



Genetics and Family Risk

Jennifer Litton, MD

LISA SCHLAGER: Well, thank you, everyone. My name's Lisa Schlager, and I'm with an organization called [FORCE](#), which stands for Facing Our Risk of Cancer Empowered. The reason I'm moderating the session is because our focus is on hereditary breast and ovarian cancer. ... FORCE is a national organization that strives to educate and support women and their families who are affected by this.

We're thrilled today to have Dr. Litton with us. But before I introduce her, I just want to encourage you to check out websites for [LBBC](#) and [YSC](#) [Young Survival Coalition] ... should you want more information on this topic, or others related to the conference. [I] also wanted to let you know that we are taping this session — so just know that whatever you say will be either audiotaped or videotaped.

... We [will have a] ... question portion [toward the end of the program, but] Dr. Litton has been kind to say that if you have questions during the presentation, please feel free to ask. We only ask that you try not to detail specific individual situations, [and instead] ... ask questions in a manner that might be helpful and applicable to the entire group. Obviously we all have our personal experiences, but we want to make sure that what we discuss can be applied to everyone, or be useful to everyone. If there are specific questions that need [a] ... more [detailed response], you can talk to the doctor afterwards.

I'd like to introduce Dr. Litton. She received her undergraduate degree from Duke University, and went on to attend medical school at the University of Massachusetts. After completing her residency in internal medicine at Baylor College [of Medicine], she began a fellowship in medical oncology at the University of Texas, MD Anderson Center, where she now serves as assistant

professor of medicine in the department of breast medical oncology.

Her clinical background is rich in high-risk genetic breast cancer syndromes, young breast cancer patients, and breast cancer diagnosed during pregnancy. Her research interests include pregnancy and breast cancer, oncofertility, genetic testing, and molecular changes of breast cancer genes.

So, Dr. Litton.

JENNIFER LITTON, MD: I want this to ... be very informal. Please let me know — this is really tailored for whatever you all want. I put together slides, and we can talk during and also after. Can I sit? Is that — OK.

When we're talking about hereditary breast and ovarian cancer syndrome, we're really talking specifically right now about BRCA1 and 2 genes. But to put that into perspective, these really only account for somewhere [between] ... 5 to 10 percent of all the breast cancers. There are definitely people with tons of breast cancer in their [families]. Quite frankly, we're just not smart enough yet to say, "Is it BRCA3?" or what other situation is going on?

We use a lot of different tools in those families. If we look at this, most of the mutations that we identify are BRCA1, more preferentially than BRCA2. Then there's another group of genes that we're still working on. But when we're talking about BRCA1 and 2 mutations, as you well know, it increases the risk, especially of early-onset breast cancer. You can see this is specifically high when compared to the population risk — 10 to 20 percent by age 40.

Not only does it increase your risk of the first cancer — and that's often where I meet people, because they've been diagnosed at an unusually young age — but unfortunately that doesn't mean you get to check that box and say, "I've had that cancer." What it really tells us is your risk for [a] second [or] ... unrelated cancer. You can have a very high risk of ovarian cancer even after breast cancer, and an increased risk of a second breast cancer. Depending on how old you are with your first breast cancer, [the risk of a second cancer] can be as high as 60 percent.

There are some red flags when we're talking to people about their family history. We call it the three-two-one rule here: three or more family members with the same or similar types of cancer. There are two or more generations affected, and if I see a cancer diagnosed before the age of 50, I'm starting to think I need to look [at] this family a little bit closer.

Why is family history so important? If a doctor says you have breast cancer in your family and you say, "Oh, yes, one [family member had it], "it's really important to [determine] ... on which side of the family [it occurred]. I actually draw out people's family pictures when I'm talking to them. As you can see on the left, this really looks like a hereditary family. It's all on one side of the family. ... There's more than one generation affected. There's breast. There's ovarian. This is a red flag. But you'll see on the right side, there's a breast at [age] 63 on one side of the family, and then a breast at [age] 71 on the other side. The squares are males and circles are women. The line between — that's a marriage. Our woman down here who has breast cancer at 71 isn't blood-related to her husband's mother.

Hereditary breast and ovarian cancer syndrome: I'm going to specifically talk about the BRCA1 and 2 genes. These are the ones that we know the most about at this point, but there are several other hereditary syndromes. One is called Cowden syndrome. This links together some thyroid, uterine, breast. When we see that, we may start to think about this syndrome.

Li-Fraumeni: This links together a whole other group of cancer syndromes. It's very young breast cancer. It's adrenocorticoid cancers. It's people with leukemias and brain tumors, and we start to think about this.

De novo [gene] mutation: ... We've also started noticing [the de novo gene mutation], especially in the last two to three years when we see someone who's diagnosed in their 20s and we rule out a BRCA1 and 2 gene. I'm starting to look for this gene, even if there's no family history, because ... about 7 to 10 percent of the time, we're seeing this mutation that happened when that particular person was made, which we call a de novo mutation. People in their 20s [who have been tested for] ... BRCA1 or 2 [and don't have it]: I'm going to start talking, and you're going to hear about this more and more. ... The cancer centers are putting together our data on this, and I think we're finding [this de novo mutation] in about 7 to 10 percent, is my estimate right now.

Peutz-Jeghers hereditary diffuse gastric cancer: This [mutation can put you at risk for] lobular breast cancer and stomach cancer.

CHEK2 [checkpoint kinase 2] is also a gene that's been associated with increased risk [for breast cancer].

The future — this kind of goes back to the future risk of developing cancer. The earlier you are at the time of your first cancer, if you have a known BRCA1 or 2 mutation, you have a higher lifetime risk of getting a second unrelated breast cancer.

Who are the appropriate candidates for genetic testing? If you have a personal history of breast cancer under the age of 50, I do think it's worthwhile to meet with a genetic counselor, draw out your family history, and try to assess your risk. If you see family history of multiple cases of early-onset breast cancer ... and ovarian cancer [associated with] ... the same woman, [or if you see] bilateral breast cancer, Ashkenazi Jewish heritage, family history of male breast cancer. ... At this point right now, I will tell you, at our center, if you have ovarian cancer at any age, we are testing.

... The newest addition is triple-negative breast cancer [before] ... the age of 60. This was based off two studies from my institution, where we looked at [the issue in] two different ways. One, we looked at all the people who came for genetic counseling, and saw that the proportion [of people who had] triple-negative [breast cancer] before they were tested was quite high. Then what we did is [test] a completely unselected population of women who had triple-negative breast cancer. We tested after they'd already been treated for breast cancer. We tested their tissue and found a 15 to 20 percent risk of ... a BRCA mutation ... [in those women with triple-negative breast cancer] regardless of [their] family history. Right now triple-negative is enough for us to test, especially [if the cancer occurred before] ... the age of 60. That will be in the national guidelines this year.

Which tests should be ordered? This is very confusing for patients and for caregivers. I want to bring this up, because some people may have been tested a long time ago. I just wanted to go through the testing a little bit.

Comprehensive testing: This is full sequencing plus the five most common rearrangement panels. When I'm describing this to a patient, I describe it like this: You have a book. You've gone through chapter one, and in chapter one you make sure that page one is followed by two, is followed by three, and that chapter makes sense. Then you move on to chapter two. By looking through each page of the chapters, the whole book makes sense. As you can tell, it's a very expensive test. We'll definitely do that. But we want to make sure we're [offering] ... the right test.

Multi-site testing: I use this test when someone is of Ashkenazi Jewish ancestry, because there are three very common mutations that happen in people of Ashkenazi Jewish ancestry. You see the difference. It's \$575. What I will do if I'm suspicious that they have a mutation, and they're of Jewish ancestry: I'll order this test first, because if we find the answer for \$575, isn't that much better? We can check a box when we're ordering it to reflex, and do the comprehensive testing if we don't find a mutation in one of those three genes.

Single-site analysis: This is what I see actually misordered quite a bit. ... If your sister has a mutation, she hands you her results and you go to your doctor. The comprehensive testing is like looking for a needle in a haystack. But now we have the GPS to the needle, so we just look for that for \$475. What I've seen misordered sometimes is someone coming in ... [when her sister has] the mutation, and [doctors] order the whole comprehensive testing for over \$3,000, [when] we can get the "yes" [or] "no" answer for \$475.

This is the one I wanted to bring up, especially if you had your testing before 2006. It's called BART, or BRCAAnalysis Rearrangement Test. ... If we go back to our book now, we know that everything in chapter one is OK. But now we're looking at the actual — are the chapters in the right order? If you're missing chapters one through five, the book still doesn't make sense. This is actually looking for that. It's in the \$600 range. What will happen is sometimes if I'm highly suspicious, I make sure that I order BART with it. Sometimes it's hard to get that paid for [by insurance]. If you have a very strong family history, your doctor can actually run some special mathematical models to get that ... included in your test. I really feel that if you're suspicious enough to run the whole test, you should probably just run the whole test.

There are some guidelines for — sure.

WOMAN: We're talking a lot about cost. In your experience, how often does insurance *not* cover?

JENNIFER LITTON, MD: Well, you want to make sure that when you — this is why it's important to talk to a genetic counselor. ... I don't want to just test everyone. You want to test the person most likely to have the mutation, and that's going to be someone who, if [she's] available, [and] affected with cancer, fits [the] ... criteria. I really don't want to go and just randomly [test] unaffected individuals, because a negative test for that doesn't tell me anything. I don't know [if there] ... was a mutation in the family and [that individual] didn't get it, and their risk is the [same as the] general population, or that there's no mutation, but just this big cluster of breast cancer [in that family]. I'm going to use different mathematical models to estimate

your personal risk. It's important to test the best person in the family. That's going to give you the most information.

If you have a strong family history, [and] you got tested before 2006, I would go ahead and talk with your doctor again, because this test has been offered since about 2006. A lot of times I'm seeing people who were diagnosed 20 years ago with strong family histories coming back now for this particular test. I did want to bring it up for that. I also feel that if I'm suspicious enough that there's a mutation in your family, I really like to try to run the entire test.

What I was going to say is that there are some guidelines out there as to who should get this test. They're usually someone with at least one or two family members with a breast or ovarian cancer at any age, [or] male breast cancer at any age. What we presented at the San Antonio meeting showed that those guidelines picked up less than half of the people ... [who have an] ... identified BART mutation. I don't look at those guidelines at all, and that paper is actually going to publish very soon.

That's why I think it's very important to talk with your doctor. Take the time to draw out your family history. Really look at how suspicious your family is, who the best person is to test, and then they can make the best kind of individualized options for you.

I figure by the time we get this up, the 15 minutes is going to be over. Let me kind of go over what do we do for BRCA-mutation carriers. For the mutation carriers, there are lots of options. Let me first say that none of them is a correct option. Everyone is very individual about this. Nothing needs to be jumped into. I have people who are 22 [years old], who are telling me their doctors told them they have to get their ovaries out right now. ... [My response is], "Wait, wait, wait, wait, wait. Wait."

For the breast side of it ... we'll do yearly mammograms, and we'll stagger them every six months with yearly MRIs. Now, that's screening. That's not prevention. It doesn't stop a cancer from forming, but it's hoping to find it as early as possible when cure rates are as high as possible, and to try to decrease the chance of needing a lot of treatment. But I will tell you, from our experience, that we still had at least

15 percent of the patients in our group who were doing high-risk screening get a stage II or higher cancer..

On the other side of that spectrum right now is prophylaxis mastectomy. That's removing the breast tissue and doing reconstruction. That can decrease the risk by about 90 to 95 percent. On the ovarian cancer front, we'll usually recommend about age 35 to 40 to have your ovaries removed, or when you're done childbearing, but not really sooner than 35 in most cases.

My talk just veered way off, so we're going to have an open discussion forum.

I just want to mention one thing, that if you're going to go through these surgeries, it's really important that your pathologist understands that you have a mutation.

[Miscellaneous conversation]

... If someone hasn't mentioned it, the pathology is very different in a BRCA-mutation carrier, as opposed to someone who's doing other sorts of surgery or taking out ovaries or things like that — just because they're having fibroids or something. We look at it very differently. We slide the tissue [in] 2 millimeter slices to look for tiny cancers that might be there. That is very important when you're talking to your surgeon, that they understand how the pathology is going to be handled.

WOMAN: Isn't it important to pick a doctor who's very familiar with BRCA [mutation] ... ?

JENNIFER LITTON, MD: I would hope so.

... Here's my interpreting [of] the results. You have a couple of options that you get at the end of this. You can have a positive test, a negative [test], and then we have to decide: is it a true negative, or is it inconclusive? [Or is it] ... the dreaded variance of "uncertain significance"?

The positive: It explains the cancer in the family. We know what we're dealing with at this point. The carrier [is] at increased risk of breast and ovarian and possibly other cancers. We then want to go through the family

and consider or offer testing to relatives [who] should be tested, and then work with the patient to determine the appropriate management plan.

There are lots of different resources for BRCA-positive patients. This is not all of them listed here. There are so many ... that are here at this conference now. We often give people patient-education materials. What we do at our center is we give family letters, because it's very hard to explain what's going on to Cousin Suzy, who you haven't seen in 20 years. You can hand [her] ... this whole packet, because it's very important if there's a mutation in the family ... to share [the information on risks]. If you feel comfortable, share [your] actual results, for the reason we talked about earlier. We have the GPS to the needle, so people can test and find out if they have that one mutation or not, and not have to sequence the whole gene. Then we refer patients to high-risk screening clinics.

There are other possible test results. The "inconclusive negative": someone with a really strong family history, and I test them and they're negative. It doesn't mean that there isn't something hereditary or something clustering in that family. It just means it's not BRCA1 and 2, [two risk-factors] that we can test for at this time. It could [still] be lots of other factors. What we do when we've ruled that out of a family, we then look at unaffected family members. We can actually use other tools to estimate their personal risk. If they have a strong risk, we can institute MRI screening and other [measures].

It's really dependent — going back to that picture that we've drawn out of that family for the family history — [on whether we tested] ... the most appropriate person. If I tested a 22-year-old unaffected person, and her cousin is the one who had breast and ovarian cancer, and I didn't test the person who was affected, do I know that ... there isn't something in the family? I don't. I tested a completely uninformative person.

If the result is not what I expect, perhaps we need to do more testing. Maybe we didn't do BART. Maybe we need to go through, maybe only the multi-site. Maybe we need to complete all the testing. We also enroll in research studies so we can track families that have very strong

family histories, but we're not smart enough right now in 2012 to tell [that family] what the gene is. There are some patients, too, where there's something so strong in the family, and we take their DNA and bank it for future use ... for [information that can be used by] their family members in the future, as we learn more about different underlying hereditary genes.

The "true negative": Your sister has this gene, and you test negative. Right? You have one gene from your mom, [and] one gene from your dad. All [of] your first-degree relatives have a 50-50 chance of having that gene. This means that their risk now [matches] the risk [found in] ... the general public. We put them back into the screening program of mammograms at [age] 40. Nothing skips generations. If you didn't inherit it, you can't pass it on to your kids.

Here's the example of an inconclusive versus a true negative. On the left is inconclusive. We tested the wrong person. It's a 37-year-old unaffected. But look. There's someone with breast cancer at 45, and ovarian cancer at 47, and [she is] untested. I don't know what that means. But if you look, when we test the correct person, there is a known BRCA-mutation in the family. This person did not inherit it. It's a very different recommendation of what to do clinically for the 37-year-old woman. ...

The uncertain variance — has anyone heard of this? ... When I'm describing the variant of uncertain significance ... [I use this analogy]: We say the word "color" here [in the United States], and [it's also said] in Great Britain. We spell it C-O-L-O-R. They spell it C-O-L-O-U-R. It sounds the same. It means the same [thing]. There's just an extra letter. I don't know if that variant is just that extra "U," or if it truly shuts the gene down. That's ... how I think about it. What we'll do is we'll look at your family history again. We'll go and see, does it track with the family — does that [specific] variant [track with the family]? We don't routinely test unaffected individuals for the variant, for [the purposes of] any sort of decision making, [because] we don't know what the variant means.

We have to work. If I see a variant in a person, I'm going to look at the whole family picture, come up with an individualized management plan [and] annual follow-

up, because what happens is they track all these, and then they'll eventually get reclassified. The likelihood of a variant depends on ethnicity as well, because I need to see it so many different times to really see if it appears to track with cancer or not. There is a variant reclassification program to be part of.

We kind of already talked about surveillance [for young women at high risk]: clinical breast exams every six to 12 months, beginning between [the ages of] 20 and 35, annual mammograms. Ultrasound is less specific, but I find it particularly helpful when I'm trying to feel if — young breast tissue has lots of cysts and fibroadenomas, and all of these different benign things. [Ultrasound is] very helpful in telling us if something looks cystic or something looks solid.

MRI: Why don't we do MRIs for everyone? Because MRI is really sensitive. It shows us everything. But it isn't as good yet at telling us what everything is. There are a lot of biopsies that go on. In fact, even at some of the bigger centers, for every four biopsies that happen, only one turns out to be something you have to do something for. You really only want to use this test in people who have a very high risk going into the test, and you're watching for "is [the scan result] getting better?" MRIs, the technology and the screening is getting better. I will tell you that the technology coming up is exciting [in the area of] ... biology imaging. I think it's all our hope one day to stop the squish. Right?

Recommendations for MRI screening: If you have a known mutation, or you have a known mutation in your family and you're not testing yet, for whatever reason, then just on expert consensus ... there's insufficient evidence right now that MRI screening adds anything ... Especially — this is usually our Hodgkin's disease survivor who had radiation to their chest wall, or Li-Fraumeni, or any of the other hereditary breast syndromes.

... This is so highly debated, [however], and we're not going to answer it here today. But if you've had a personal history of breast cancer or ALH [atypical lobular

hyperplasia], LCIS [lobular carcinoma in situ], or ADH [atypical ductal hyperplasia], or any of these kinds of pre-cancers [MRI is not recommended surveillance]. Right now we recommend not using [MRI] for non-high-risk women.

Consider genetic testing with [those] diagnosed at a young age — you have a family history or triple-negative or medullary-type of breast cancer. Counseling both before and after is paramount, because you need to put your test results in context to what your family looks like. It has repercussions on family dialogue, family planning, as well as reproductive concerns and preventative recommendations. ...

[Applause]

LISA SCHLAGER: For questions, we'll ask that you come up and use the microphone, and just state your questions clearly.

JENNIFER LITTON, MD: If you're too shy to come up to "the microphone, you can come up to me after, too. That's just fine.

WOMAN: Hi. ... I am BRCA1. I was diagnosed five years ago. I've had two babies since ... — I'm 38. The recommendation is ... for the hysterectomy. Is it recommended — my gynecologist is recommending everything taken out, or [is it] just fallopian tubes and the ovaries [that are] recommended [for removal]?

JENNIFER LITTON, MD: ... Definitely the ovaries and the fallopian tubes. A lot of people are not recommending having your uterus out, though I don't think that that's wrong to do at all. It's just a bit of a bigger surgery — some additional side effects to the surgery. I would just sit down and have a strong conversation [with your oncologist]. Some people, if they know they don't want to remove their breasts, and they want to try tamoxifen — although I will tell you I'm not a personal huge believer of the amount of risk-reduction of tamoxifen in BRCA1 mutation carriers, since —

WOMAN: I've had a double mastectomy, so I'm done with that.

JENNIFER LITTON, MD: Then never mind. [Laughter] Definitely fallopian, definitely ovary, personal decision on the uterus is my kind of gist on that. In fact, we all think of ovarian cancer as starting in the ovaries, when in fact in most mutation carriers [it] actually starts in the tube.

Oh, can I just add one quick thing? No, no, no. Stay, stay, stay. There's a lot of debate on whether or not you should do hormone replacement or anything after that. There's no right answer. ...

... There's no right answer and I can't give you a clinical trial that's going to tell you [more about] safety on this. But when I think about this, especially for people who've had bilaterals and do not have — if they do not have an estrogen-fed tumor, you just took away a lake of estrogen, right, when you take out your ovaries. We're giving you back a cup. If you think of it that way, I — you know, you're still a delta negative ... [regarding] circulating estrogens.

If you have a known breast cancer that's fed by estrogen, there's no doctor that's going to tell you to ... take hormone replacement therapy. But I kind of think of it that way. The circulating estrogens we replace are certainly less, especially in the setting of bilateral mastectomies, not a hormone fed, because the menopausal symptoms are immediate and hard when the ovaries come out.

[Next question?] ...

WOMAN: Hi. Thank you for being here and educating us.

I just wanted to try to get a little bit of clarification. If there is an individual who has had breast cancer young, has had relatives [who] have had it young also, [and] also has a relative at postmenopausal [age] taking the initial BRCA testing [and] getting negative [results] is there a benefit to actually going through the whole genetic process, because you have daughters? [The genetic testing] ... wasn't through a whole genetic system — it was just the oncologist doing that —

JENNIFER LITTON, MD: That's my job, so I'm going to say "yes."

WOMAN: You're going to give me a pitch. [Laughter]

JENNIFER LITTON, MD: But it is, because I think spending the time to draw out that picture makes a bit of a difference, because what I see misinterpreted a lot of the time — first of all, I want to make sure the appropriate people were [tested]. If I have two sisters, and one was 40 and one was 45, and we tested one, I still may test the other sister because we all have a 1-out-of-8 chance anyway. We call those phenocopies. In other words, you have an aunt. Aunt Suzie was 60, and she tested negative. But you were 40. I wouldn't just say, "Oh, you're negative because Aunt Suzie tested negative." I would test you, too. I'd look in the family. There might be other people I'd want to test.

Second of all, I see this test misinterpreted. [A person may] ... say, "My sister was tested, and she was negative for the BRCA gene. So, I'm good. There's nothing hereditary." No, no, no, no, no. This test looks for two specific risk factors. There are millions of risk factors. What I want to do is take your family history, and I'll use other mathematical models. Specifically what I use in [my] clinic — because our clinic's busy — I'll use the Claus, C-L-A-U-S model. I can get a quick overview for the unaffected individuals, because I want to know: Do they have a 20 percent lifetime risk? Because [if they do], I'm going to add MRIs on. They might want to do something like tamoxifen or raloxifene, or hopefully, in the future, exemestane if [they're] postmenopausal.

... A negative test does not mean there's nothing else to do. Does that make sense? ...

WOMAN: Just a quick question: In a screening environment, when you're doing screening imaging, is it advantageous to offer high-risk screening? If so, you mentioned Claus [models], are there any other models that —

JENNIFER LITTON, MD: The models that we use — I don't use the Gail. That's the one you go on and you write Gail risk, and it's the NCI [National Cancer Institute's] risk tool.

... It's really not based on family history as much. [In the Gail Model,] if you got two unnecessary biopsies, your risk is now [more than] 20 percent, and that doesn't really tell me much [about a woman's risk based on family history]. [Editor's Note: [See a comparison of the Gail and Claus models.](#)]

The guidelines right now are on family-based [risk]. If you look in the American Cancer Society guidelines, they'll say BRCAPRO. Right? The BRCAPRO model tells you your risk of having a BRCA1 or 2 mutation. Embedded in that model is the Claus model that gives you the secondary estimation risk of an unaffected individual. ... Sometimes I'll look at the family model, because all these models have ... good things and bad things, and they may not take account of this cousin or that. There's another one called Tyrer-Cuzick. ... Once I draw out the picture of the family, I'm going to use whatever model I think is best ... to get your highest risk, to get you to the MRI-screening that's based on family. I'll use Tyrer-Cuzick. I don't use some of the other ones, [like] BOADICEA, but it's a good one. I'll use Claus quickly, to get a kind of quick idea.

There's a cancer-gene program out of UT Southwestern that's excellent. It's online. Your doctor can plug in the entire family pedigree, and it will pop out all the different models for you. ... In a clinic situation, with five minutes to go through the models, [that's] not going to happen. But what happens usually is after the visit we'll plug in the whole model, and come out with all the risks. If something gets you to 20 percent, then I'm going to offer screening.

WOMAN: I'm BRCA negative. My sister's BRCA negative. I was diagnosed at 34. She was diagnosed at 40. She's had the BART negative. I have a question about the gene mutations that haven't been sequenced yet. What are the sciences on that? Because she has a 17-year-old daughter, and I'm wondering about her, and what the best thing we could do for her is.

JENNIFER LITTON, MD: For your daughter, she's going to be considered high risk. Clearly she should start her screening by 23 or 24. She should clearly be a candidate for MRI screening. I can tell you right now, based on the Claus

model, with her first and second-degree relative in the 30s, [her risk is more than] ... 20 percent. It's going to be higher than that.

WOMAN: OK.

JENNIFER LITTON, MD: We are working on it very hard. I will tell you some exciting things about cancer research right now: ... about five years ago [it cost] \$30,000 [to] \$40,000 [per sample] to sequence genes in a meaningful fashion. ... Now ... it's costing me between \$500 and \$1,000 a sample, which means that we are on the verge of major discovery. ... My soapbox right now is that this is not the time to pull back funding. ... Right now our technology has caught up to what we want to do. I think the next five to 10 years [will be] very exciting.

I don't see anything coming down the pipeline in the next five years that is going to get you to the risk-reduction of 90 to 95 percent. I don't see it right now. I do see it for our kids' lifetimes, that hopefully this will be a gene therapy, something that we turn the gene back on in our lifetime. That's something we're really working on.

WOMAN: OK. I'm BRCA2. They thought I would be BRCA1. Do you stop testing because, "Oh, OK, you're BRCA. We don't want to test P10," because they told me they would test me for the P10 if I was negative. This was 11 years ago. I'm 12 years out. I was 27 when I was diagnosed. My mother and my aunt were both diagnosed postmenopausal, in their 50s. ... Is that something — I don't know. I have to sit here and think, "Well, gosh, what if it's something else? What if it was a different mutation?"

JENNIFER LITTON, MD: It's likely the BRCA2. Just because you have it doesn't mean you have to be diagnosed premenopausally. It's just one of the red flags that makes us think we've got to look at this family. In fact, most BRCA2 mutation carriers tend to get their cancers a little bit later than BRCA1.

WOMAN: Well, that's what they explained to me, and that's where — it just makes me think, "Gee, it could be something different."

JENNIFER LITTON, MD: It's not a hard-and-fast rule. I just had a 75-year-old lady with her first cancer with BRCA1. There's no hard-and-fast rule with it. But that's likely what's going on in your family, as far as that risk. You're already under the high-risk surveillance, so even if we found something else at this point —

WOMAN: Hi. I'm BRCA2-positive as well. I got tested. I have two full sisters. They both tested. One was positive; one was negative. My mom passed during that time, so she couldn't get tested, but my dad has two more daughters, so I asked him to get tested. He was negative. So now —

JENNIFER LITTON, MD: We know it's your mom.

WOMAN: — we know that side is safe, and it was my mom. My sister chose to do the prophylactic surgery. ... I'm the youngest of the three. ... [Inaudible] "Well, why couldn't you guys take that bullet and figure it out for me?" But I have three daughters, so I'm going into this, and I guess I have the same question.

JENNIFER LITTON, MD: What do we do for them?

WOMAN: Yes.

JENNIFER LITTON, MD: OK.

WOMAN: You mentioned, and I wrote that down — 23, 24 maybe, we start doing extra screening. I know testing is a — right now —

JENNIFER LITTON, MD: We want to wait until they're adults.

WOMAN: We want to wait until they're adults, right. Yes, definitely, because that's something hanging over their heads. It's really frustrating. But I also — one other question is ... I guess I want to know what more can we do for them, so that they're not having this over their heads as well. Also, the privacy issue with testing, and not being held accountable for life insurance, health insurance, if you are tested.

JENNIFER LITTON, MD: Those are all really fantastic questions. First of all, we really don't see — I've seen young patients [who] are unusually young. They're not usually BRCA. It's usually [a] P53 [mutation] or some other — the 13-year-old [with cancer] in the news is not usually [due to] this [BRCA mutation]. OK?

We wait until they're consenting adults. That's a conversation that you're going to have to have with them. I don't know how much — people feel very differently about sharing: when to share, when the right time to share is. I don't think there's a right answer for that. I think it depends on the family.

WOMAN: They know. They hear me talk about it — they know. They know about their aunts. ... So they know that this is something they'll have to eventually —

JENNIFER LITTON, MD: Right. We usually recommend to start at about age 25, or 10 years younger than the earliest age of diagnosis. That's where I was kind of getting in at that 23, 24. Why do we say 10 years? Because there's no great — there's no safety of saying, "Well, my mom was 55, so I'm safe until I'm 55." That doesn't exist. In fact, I published a paper last year showing that [with] these genetic syndromes, we were diagnosing something called anticipation with earlier — it's something like with Huntington's syndrome, or Fragile X, or these other genetic syndromes. It's happening at earlier ages.

Is that really the gene, or is it that we're screening more, and all the environmental stuff [contributes], and it's a perfect storm? We can't sort that out yet. But the next generation, we will. We're collecting blood, tissue — things like that.

Right now it would be a screening. I would not recommend for them to have their ovaries out at a very young age. They should live their life, have children if they want to have children, do all of those things — but do consider [talking to a doctor about the need for prophylactic surgeries and other preventive treatments] by 35 to 40, when they're done having kids. Being part of research studies is always important, because we can't answer these questions without that.

The life insurance issue is an issue. Right now we have a law called GINA, G-I-N-A [[Genetic Information Nondiscrimination Act](#)]. That's supposed to protect you so that no one can deny you health insurance based on this.

WOMAN: Employment.

JENNIFER LITTON, MD: Employment, yes. I've never seen a case go against it yet. But it does not cover life insurance. What a lot of my patients will do is wait until they graduate from college, or they may do high-risk screening until they decide they want to do something more permanent. They'll get their life insurance before they ... finally test. That's exactly why the American Cancer Society guidelines said you don't have to have a BRCA-mutation yourself. You just need to have one in your family. We'll still high-risk screen you up until you get tested.

WOMAN: Is there anonymous testing ... that you could [inaudible]?

JENNIFER LITTON, MD: There used to be, but there really isn't now. I suppose you could pay out-of-pocket, cash, and give someone an assumed name. But that's not going to get you anything more, because if you're going to act on [any positive results], they're going to want to know you're a BRCA-mutation carrier. As far as health insurance and employment, I can't imagine that that law is not going to hold up.

WOMAN: ... What you just said. [Inaudible] ... When you get your results from the BRCA testing, that's private information, correct? If you don't disclose that, life insurance policy —

JENNIFER LITTON, MD: It will depend. I would make sure that — individual policies are all written individually. Make sure you really read that and make sure. But most people will test after. I don't know if you have anything else to add to that, since their program is actually a phenomenal —

LISA SCHLAGER: Yes, what she's describing — it also applies to disability insurance. It's currently not covered under the

GINA law. We are working to remedy that situation. But it's very bureaucratic.

With the life insurance, the issue is that sometimes when you apply for life insurance they could request your medical records from your doctors. Therefore, that information could be in your records, and they could potentially hold it against you. You're going to be asked a lot of questions, probably, [by] your life insurance [carrier] about family history. I don't know if they might ask questions about genetic testing. But there's just that risk that you could be denied. It's unfortunate, but it's a real risk at this point. We do encourage people to try to get their life insurance lined up before they actually have the official testing.

WOMAN: Hi. I'm ... from the [Cancer Legal Resource Center](#).

LISA SCHLAGER: Oh, great.

WOMAN: Even if you do get through the underwriting process then, and as bittersweet as it is, if there's an award of life insurance benefits, before that award is paid out they'll make sure that the application was processed without any fraud or intentional misrepresentation. You definitely want to make sure that if you're certifying that you are attesting to everything being true and correct, that your beneficiaries will definitely receive those benefits.

[Editor's Note: If your genetic testing reveals a high risk for cancer, you may want to have your life insurance policy reviewed by an attorney to find out what your responsibility is regarding disclosure of information to your insurance company.]

JENNIFER LITTON, MD: Thank you.

WOMAN: I have a quick question. [I am a] ... BRCA1, triple-negative carrier. I have two boys. I think on my dad's side — we're guessing, because his sister has ovarian cancer [and] his other sister had intestinal cancer, so we're guessing it's on that side. We haven't really sat down for ... [Inaudible]. What do I need to do —

JENNIFER LITTON, MD: For [your] boys?

WOMAN: — I'm thinking I carried it from my father, also for their preventative and for their children, if they have girls or boys? What other cancers do we need to look for?

JENNIFER LITTON, MD: That's [a] fantastic [question]. One of the ones we're specifically — the only change in your boys' screening at this point, in 2012, is that we recommend prostate screening to happen 10 years earlier, so [at age] 40 instead of 50. You can see in the news, even, prostate-screening has gotten a lot of issues, but I think at this point — now, they've got some years to go, so there may be lots of changes, so keep in touch with your doctor about those changes.

They would each have a 50-50 chance, individually, of inheriting this from you. It doesn't matter — this is also a big misconception. Does it go down the male side? No. You get one gene from mom, one gene from dad. That's still a concern. They would each have a 50-50 chance.

It may or it may not be important to them when they go on to have children of their own. Again, very individual. There are some people that see the BRCA mutation as a barrier to having children in their future. If that is the case, there is certainly technology that can overcome that, using IVF [in vitro fertilization] and only implanting embryos that don't have that mutation. That is being done. Or just so that they know it, so if they have it when their daughters are getting to an age, they should consider testing.

... I know it — I don't know it. But I can imagine it's horribly scary, and all of the issues going on with giving that to a child or not — but knowledge is power here. Instead of just waiting for it to control or happen, you control it. Your testing, and your just being on top of their issues, [are] going to be the most important [safeguards for them]. For men, we really don't do much differently right now until they're 40. There are some men who have known BRCA mutations who have a lot of breast tissue, what we call gynecomastia, and we will do, sometimes, mammograms for them. But their risk of breast cancer is about 4 to 6 percent.

WOMAN: I have a question similar to the last question. I'm BRCA1-positive. Both my sisters are BRCA1-positive. My mom died of breast cancer. I'm the only one out of the three of us diagnosed. My older sister had a bilateral mastectomy, and she just had her ovaries out, and the same for me. But going forward now, we feel like, whew, OK, that got taken care of. But are there any other screenings that we need to think about now?

JENNIFER LITTON, MD: What we usually do at our — and there's no 100 percent right answer on this, too. I still meet with my BRCA-mutation carriers once a year. We review the family history. We review any other health issues. Whether or not they've been diagnosed, I still do a chest-wall examination. You should be doing that.

When you remove [the breast or breasts in a BRCA carrier] ... it should be a cancer surgeon doing this. But [the surgeon will] have to leave behind about 5 percent of tissue to have skin. You really want skin, because it would be a very bad cosmetic outcome without that. Right? They take the tissue all the way down to the chest wall, to something we call the fascia. The cells don't really go between there and the muscle, OK, if they've done the surgery. But [it is possible], in that little tiny 5 percent [of tissue, to have cancer cells develop]; it's right underneath the skin. I tell my patients to continue to run your hand from the top of your clavicles over your reconstruction, and also under your arms. I can't say I've never seen something come up, because I have, but very rarely. It's been like a nodule right underneath the skin. You have to be aggressive. If you see something like that pop up, bring it to the attention of your doctor.

Sometimes I've had people have the mastectomies, but unfortunately it wasn't as skin-sparing as we would hope, and there's a big rind of tissue. For me, then I'll continue the MRIs and the mammograms if I don't feel they've had sufficient risk-reduction, honestly. There's no right or wrong answer. Sometimes I'll get a test to see how big that rind is. If the surgery's done properly, at this point I don't do MRIs or mammograms, because we're mammogramming implants and tummy tissue.

WOMAN: What about colonoscopies, or what age do you recommend —

JENNIFER LITTON, MD: Absolutely colonoscopies, you should continue to be doing that. Also I would just put on the — the ovarian risk. ... I've seen somewhere between 2 to 5 percent risk of something called primary peritoneal carcinomatosis, so a lot of times make sure you continue to have your yearly gynecologic visits. They're continuing to really work on trying to find something, to find that earlier than what we have right now.

WOMAN: What age do you recommend starting colonoscopies?

JENNIFER LITTON, MD: Well, right now it's 50. But depending on your family history, we may change that, if there's colon [cancer] in your family, or things like that, and if there's a different genetic syndrome, if it's Peutz-Jeghers, then we change that completely.

WOMAN: Hi. My father's mother, she was diagnosed with breast cancer when she was in her 40s, [and] had two rounds of colon cancer. She's 99 and lives in her own apartment. Rock on, Grandma! My mother's mother, she was diagnosed with breast cancer probably in her 80s [and] died 10 years later. Nobody knows what kind of cancer that was.

I was diagnosed at 38, triple-negative. Back then they said "no," not to test, because it was just my grandmother's [side of the family] at that point.

JENNIFER LITTON, MD: You didn't have a first-degree relative.

WOMAN: Yes. So —

JENNIFER LITTON, MD: Does your father have any sisters?

WOMAN: Yes. She hasn't had any issues.

JENNIFER LITTON, MD: That's OK. Can I just — I'm listening to your question. I'm sorry, but I just want to bring this up, because I'll forget. That's an important thing when you're

drawing out the picture. I cannot even tell you. You just asked the question. "Is there breast and ovarian cancer in your family?" "No." "Move on." No, wait a second. What's your family structure? What if the dad [is] an only child, the dad has two brothers, you don't have females in two generations? That all needs to be taken into account. I'm sorry. Thank you.

WOMAN: No problem. Anyhow, 10 years ago it wasn't an issue. I was having my yearly [visit with my] breast surgeon. My mother was diagnosed almost 10 years later with breast cancer, so just recently. Now she's saying, "You should get tested. We might need to take out your ovaries," and things like that.

JENNIFER LITTON, MD: They didn't miss something. We published these papers in the [past] year. So that's the change, and that's why —

WOMAN: Well, that's what she said.

JENNIFER LITTON, MD: That means your doctor [is] on it and aware of the data, and doing the right thing. It's your choice to test or not. But it is certainly, just based on the triple-negative alone, would be enough for me to test your —

WOMAN: That's exactly what she said. She said, "Ten years ago it was 'no.' But now that it's 10 years later, and you're triple-negative," [she feels] they need to do it.

JENNIFER LITTON, MD: Can I just say that there would be — the reason we're publishing this is that women very similar to yourself have been, for the [past] decade, at MD Anderson signing up on a research study. We've been tracking people for 10 years. We're going to continue to look at these questions, but that is why this is all happening, [for] people like yourself who have become very involved and advocates.

WOMAN: OK, thanks.

JENNIFER LITTON, MD: So yes, I would definitely recommend it. It's your choice whether or not you want to do it. ... But it's a clear recommendation.

WOMAN: I have a question in terms of BRCA1. On our paternal side, I'm BRCA1-positive. Every female, looking at our family tree, is BRCA-positive. Some have had a diagnosis. Others are [taking] prophylactic measures. But it doesn't skip a woman. Are some [BRCA genes] innately stronger, or more aggressive?

JENNIFER LITTON, MD: That's a fantastic question. Right now we really don't have data to prove that one way or the other. We're certainly looking at things like that. It also sounds like all the women just had the 50-50 chance. ...

WOMAN: We're all — my first cousins, our fathers are carriers. But they do not, thankfully, have a diagnosis of cancer. I just think — I haven't seen any studies on it, but —

JENNIFER LITTON, MD: So far they've been trying to link things like that and nothing definitive has come through. You just have to continue to test.

WOMAN: Hi. I had Wilms' tumor 32 years ago, and now [I have] breast cancer. Have you seen any link? I've talked to a national Wilms' tumor study. They've seen a lot of Wilms' tumor patients with breast cancer. There's not enough research out there.

JENNIFER LITTON, MD: There's not enough research right now. There is one very, very rare syndrome that I think I've only tested for once. It's escaping me. But I've never seen anyone positive for it. You didn't have radiation or —

WOMAN: Mm-hmm.

JENNIFER LITTON, MD: OK. But it wasn't mantle cell. It was down below. It was?

WOMAN: It was down below.

JENNIFER LITTON, MD: It was down there? You could have had scatter [of the radiation beyond the treatment site] from that as well. Any time you have radiation we know you have an increased [risk]. But I would still, based on young age, still rule out the more frequent issues.

WOMAN: I'm BRCA2-positive. I've been tested for P53 mutation, and that was negative.

JENNIFER LITTON, MD: OK. But BRCA2-positive?

WOMAN: Positive. Yeah. Thank you.

WOMAN: ... I'm BRCA1-positive, triple-negative. My sister tested negative and felt very guilty. I'm the baby. My brother will not be tested. He has a daughter. Can she just skip him, and will insurance cover it, since they know where to look?

JENNIFER LITTON, MD: I can't comment on family dynamics thus far, but I think you have to respect people's personal decision not to test. That's their choice. But if your brother feels comfortable [with you sharing] ... your results — I mean however you and your niece feel.

WOMAN: My niece is in her 30s.

JENNIFER LITTON, MD: She can test. You just give her a copy of your results, and she can do the testing. There's not a [rule that] you have to do [the testing] "exactly this way." But, there's a known mutation in the family. Does he have other kids, your brother?

WOMAN: He has one adopted daughter and one [biological] daughter. ... So it's just the one daughter [who may need a measurement of risk].

JENNIFER LITTON, MD: If she wants to test —

WOMAN: I was very upset because —

JENNIFER LITTON, MD: I would test her if she were in my office.

WOMAN: — he wouldn't get tested. He wouldn't get tested, and so the day I was having my mastectomy, she was actually getting breast implants, which I knew would make it harder to find anything. I don't know. It sort of upset me. But she can just skip him, and go head and have it?

JENNIFER LITTON, MD: For a \$175 test if she has your results, \$3,300 test if you don't share your results.

WOMAN: OK. I can just go to my genetic counselor, and get copies of that to give to her.

JENNIFER LITTON, MD: Take a copy of your test results with the actual location. If you give that to her, she can go and get tested. If she showed up on my doorstep or any of my colleagues, we would definitely test, even in the absence [of those results]. ... There are some people I test — their mom [had] breast cancer at a young age, and their mom won't test. I don't have anyone better to test, and they're very concerned. I don't tell people they can or cannot test. I mean, that's not — you want to try to put it into the context of testing the most appropriate person. But sometimes the most appropriate person lives in another country or — so we do the best we can. If your niece wants to test, and she has your results, I think everyone would test her.

WOMAN: The insurance would cover that?

JENNIFER LITTON, MD: Everyone has different insurance. ...

WOMAN: Right. Thank you.

JENNIFER LITTON, MD: That's why — [the] take-home [message is this]: When you go to your genetic counselor, have your family's results in your hand. It will make everything [simpler]. ...

WOMAN: My question is about insurance. I want to know, are you the only company, genetic, that does it in the country? ...

JENNIFER LITTON, MD: OK. It's not me, because I'm a physician.

WOMAN: OK.

JENNIFER LITTON, MD: There is [only one right now]. It's in Salt Lake City, Utah. ... But there is a monopoly in the country right now. ... That's going up to the Supreme

Court. Maybe our legal friends in the back can help us with that. ...

WOMAN: OK. And my second thing — thank you. My second question —

JENNIFER LITTON, MD: This is not a commercial for them. I have no way — I'm not with them. [Laughter] ... [Inaudible]

WOMAN: But it's the only [testing] they can get —

JENNIFER LITTON, MD: But it's the only way.

WOMAN: I understand.

JENNIFER LITTON, MD: Different countries have their own — the other countries, like the European countries test ...

WOMAN: ... OK Well, with my insurance, and I do consider myself to have good insurance, it was still going to cost me [more than] \$1,000 to do the testing. It's very expensive. That's why I ask is there more than one company that does this testing.

JENNIFER LITTON, MD: There isn't yet.

WOMAN: OK. Thank you. ...

JENNIFER LITTON, MD: ... The other side, too, is that ... I've had a lot of help with research from that company. ... I'm [in] no way paid [by them to speak on their behalf]. I do not take any money [from them]. ... [My point is that] it's more complicated than we're going to fix here [today]. But it's not all good or bad.

WOMAN: I was diagnosed in 2007, and at the time I was 43. We talked about genetic testing because my aunt, my mom's only sister, died of breast cancer. She was diagnosed at 38. It was kind of iffy. My one sister just really, really felt like she had it. She was tested. She was positive. My mom was tested. She was positive. My cousin whose mom died was positive. I was negative. It's one of those things where it's not for sure just because that person had it.

But my doctor actually felt that there may be some kind of a genetic link that hasn't been discovered yet. He just wanted to put that out there for me.

JENNIFER LITTON, MD: OK.

WOMAN: Do you know of any kind of a genetic link that would —

JENNIFER LITTON, MD: I think you picked the one-out-of-eight straw in a family that had a mutation. That's kind of what we go back to talking about, that I'll look at the family and just because I test one member, I may test other people. One negative test does not mean it's not in the family.

WOMAN: I just wondered, with the technological advances of testing, they found ... [Inaudible] carcinoma at a young age they didn't typically find, because of the digital mammogram process. Is there a technological change that might make it necessary to retest what they had given you, your findings from before? If you're negative, do you stick with that "negative" the rest of your life? Or does the technology change where you should go back and have it done again, maybe 10 years down the road?

JENNIFER LITTON, MD: Well, the technology — I wouldn't redo what's already been done. But they do make some improvements, like that BART test we talked about, that was an improvement on the original testing in 2006. Sometimes, if a new part or a new test will come up, we keep — in our institution, we keep a database. ... If a new test or something's been developed, we will invite people back to improve their testing. But I wouldn't just go back and retest what's already done.

Thank you all so much. I hope this session was helpful.

[Applause] ...

[END OF TRANSCRIPT]