

**GAIL J. HURT:** Good morning. Thanks for the opportunity to talk with you about hereditary breast cancer and genetic testing. I think in the past when we've had these symposiums, we've tended to focus just primarily on what we call the BRCA genes, BRCA1 and BRCA2. But I think this year we have some updates that I hope you're going to find interesting as well as useful.

Most women are surprised to learn that the hereditary breast cancer is pretty rare. It's not all that common. I tell women if we had a room full of 100 women who had breast cancer, probably only 10 of them would have it as a result of what we call a genetic mutation, kind of like a misspelled word, in one of the genes that causes it not to work properly. And that puts folks at high risk for certain cancers.

So just to give you an idea of where we've been with all this, with hereditary breast cancer and genetic testing-- and this will be very brief because of time-- it was Dr. Paul Broca back in the mid-1800s who took notice that cancer seemed to be running in families.

I know you can't see all this, but the little black circles there represent breast cancer in the family, and this is his wife's pedigree. But he noticed that in some families, the grandmother and then the mother would develop breast cancer, and then the daughter would grow up and she too would get breast cancer. So he was probably one of the first people to acknowledge this.

But it really wasn't until the 1980s that a young medical geneticist by the name of Dr. Mary-Claire King started to look at this. She believed that this was something that was hereditary and, at the time, not many people believed that. In fact, some folks openly criticized her.

But she set out to prove it one family at a time. Doctors would refer patients to her. They would call her up and say, I have this family. You might want to look at them. There's a lot of breast cancer. And so she would look at these families to try to find the cause. She believed that truly it was hereditary.

And in 1994, she discovered the first breast cancer gene, BRCA1. At the time, one of the commercial laboratories, Myriad Labs, patented this. And that meant that other labs around the country could not offer the test. They could offer a panel of genes, but they could not include the BRCA genes in this. And that's changed now. We'll talk about that in a bit.

So we think-- we always say the BRCA genes are the big players with hereditary breast cancer. And they probably do make up the majority of causes of this, but we really don't know exactly what percentage. I think we'll learn more as we do more and more testing, and we look at more and more genes.

So how do we find families that actually need to be tested? Well, the tool that we have is cheap. It really doesn't cost anything. If I asked all of you in the audience today if you know your family history, how many of you could honestly say that you know who in your family has had cancer, and what kinds? I think it's important, but we don't often know that.

So as clinicians, we should go back three generations looking at families. We always include maternal as well as paternal. And a lot of times, women will not often report the paternal side because they think, well, we're asking ovary, so dad's side doesn't count. And truly, some of the women are told that, unfortunately. So we always include both sides because the father contributes equally to the gene pool.

You want to know about all family members, not just those who have cancer, because you want to get an idea of the size of the family. In some families, there may have been 12, 14 kids. That's a large family. So it's not unusual to see a lot of cancer occurring. But other families are going to be smaller, where there are not a lot of females who may have developed cancer. We call that a limited family structure.

So when you do the family history, you want to record the types of cancer, the age at diagnosis, and which side of the family it occurred on, maternal or paternal. Because sometimes you'll have cancer on dad's side. You'll have cancer on mom's side, but it's a different bloodline.

So Dr. Jeffrey Weitzel, who was our keynote speaker a few years ago here for our symposium, did a study where he looked at over 300 women who had-- they were diagnosed prior to 50-- but they had small families, a limited number of females. And he tested these women, and one out of seven ended up having a BRCA mutation.

Now, these families, these women, would have been missed if we used only our risk models that look at how many people have had cancer in the family. So he concluded that anybody under 50 is appropriate for testing. And that's kind of where we start. If somebody comes to our clinic and they're diagnosed prior to age 50, then we're going to be asking more about the family history.

This is a busy slide, but I wanted you to have the current NCCN Guidelines that show the things that help us to identify these families where it could be hereditary. Again, diagnosis at a younger age than what we would normally see. Most women are diagnosed postmenopausally.

But with hereditary cancer, one of the huge red flags is a younger age at diagnosis. Some folks will have two primaries. And you will also see, in some families at least, ovarian cancer, fallopian tube cancer, or primary peritoneal cancer. That's a huge red flag.

We know that in the Ashkenazi Jewish population, one out of 40 individuals are going to have a BRCA mutation. And there are three common what we call founder mutations that we can test for quite easily that are going to pick up about 90% of the mutations in the Ashkenazi Jewish population. That test is going to be much less expensive. It's called a Multisite 3. And again, that's going to rule out most, but not all mutations. So there's a higher incidence in some populations of people.

If there's a BRCA mutation in the family, then certainly we can test and do that quite easily. And that's a single-site analysis, so it's much less expensive. And when we see males with breast cancer too, that's another huge red flag. So we recommend testing in any of the males who are diagnosed, regardless of family history, because that's pretty rare.

So I kind of highlighted some of the changes that have come about with NCCN Guidelines more recently. They do acknowledge that limited family structure. And they also have included people who have triple negative breast cancers diagnosed prior to the age of 50. That was fairly new.

And then pancreatic cancer. As you'll see, pancreatic cancer we see occurring in BRCA2 mutation carriers. So NCCN Guidelines now acknowledge that and include it. And then sometimes you'll see families where maybe there's more pancreatic cancer than there is breast cancer. I have a patient coming in soon who's got, I think, there are three pancreatic cancers in the family, including her own, and there's also breast cancer. So in some families, pancreatic cancer is expressed more often than the breast cancer.

So these are the risks as we know it, and these risks may change as we learn more. There are a few differences between BRCA1 and BRCA2 mutation carriers and the types, also, of cancer. BRCA1 breast cancers, the majority tend to be triple negatives. The reverse is true with BRCA2. Most of those are ER-PR positive.

You can see the risk for breast cancer. There's females, about 57% to 87%, with BRCA1. 1 BRCA2, not a lot of difference there. But the risk for male breast cancer is actually higher with BRCA2 mutations. It does occur with BRCA1. In fact, we have a family now where a gentleman has breast cancer and his mutation is BRCA1.

The big difference, I think, is where ovarian cancer comes into play. There is a big difference there. So with BRCA1, the risk is much higher, as you can see, 39% to 40%, compared to about 11% to 18% with BRCA2. I still think, even if that risk is as low as 11%, that's still high for a cancer that's very, very difficult to detect until it's at a more advanced stage.

I think this is helpful when we meet with folks who are contemplating perhaps having mastectomies, bilateral mastectomies, and they're young. And we talk about lifetime risk being as high as 84% to 87%. That can be overwhelming. So I think it's helpful if you can break it down into decades of life.

So even in a mutation carrier prior to age 30, the likelihood that they're going to get breast cancer is going to be less than 5%. Does it happen? Yes. We see it happen, and we've had it happen, but it's rare. It starts to go up. You can see a difference between BRCA1 and BRCA2. It starts to go up by 40 years. With BRCA1, it's almost 20%, whereas with BRCA2 about 12%.

But by 50 years, the bottom line is about half of the mutation carriers are going to develop breast cancer, and then it continues to go up with age. So I think that's helpful when you're having that discussion, particularly with some of the younger patients.

As if it isn't bad enough to be at risk for breast and ovarian cancer, there are other cancer risks that go along with it, and particularly with BRCA2 mutations. You can see the risk of prostate cancer is increased in males and, again, pancreatic cancer. But of course, that's more with the BRCA2 mutations than it is with BRCA1.

There was a question initially about colon cancer and whether the risk for that was also increased when the genes were discovered, but studies have not found that to be true at this point. Again, male breast cancer with BRCA2. And then we can see these other cancers that go along with this.

So I'm often asked, which is better, to have a mutation in BRCA1 or BRCA2? Well, it's kind of a trade-off. The risk for ovarian cancer is much higher with BRCA1, but then you have these other cancers that are more prevalent with BRCA2. So I don't know. I think it's tough. Again, I would just emphasize, if you have patients who have pancreatic cancer, consider testing for BRCA2 mutations in those because, again, that is sometimes a very common cancer in mutation carriers.

So when a woman comes to you and she's concerned about her family history and she's contemplating having genetic testing done, where do we start with that? Well, this is our strategy. It's always, always, always best to start the testing process with an affected family member because they're more likely to harbor a mutation. So if the patient comes in, you want to find out if some of these affected family members are still living, assuming the patient herself has not had a cancer.

So we would start with that. And then once we find a mutation, it's easy to go on and test other family members and determine whether or not they inherited the mutation. This is autosomal dominant. So each child of a mutation carrier would have a 50/50 chance that they inherited it. The cost is going to drop, too, considerably. Currently, it's been over \$4,000 to test, to do full sequencing and try to find the mutation in the family. But once it's found, it drops to \$475 or less with some of the other labs.

And again, with the Ashkenazi Jewish population, you'd want to do that Multisite 3, start with that. If it's negative, you can go on. And depending on family history, if it's strong, you may want to go on and do the comprehensive analysis just to rule out mutations.

So you would think, and most women who come in think that it's either going to be yes or no, positive or negative. But as you can see, that's not always the case because there's a third possible scenario, and that's called the genetic variant of uncertain clinical significance. I hate that test. It's ambiguous. I hate that result. Very confusing to patients. But we'll talk about each of these.

When somebody tests positive, this is what we can do. They have options. I think this helps women to not be blindsided by the cancers because they can take action to reduce their cancer risk. So they can choose to have close surveillance. We'll talk about that in just a minute, what that involves, versus bilateral prophylactic mastectomies or using drugs like tamoxifen to lower risk.

And tamoxifen has been shown to lower breast cancer risk even in BRCA1 mutation carriers, even though those are the triple negatives. The best risk reduction with tamoxifen is going to come with BRCA2 because most of those are ER-PR positive. But there is some benefit even in the triple negatives. And then ovarian cancer. We strongly recommend that folks consider having ovaries removed by mid to late 30s because it just is difficult to detect.

Again, these are the NCCN Guidelines. You can see that they still include the breast self-exam starting at 18. And we were just told that ACS no longer recommends that. So there's some discrepancy there. But they should be having a clinical breast exam every six months starting by age 25. And again, even though this shows annual mammograms and breast MRIs starting at 25-- I'll show you another slide in just a minute-- that's been modified a little bit.

And then also just to discuss the possibility of risk reduction by having bilateral prophylactic mastectomies. And when a woman is beyond-- when she's completed her family or by mid to late 30s, consider having ovaries removed. And it's important to always remove tubes. We've actually had folks come in who had ovaries out and didn't have tubes removed and had a fallopian tube cancer. So remember that not only ovaries, but tubes. And primary peritoneal cancers are also part of this [INAUDIBLE].

And I think it's important that they do that where they have good pathology, good pathologists, to look at this because they're looking for possible occult cancers. Early stage ovarian cancer would be fairly easy to treat if we could catch it early. But by the time it's detected, it's typically a stage 3 or a 4.

And again, they still have the transvaginal ultrasound and CA 125. CA 125, as many of you know, is just not very helpful at detecting this. It's only elevated more with women who have an advanced stage of ovarian cancer and not an early stage. So you also get false positives, which are going to lead to more invasive tests and perhaps surgery needlessly. So it's just not a very good marker.

I hope one day that we'll have better markers and be able to detect it earlier, and folks won't have to have their ovaries out. But we're just not there yet. And again, chemo prevention with drugs like tamoxifen to lower risk and consider some of these imaging studies.

So this just shows you some of the updates from 2013. Again, I mentioned the annual mammograms and breast MRI screening. The thought now is that perhaps we should delay the mammograms until a woman gets to be 30. Because even though the amount of radiation with a mammogram is quite low, as Dr. [INAUDIBLE] pointed out, we're exposing them over a longer period of time if we start at 25.

So consider doing breast MRIs starting at age 25, and then at 30 adding in the mammograms. And our radiologists recommend alternating those so that they're getting one or the other every six months. For men, prostate cancer screening, if they've got a mutation, should start by age 40. They included that.

Surely you didn't think that I would go through this without showing a picture of Angelina Jolie, who came forward this past summer to announce that she was having bilateral mastectomies to reduce her risk because she had been found to have a genetic mutation. And she has done more to raise awareness about this. And one of the labs, I think Myriad, has kind of been backlogged a little bit because so many people are coming forward and wanting to be tested.

And we're getting lots of calls. And really, one of my fears was that we would get calls from folks whose grandmother had breast cancer at 90. Do I need to be tested? But quite honestly, the folks who are coming in, it's surprisingly quite appropriate. I think they just had no idea. And I'm hearing that from folks. I had no idea that this was important until I heard Angelina Jolie's story. So she has raised awareness certainly.

So we talked about if somebody's positive, what happens? That's fairly straightforward. I think it gets a little trickier when somebody's test result comes back negative. The last thing we want to do is give false reassurance and say, well, your test was negative. This was not hereditary. Go forth and have a good life. Don't worry. It couldn't be passed on.

That is not the message that we want to give folks, particularly if they have a strong family history. The only time we can do that is when a mutation has been identified in the family, and we test this person and it's negative, we can say, you did not inherit this. Your risk is about average. And this is one time in your life you really do want to be average. We strive to be above average, but you don't want to be there with this.

So it's definitely different if a mutation has been identified. But if it hasn't, we can't rule out the possibility that there are other genes or there are rare mutations that just couldn't be detected. So you kind of have to, in those cases, base your clinical management and any surgical decisions and risk reduction decisions on personal and family history.

So this is the third possibility and the one, as I mentioned, that I hate the most. And that's the Genetic Variant, or GVUS, as we call it. Sometimes when you're looking at these genes, a change is found that may or may not increase cancer risk. We don't know, because it may be the first time that scientists have actually seen this particular change. And so they don't have enough data yet to know how to classify it. Once they do, they can come back and reclassify. That can take years.

It turns out, in some cases, to be what we call a benign polymorphism that doesn't increase risk at all. But in some cases, it can be what we call a deleterious mutation that does increase risk. So in those cases, it's like saying we found something, but we really don't know what it means. And so we've effectively increased somebody's anxiety level without giving them concrete information. Again, it can take years before that gets reclassified.

We always tell women who have this, if you move we need to know how to find you. Do you think that happens? Not always. It's hard to track them down sometimes if it's seven or eight years later, and we get test results back.

So when testing first became available, I think the hit rate with these variants was about 30%. It was pretty high. But as more testing has been done, then they've had a chance to observe these and to classify them. And I think with Myriad now it's about 3%. Ambry Genetics reports about a 4%, 4.4%, hit rate with these variants.

So we've talked about the past, how the genes were discovered. Let's focus just a minute on the future and where we're headed with genetic testing. And there's something called next-generation sequencing that moves beyond just the BRCA testing. As most of you know, back on June 13, the Supreme Court handed down a ruling saying that you cannot patent DNA. So that meant that Myriad lost the patent, and that opened it up to other laboratories to be able to include these BRCA genes with their panels of tests.

I will say, giving credit where credit is due, Myriad Labs has tested about 10,000 women at no cost through their financial hardship application. We've tested quite a few. So they've done a good job with that. But now we can actually do panels of genes and include these BRCA genes. So it's a more comprehensive test.

One of the labs, and this is Ambry Genetics, but these genes right here-- and can't see that one-- in the pink they include this as part of their-- what is it called-- BRCAPlus, I think, is what they call this test. They include these genes that increase breast cancer risk and don't just focus on the BRCA genes.

BRCA is part of this, but you can see P53, PTEN, and some of the others. They have a test that goes even beyond that that offers a more extensive panel that's going to focus on some of the lower penetrant genes, and that's even more comprehensive. So if you've got a patient who's got an incredibly strong family history, you may want to include doing some of these panels.

University of Washington, where Dr. Mary-Claire King is located, she and Dr. Tom Walsh have developed a test called BROCA, the BROCA Gene Panel. And it actually analyzes 42 different genes, including all 18 of the breast cancer genes. So it's very comprehensive. An interesting thing is that the cost is \$3,300, whereas women have been paying \$4,000 just for BRCA sequencing.

So if a woman came in and she's got a strong family history, of course you want to start with those BRCA genes. You want to include those. But until this ruling came down, you could not offer a full panel and include the BRCA genes. So I think this is going to be really helpful. The only way a woman could get this done was to, first of all, have that test for \$4,000. If that was negative, then you had to move on do another test. And pretty soon, that was thousands of dollars, and insurance is not going to cover all that.

So the fact that we can offer these more comprehensive tests, I think it's good, but it also adds another layer of complexity to everything, too. It's going to pick up mutations in genes that we weren't picking up on before. And I have this fear, really, as I look back over all the patients we've tested over all the years, and we were only testing essentially for the BRCA genes, we missed some. I know we have. And so this, hopefully, will help us detect mutations in other genes.

So it's going to be particularly useful in women who have these strong family histories, and it's even less expensive. Again, more complex. You're going to find more genetic variants that can't be classified because we're testing more genes. And not as much testing has been done in those genes, and we don't always know as much about the actual risks and how they should be managed.

The turnaround time is going to be longer. It can take 12 to 16 weeks to get these results back. I remember back in the day, as we say, when we first started doing genetic testing the turnaround time was about six months. There was no way somebody could get results back in time to make a surgical decision.

Now it's about 7 to 10 days with Myriad. If you do these panels, it is going to add more time. But is it better to do a test that's more limited because you can get the results back faster, or to extend that time and maybe pick up a mutation that would have been missed with that first test? Tough, tough choices, tough questions.

One thing I wanted to point out-- I think this was just presented at ASCO this year-- is that they use that BROCA test that I mentioned that Dr. King had developed. And they looked at almost 250 African American women, and they did that 42-gene panel, including that 18 breast cancer genes.

And they found that 22% of these women had a deleterious mutation. Now granted, the majority, again, the mutations were in BRCA1 or BRCA2. But you can see that left nearly 20% that had mutations in other genes that would have been missed. So there is a higher incidence of mutations in African American women.

I just wanted to show you a couple of pedigrees here. I don't know how much you can see on this. But this is a case where the patient came in with a new diagnosis of breast cancer at 43, and she really didn't think she had a lot of cancer in her family. But that was the first red flag. She was younger than what we would expect. So we decided to test her. She thought maybe way back in her dad's side of the family a couple of paternal great-aunts might have had some kind of cancer, but she didn't know what kind.

So we tested her. And from the time we did the test until she came back to get results, she learned that those paternal great-aunts had actually had breast and ovarian cancer. Not only that, but 14 cousins that she didn't even know about had also had cancer-- breast, ovary, and other kinds.

So if you look at that pedigree, you can see dad didn't have a cancer. He had two sisters. They were in their 70s. Neither one of them had cancer. So if it's paternally transmitted, sometimes you just don't pick it up as easily. And I think this is just-- it's a sad case, because there were so many people in the family, as it turned out, and once she started digging she found all these cousins, because her cancer was pretty advanced when she was diagnosed. So knowing family history is huge.

This one just illustrates a case where we had a young woman who came in. She was very pregnant. She had a new diagnosis of breast cancer. And unfortunately, it was metastatic to the liver when it was diagnosed. Now, what she reported in her family was that mom had breast cancer at a young age. Maternal grandmother had breast cancer at a young age. She knew that her brother-- she had had a brother who died from what she thought was a bone or a brain cancer. She wasn't quite sure about that.

But we tested her, appropriately, for BRCA1 and BRCA2. She was negative. But she was young. She had me talk with one of her relatives who was a better historian, and we learned that one of the relatives had had several primary cancers. And her brother apparently had died from a second primary cancer. He had had a brain tumor that got radiated and then developed bone cancer within the radiated field and died from that.

So it turned out that this family is a Li-Fraumeni family. It's caused by a mutation in P53. And in those families, the cancer risk is high. They are wide open to getting almost any type of cancer. And one thing that you try to avoid with Li-Fraumeni is radiation, because there is a higher incidence of getting a second primary within the radiated field. Of course, if it's palliative radiation, that's certainly different, but want to avoid radiation.

So it's important, particularly if somebody is coming in with a new diagnosis of breast cancer, they're contemplating, should I have a lumpectomy followed by radiation, or should I have bilateral mastectomies? This is important to know. And I think we're going to be picking it up more as we do more of these expanded tests.

This just shows a family where there was pancreatic cancer. The gentleman that you see here with the little arrow was referred by one of our oncologists. He had pancreatic cancer, and he reported that his sister had breast cancer at 45. So we tested him. He had a BRCA2 mutation. Again, this is a family with pancreatic and breast cancer.

And we've got a 36-year-old female who was referred because she had bilateral breast cancer. What else would you want to know about the family? What would you do? Well, you'd get a good family history. And you can see that she also had not only the breast cancer in her 30s, but a phylloides tumor. And then two of her sisters-- I think the line is disconnected here-- had ovarian cancer at a young age.

So she was BRCA negative, but she had this P53 Li-Fraumeni mutation. Again, that would be missed if we stopped with just doing BRCA sequencing. This is atypical. I have to say, there's nothing about that family that would have led me down that path. We usually think of Li-Fraumeni as including childhood cancers, but not always. Some of these are just atypical.

So the last one, you've got a 37-year-old female who was referred because she had a new breast cancer. First thing you're going to do, get the family history. You can see here that the patient had breast cancer in her 30s. She was BRCA negative. Mom had ovarian cancer. On dad's side, the grandmother had breast cancer at a later age.

This one turned out to be Cowden's caused by a PTEN mutation. Cowden's is kind of a not so common syndrome, but we know that it increases breast cancer risk, along with a lot of other cancers as well. So it's important to know and to identify these patients.



Sometimes they'll have certain clinical features-- macrocephaly. I think the head circumference is, in females, about anything over 57 centimeters. Out at City of Hope, Dr. Jeffrey Weitzel and his group say that they always, with any new breast cancer patient, take out a tape measure and measure the head circumference. Women are going to look at you a little funny if you're doing that, but sometimes that helps to pick up on Cowden's.

So just to summarize, I think one of the most important tools that we have at our disposal is going to be that family history. That's crucial. Again, talk to your patient, have them talk to their family, find out about family history. And then refer them, if they're appropriate, for genetic counseling. And not every patient we get is going to need to go on to have the actual testing. Sometimes one of the best things we can do is to reassure folks that maybe they're not at a high risk for getting these cancers.

So I think, genetic testing, hopefully we can help women to keep from being blindsided like so many in their families have been. I think it's just the saddest thing to meet with somebody where you look back at that family history, there were tons of cancer, and nobody recommended testing, and then your patient comes in with a new diagnosis. So hopefully, this gives folks a heads-up so that they can take steps to reduce risk. So I'll stop with that.