most of those uncertain results over time we will gain experience, we'll see them more, we'll have more knowledge around the world, and we'll be able to interpret them, but that may not happen for a year or five years. So, until you get a certain final interpretation, I would talk to your doctor, see what their take is on it, and I would not necessarily run to get a mastectomy or get an oophorectomy just because there was an uncertain result. That is not the message that you need to go and now have surgeries done or have any extreme measures taken. Next slide.

So, as we look at these, this is just another way I want to be able to show you your level of risk. Again, with this top line, if you find out that it's BRCA-positive, if you know there's a BRCA mutation in your family, that's what that second column is, and you know that you have that BRCA mutation, we now put you into a high-risk category. On the second line there, if we know there's a BRCA mutation in your family and you did not get it, great news, you are at average risk. You are at what we call population risk, nothing special. Now, on the other hand, if we don't know of a mutation in your family, if you end up BRCA-positive, you'll go into this high-risk -- or, I'm sorry. If we don't know about a mutation in your family and you don't have a mutation, you're still at increased risk because there could be, as I said, this BRCA25 or some other gene that we'll identify in the future. Next slide.

So, let's start thinking about, then, all the different tests that have become available over the last six or seven years, because it's gone well beyond this BRCA1 and BRCA2. Next slide.

When you think about this, I'm going to go back to that pink slice of the pie. That's what we've been talking about mostly so far is BRCA1 and BRCA2. But we now have the ability to look at this blue slice of the pie, and that's because we know there are a lot of other genes that account for that blue slice of the pie, and laboratories have started developing tests that are not just BRCA1/BRCA2, but now include many other genes as well.

There is good news and bad news that goes with this. The good news is, you get more bang for your buck. You actually get a better test, you get more information, but the information is varied. It tells you about -- I'll show you some categories in a second. It tells you about some high-risk genes. It also will tell you about some moderate-risk genes, where the risk that we're talking about is not as high as what I just was talking about. We'll also talk about some genes that are relatively

low risk. They increase the risk but not nearly as much as BRCA1 and BRCA2, and it is very, very important to distinguish between those. All of them are not created equally. Next slide.

So, I've broken this out for you and into three high-risk, or three different risk categories. So, on the left, those genes that I consider to be high risk, and for me high risk, just to put a number on it, means fourfold risk or greater. So, if this risk is four or more times the average risk, I would put it into this high-risk category. And you don't have to memorize the names of these genes, but I've listed them here. These are all different cancer-susceptibility genes -- APC, BMPR21A, BRCA1, BRCA2. These are not all genes for breast cancer, but these are in general high-risk genes for a number of different types of cancer.

Okay. In addition to the high-risk gene, there are moderate-risk genes. And when I talk about moderate, generally those are genes that are in the two- or three-, rarely fourfold increased risk. Usually two- to threefold increased risk. There's still certainly higher risk, but they are not what I think of as the highest risk, and so these genes are things like ATM, CHEK2. And, again, you don't need to remember the names of all of these, but to realize that they are, to me, a different level of risk.

Finally, all the way on the right, I want to bring your attention to the fact that we don't know everything, and that's for sure when it comes to genetics. So, there are some relatively newer genes that have been identified that we actually don't have good estimates of risk yet. We will over time. We get smarter the more research we do, more experience we have, but some of these genes could end up at the end of the day falling into the moderate category. I think it's rare, but some of them might even fall into the high-risk category. And as we have more information, your doctor should be able to give you more guidance on that. Next slide. I'm just going to -- this is actually a duplicate slide. Robin, if you can just go to the next one after that. Thank you very much.

So, there is a way that I think of looking at these, and it may be a little bit complicated. So, if it doesn't sink right in, don't worry about it. But what I'm trying to show you is that on the left are these different categories of risk. So, some are very high risk, some are moderate, some are low risk. It generally is the case along the x-axis, or along the bottom here, when I say how frequently they are in the population, how frequent they are in the population. The very, very highest risk genes are also the rarest ones in the population. The ones that are at moderate risk are more common, so we see them more frequently; they fall into that rare category. And some of the genes that are low-risk genes, we actually see very commonly, so they're kind of inversely related, how impactful they are and how common they are. Next slide. And if you didn't get that message, don't worry about that too much.

One of the newest things is we actually just published this paper that shows that there is also some overlap between genes that we used to think about for colon cancer and genes that we think about usually with breast cancer. So, if you have in your family breast cancer and colon cancer, it could be one of these two genes, MSH6 or PMS2. And so knowing this is actually helpful, because colon cancer is a very, very preventable form of cancer, and if you have one of these genes, we want to make sure that you're getting your colonoscopies. And, again, the reason I'm mentioning this is because we have expanded the number and the genes that we include in hereditary breast cancer testing to include genes, in this particular case, that people used to think of for colon cancer. It makes sense, I think, to be able to keep your bases covered. Next slide.

So, one of the things that's happened in a good way is that the cost of all of this testing has come down. We got rid of gene patents in the Supreme Court. We developed some new sequencing

technology, and all of this has had the effect of doing wonderful things for patient care. It has made it much less expensive, so we can actually decrease the cost. We can sequence more genes, we can get results much faster. That's been very helpful to guide women once they get a cancer diagnosis on a biopsy to make a surgical decision. And we get more robust testing, that is, that we are more likely to have a test that can pick up more of the genetic changes that we see. With this, the tendency for laboratories has been to say, well, more is better. You can do more and more and more and you'll get more information and more is better. And for some people that is true, and when that's true, then I'd love to be able to give them knowledge.

Knowledge can be power for many people. But I will say, and I will warn you, that for some people they will get some of these variants of uncertain significance I talked about before, and uncertainty makes them anxious. It makes them nervous, and I can say that we've done studies of this for a small number of women, that's not a good thing. So, I just -- it's important to figure out which one of those buckets you're in. If you're one of those women or men that say knowledge is power, bring it on, then you can go with what I call the papa bear version of this, big, big, big. Other people, like I say, get nervous and anxious, and I give them the baby bear version of this. And the nice thing is that it's not one size fits all. Different sizes, different number of genes, different sizes of the tests that we do need to be tailored to the woman and to that situation. Next slide.

So, as we're doing this, I put just as an example, and this is just one example, but here's an example of a gene test called BreastNext. It includes 14 common genes associated with breast cancer, and that is something that some people like doing. Next slide.

I'm not here representing any one company that is doing the testing, just telling you generally of that testing. But there is another laboratory that has a test that is called MyRisk, and they've developed that test so that it actually covers very widely many, many types of cancer. It covers breast cancer, ovarian cancer, stomach cancer, colon cancer, prostate, pancreas, everything. And so the reason I'm saying this is, again, you've got choices. You can be able to say I want screening for all types of cancer. Maybe there are several different types of cancer in my family and I want to keep my bases covered, and there are tests for you in terms of doing that. Next slide.

So, within this, I want you to remember that some of you have had testing before and it might be time for a refresher, for an update. Again, this is very likely to be covered by insurance, if you decide you want to do it. If you have Medicare, very often covered by Medicare as well. And I just put, to remind you, the bullet points of people who did at one time, BRCA1/ BRCA2, if your results were normal, the people who are most likely to get an answer if you expand and go on to additional testing, or when there is a strong family history, three or more family members; when you've had bilateral breast cancer or more than one primary diagnosis; if you had your breast cancer at a young age, less than 50; or if there is a history of a man in the family with breast cancer, or if you, yourself, are a man with breast cancer; and, again, the combination of breast and ovarian cancer. Next slide.

So, when we think about this, again, there are different exposures in this, or different sort of levels of strength. BRCA1, very high risk. Some of the other genes that we're talking about now, lower risk, or even if it's a newer gene, even potentially an unknown level of risk. Next slide.

With the variance of uncertain significance, again, I'm showing you on the bottom here that this is difficult for us right now. If you get one of these variants of uncertain risk, you may be in, I call it genetic purgatory. There is a period of time where we just don't know what that level of risk is, and, again, what I usually tell patients is that I will give you a second opinion, and my second

opinion is usually pretty good about being able to tell you whether to worry or not. But if I tell patients don't worry, it really means don't worry about this. It's very likely to be a low level of risk and just table it for right now. Statistically, more than 90% of those uncertain results will end up being essentially re-categorized as being normal, low risk or no risk type of genetic changes. So, in other words, nothing to worry about. So, in general, my message is don't worry about variants of unknown significance until your doctor tells you to do so. Next slide.

The last thing I want to say just in terms of wrapping up is some people have been worried about, is there some way that this could come back to bite me? Is genetic testing something that could somehow hurt me or hurt my family member, a daughter, a son? And there is a federal law in place called the Genetic Information Nondiscrimination Act, or GINA. We passed this to protect people so that you could not have your insurance rates raised, you could not be denied insurance, you couldn't be discriminated against in your employment from getting a job, that you would not have to worry about those things.

I will say that this is not at all a perfect law, though, and there are some holes in it that I wish weren't there. But it does not protect you in terms of your life insurance, disability insurance, or long-term care insurance. And so in theory, someone could ask you if you've had genetic testing, what was your test result. Oh, you're at higher risk of cancer, you know, I'm going to raise your rates in terms of your insurance. In my experience over the last 20 years, that hasn't been happening, but it is a theoretical possibility. For people who have already had cancer, I have to say that the insurance companies are making their decisions based on your actuarial tables of having had cancer; they're not doing it based on genetic test results. So, I'm not at all worried about people if -- is this making their risk any higher than it already was.

Okay, very last slide, just to sum up what we've been talking about tonight and then we'll open it up for questions. Again, for anyone who has had breast and a family or a personal history with ovarian cancer, definitely be thinking about what I've been talking about. There are women who I hope that even though they had negative testing in the past, there is some benefit to being retested with the additional genes that we've been adding for this. Not all of those genes are yet immediately understandable in terms of what exactly the level of risk is, but with time I do think we're going to get much better clarity. And one of the things I wanted to emphasize is tonight's discussion was not about sequencing of the cancer itself. That's a different talk for a different night. But tonight was focused on being able to look at the hereditary factors and, in particular, if you're listening tonight thinking about your kids, these are factors that can be passed down in the family. Okay, so let me stop there and we'll open it up for questions.

Robin Perlmutter: We have a question in the chat. Is the MyRisk now available? I've had three different cancers.

Wendy Chung: Yes. The MyRisk is now available. There are -- there is a test that's called literally MyRisk, and there are several other laboratories who have things that may be branded differently, but they're the same, essentially the same test. So, if you talk with your doctor, this could either be -- you could go to your oncologist. I'm sure they can be able to point you in the right direction. If you google it for the National Society of Genetic Counselors, NSGC, they have a place that says Find a Genetic Counselor, and they will also help you with that. But with three cancers, I'm virtually guaranteed that your insurance will cover the MyRisk test or something comparable to that.

Robin Perlmutter: Thank you.

Unidentified Participant: I have a question. I was genetically tested 11 years ago and I have a BRCA1 mutation. Would it be beneficial to be retested with the expanded protocols?

Wendy Chung: It is very likely that unless there is something in your family history that does not go with BRCA1, that BRCA1 is the one and only answer for you. I have literally a handful of patients who have more than one genetic change in more than one gene, but it's very unusual. And so you usually see if you're seeing cancers in your family besides breast, ovarian, perhaps pancreas, then it probably is just BRCA1. But if you're seeing a lot of other things, especially early onset, then there might be reasons to go on and expand the testing.

Unidentified Participant: Okay, or the MyRisk would cover that? Let's say, there's already colon cancer or lung cancer, or…

Wendy Chung: Uh-huh. So, the MyRisk will cover colon cancer, as an example. Lung cancer, just because you mentioned it, is more often associated with other environmental factors, smoking, other pollutants, things like that. But especially if that person didn't have a smoking history, then you can certainly go on to MyRisk or the expanded panel.

Unidentified Participant: Okay, thank you.

Wendy Chung: Sure.

Robin Perlmutter: Okay, we have two questions in the chat, Dr. Chung. One is: I was diagnosed with breast cancer when turning 50. I was told that I most likely didn't have the BRCA gene because I was 50. Is this true? No history in my family.

Wendy Chung: Yes, so with no history in your family, if you're not Jewish, it is most likely the case that it is not one of the BRCA genes. So, to give you some statistics with this, your chance of having one of the genes -- even if you went with a relatively large one of these tests, your chance of having one of these genes would be somewhere in the neighborhood of 5% to 6%. So, it's not a huge percent, but it's not zero, either. And so what I'm finding these days is that almost every woman who gets a breast cancer diagnosis less than 70 is at least thinking seriously about doing one of these genetic tests. Oftentimes just to rule it out, just to make sure. But this testing is relatively inexpensive now. Just to give you some sense of this, there are laboratories that are doing the testing now for $250, and I realize that's not nothing but it is much, much less to, in the old days, some of you will remember, it was thousands of dollars, $4,500 even for testing. And the point that I'm making is that it is not a very expensive test anymore.

Robin Perlmutter: Okay, thank you. We have another question in the chat. I had endometrial cancer. I have cancer all over my family tree. Both of my parents had breast cancer. My sister had colorectal cancer, also aunts and cousins. A couple of years ago I had the MyRisk test done and nothing was found. Do you think it would be beneficial to redo the test?

Wendy Chung: That's a good question. Just based on what you said, it does sound like a significant family history. The testing does change. I will say if you had something like the MyRisk two years ago, the incremental improvements in the test are unfortunately not huge within the last two years. Within the last five years, definitely huge, but within the last two years probably not so much so. If I were you, I would sit on the sidelines for now. It may be two, three more years I would check in again, because there is enough that is concerning to me about what I heard in the family history that there might be something going on, but you're pretty close to up-to-date right now. And I don't want you to waste your time right now, because one of the things I worry about is that if you go

back to get testing in the future and the insurance company would say we've already paid for that, we're not paying for it again. And I want to make sure the incremental improvement is really substantial the next time you go in for the testing. So hold tight for right now is my advice.

Unidentified Participant: Thank you.

Unidentified Participant: If we get the genetic testing, does it have to be interpreted by someone or is it written plain enough for us to follow?

Wendy Chung: So, it's a great question. I hope the laboratories are writing what I call the executive summary in a plain enough language for you to understand. I will say that not all labs are created equal, but hopefully what they put, they kind of box it. I hope, at least, they put it in a box on the first page in bold letters, either it's a normal result or it tells you it's positive and the name of the gene and specifically the genetic change. I will say, though that it is -- I always find it helpful for one of the doctors to put it in the context of your situation, your personal situation, where you are right now with your cancer or not, with your age, with your other medical issues or not. But I do think contextualization is something the laboratories cannot do. They don't know you, they don't know what medications you're on, they don't know what your family history is. So, even though I hope the test results is something legible that you'll understand how to read, the doctors, your nurses, your nurse practitioners, all those people, I think, are helpful to be able to help you make decisions about how to use that result.

Unidentified Participant: Okay. If they do, it sounds good. Thank you.

Wendy Chung: Sure.

Robin Perlmutter: Thank you. Dr. Chung, can you comment on when you have positive results and you have, say, your BRCA-positive, and you have daughters and sons. So, at what point do you -- is there an age range where it makes sense to start considering the test?

Wendy Chung: That's a great question. So, I like to -- my mantra is get news you can use. So, what I mean by that is when would you start using that information to do something different? And so we start screening for women, in particular, for BRCA1/BRCA2. We start screening them for breast cancer at the age of 25. That's the earliest we see any breast cancers coming up. And we don't see the ovarian cancers coming up until the late 30s, usually the 40s, if even then. So, for women, I usually don't test them. I mean ,they can get tested theoretically whenever they want to once they're adults, but I usually don't strongly encourage it until they get 25, because that's when you need to start doing the screening. There will be -- I'll put sort of a novel idea out there. There are some young ladies, even young men, that are coming to me these days that are saying even though I'm not worried about myself, or I know what to do for myself, I'm at the point of having -- wanting to have children, and I am worried about passing these genes on to my kids. I'm worried, can I prune my family tree? Can I do something to make sure the next generation won't have to worry about it? And if that's the case, then that's an issue whenever it is you're planning on having kids, whether it's 21 or 31 or 41, whenever that age is, then it is relevant to know your genetic status at that point. And there are, I know it sounds kind of sci-fi, but there are ways of doing what we call pre-implantation genetic diagnosis. It's a way of making a baby using in vitro fertilization. I think people have probably heard about that. And then before you get pregnant they figure out which one of the embryos will or won't have BRCA. I'm not saying that most people do this; most people clearly do not, but it is something that a small number of people will think about. And before you go through that, you'd obviously want to know your genetic status.

Unidentified Participant: Thank you. That was good information.

Unidentified Participant: So, I had breast cancer at the age of 42, and it was about 20 years ago and I was never tested. Now, if I get tested and nothing shows up with any kind of gene mutation, it sounds like it would still be, you know, appropriate for my daughter to be tested because I had breast cancer, correct?

Wendy Chung: So, you brought up an amazingly good point. I am so glad you asked your question. So, within the -- if you're concerned about your daughter, you are always the best person to start the testing with, because you're the one who had the cancer. And the question your daughter is really asking is, why did my mom get cancer and could there have been a genetic factor that she passed down to me?

Unidentified Participant: Uh-huh.

Wendy Chung: So, let's just think this through for a second. If you take the genetic test and you come out normal, you don't find any genetic factor, then there is no genetic factor to test your daughter for that you would have passed down to her, because she's going to be normal, right? If you were normal, she's going to be normal for that same factor, unless there was something coming from her dad's side of the family. So, the best, you know, way, the order in which to do this is, start with you. If you're normal, don't bother with your daughter. On the other hand, if you come back positive for something, then it's worth testing your daughter for whatever you came back positive for. Does that make sense?

Unidentified Participant: Yes, thank you.

Wendy Chung: Okay. Now, on the other hand, just one other thing I'll warn you about. If you test normal, your daughter doesn't need to get genetic testing, but she still has a mom who had breast cancer at the age of 42, so I would do more careful screening for her. And my general rule of thumb is I'll start your daughter's screening 10 years before your diagnosis. So, if you were diagnosed at 42, I would start her breast cancer screening at 32.

Unidentified Participant: Right. And it would it be more than just a mammogram, also an MRI would you recommend for her?

Wendy Chung: So, depending on the rest of the family history, then, yes, mammogram plus MRI and, again, doing that every six months alternating.

Unidentified Participant: Okay, thank you.

Wendy Chung: Sure.

Robin Perlmutter: Thank you.

Wendy Chung: Great questions tonight. You guys are really on the ball.

Robin Perlmutter: Okay, folks. Well, that wraps it up. I want to thank Dr. Wendy Chung for your passion, your dedication, your commitment to the cancer community, and all the great work you're doing, and for this wonderful presentation this evening. I also want to thank all of you folks for coming online tonight and listening to this very important presentation. I want to wish you all a good evening. Thank you.

Wendy Chung: Thank you.