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What to Look for When Testing for Hereditary Breast Cancer

Announcer:
You're listening to a special focus on breast cancer from *Advances in Women's Health*, sponsored by Lily.

Dr. Birnholz:
Coming to you from the 42nd annual San Antonio Breast Cancer Symposium, this is ReachMD. I'm Dr. Matt Birnholz. Joining me today is Dr. Nadine Tung, Associate Professor of Medicine at Harvard Medical School, and Director of the Cancer Risk and Prevention Program at Beth Israel Deaconess Medical Center. Dr. Tung is presenting on genetic testing for hereditary breast cancer, addressing evolving perspectives, and a very hot topic on who should be tested. Dr. Tung, welcome to you.

Dr. Tung:
Thank you.

Dr. Birnholz:
So before we dive right into this central question of who, I'm fascinated on behalf of our audience to get a refresher on the what, specifically regarding hereditary mutations because, as I understand it, it's a more crowded field of mutations transmitting risk of breast cancer than we might have thought several years ago. And you've been on the forefront of research identifying many of these mutations. Can you give us a little walkthrough of that?

Dr. Tung:
Sure. So I think everybody's familiar with BRCA1 and BRCA2. Those two genes represent the high-risk breast cancer genes for which an inherited mutation increases the risk of breast cancer more than five-fold. And other than BRCA1 and 2, there have been a few other, much rarer genes that fit in that category and have very specific criteria for testing. What's more recent are these more moderate-risk breast cancer genes like ATM and Chk2 for which an inherited abnormality or mutation increases the risk maybe two-fold to four-fold; that kind of ballpark. And then even more recent are what are called SNPs, very, very, very common genetic variants that increase the risk of breast cancer less than two-fold. Those are not yet routinely being tested for, but are going to make their way into genetic testing very soon. In general, most of the panels that are offered to breast cancer patients and other patients have a list of genes for which they at least increase or double the risk of cancer if there's a mutation in those genes.

Dr. Birnholz:
So that seems to be a threshold; if the cancer risk is at least doubled -

Dr. Tung:
Correct

Dr. Birnholz:
Then it enters that level of significance to make the panel?

Dr. Tung:
Correct.

Dr. Birnholz:
Okay. I'd love to ask you more about those panels because the technologies behind that are rapidly evolving, and the needs to be able to identify some of these newly-discovered mutations are very apparent. But first, help us differentiate the difference between germline

testing and tumor testing, because this is something you have been speaking to many people about.

Dr. Tung:
Absolutely. And many do get confused by it. So germline testing is typically a blood test, perhaps a saliva test, and it's really looking for the inherited abnormal genes that predispose one or increase one's risk of developing cancer. And this testing has primarily, again, been used to try to assess what an individual's risk of a future breast cancer is so that prevention and screening strategies can be tailored to that. Now, increasingly, finding an inherited mutation is now informing how to treat particular cancers, and that's more recent; whereas, and I should add that germline testing is typically done by either genetic counselors or often with genetic counselor involvement; whereas, tumor testing or tumor genomic profiling is usually carried on by the medical oncologist, and is sent on the tumor, although more recently can be also through blood, but is really looking for abnormalities that have been acquired in the tumor; not inherited in the patient, but acquired in the tumor that can really inform which targeted therapies might be particularly effective in that tumor.

Dr. Birnholz:
Fascinating. So when we refer to heterogenous tumor types, for instance, we're not necessarily coming back to an inheritable form --

Dr. Tung:
Correct

Dr. Birnholz:
-of cancer, in that case. Just as a clarifying point.

Dr. Tung:
Correct.

Dr. Birnholz:
Well, let's come back to the panels then. This is a fascinating subject. It is rapidly evolving. Is the technology keeping up with the demand? On your end, you've obviously been so, um, far ahead of finding the mutations, doing the research to really identify their significance. Is the technology keeping up with being able to help you and your patients identify them?

Dr. Tung:
Yes. Or interpret them is really probably the question. So I think that the next generation sequencing platforms, they're probably pretty good at what we would call analytic validity. In other words, if they test your blood or your tumor over and over, they're usually finding the same mutations. The two terms though that are worth thinking about are clinical validity and clinical utility. So, clinical validity just means we've found this mutation, but what does that really mean? For example, in the germline setting, how much does it really increase the risk of a cancer, which cancers, and can we be certain if many different people study this particular mutations in Chk2 or ATM, are we all agreeing on what the risk of breast cancer or ovarian cancer or other cancers are? So that speaks to the clinical validity because it should be well established and consistent so that we know what kind of risk we're talking about. Then we get into a couple of other terms. Clinical actionability means that if we find a mutation in that gene, we're going to do something different. If we find a Chk2 mutation, we're going to recommend an MRI, a breast MRI. And then clinical utility means we're going to change our management and it's going to benefit the patient. So I think we're further away from clinical utility. We find these mutations, where not even for some of them in these genes agreeing on what the risk of cancer is and what the spectrum of the cancer's associated are, but for some where we're there, and we know what the risk is, we've started to change our management, but maybe we haven't quite proven that it's benefitting the patient yet.

Dr. Birnholz:
And further downstream, because of that lack of clarity or that debate, the question that is on everyone's mind that I've kept our audience from hearing, who should be tested becomes very complicated.

Dr. Tung:
Absolutely. So we can back up, and let's even just talk about the established genes, even if we just focus on BRCA1 and 2 and forget about what should be included in the panels. But even if we ask that question: Which breast cancer patients should be tested for BRCA? Recently, the American Society of Breast Surgeons in the United States has endorsed offering germline genetic testing to every breast cancer patient for BRCA1 and 2, PALB2, another high-risk gene, and then other genes as appropriate. On the other hand, most oncologists or those treating breast cancer patients, at least in the United States, tend to use the NCCN guidelines, National Comprehensive Cancer Network, which are quite broad and very, very sensitive. You do not miss many BRCA mutations if you accurately use the guidelines. So there was a study by colleagues that asked that question: How many BRCA mutation carriers are we going to miss if we don't test every breast cancer patient? And it turns out you're missing less than 1%; you're probably missing like

0.6%. So it's never going to be zero, but it's very, very low. And we have to ask ourselves; that's one side, but if we're going to test everybody, there's expense of course involved in that, and also we just don't even have enough genetic counselors to be involved, to be discussing all of the findings from the panels. So I think that, you know, without new genetic testing surface models that allow us to handle such large genetic testing, it – it would be challenging, uh, in a timely fashion to treat every breast cancer patient when they're just diagnosed. And this information is important. Again, on the other hand, some really argue that the criteria may be sensitive, but they're just not being implemented, uh, because studies do show that less than half of the breast cancer patients who meet the criteria are being offered testing, especially in the minority populations. So we're missing a lot of patients. And is the best way to get at this to just take away all the cumbersome criteria and say everybody's going to be tested? Or everybody under 65 with breast cancer? Or is it to try to use technology or other methods to try to not miss the ones who truly do meet the criteria and to try to stick to the criteria, but implement them accurately?

Dr. Birnholz:
Do we have a sense of some of the factors behind this massive disparity that you just spoke to?

Dr. Tung:
Yeah. I think there are a lot of barriers. It can start with the clinician failing to recognize the criteria or being very busy and treating the patient and just forgetting to recommend it. But even when it's recommended, the classic model is that then the patient meets with a genetic counselor, sometimes that's a second appointment, and that right there can be an obstacle for the patient to follow through and meet with a genetic counselor. Sometimes there is cost. I mean, even if somebody has insurance coverage, there may be a deductable. Although that has really become less and less, it's still not zero. So I think it's – there are a lot of issues, and there are many, many studies that show we could do much better. And truly it's probably no more than 50% who are supposed to be tested, or at least be offered the testing, are actually getting the testing.

Dr. Birnholz:
And this brings – you mentioned action models, needing to develop more consistent action models or something that's going to be more effective to help address that gap. But it brings to mind patient populations who are not even patients yet. The undiagnosed, but either aggressively curious, or knowing they have a family history, patients who are thinking maybe direct-to-consumer testing is where I should go. What role does that have or should it have in this whole debate?

Dr. Tung:
Right. So I'm not a big fan of direct-to-consumer genetic testing. I like to refer to that as recreational genetics. I think that, you know, genetics are complicated, and I don't think that they should be conducted lightly without sufficient pretest counseling or at least somebody should be supplying informed consent to understand what they're testing for. It has implications not just for themselves, their entire family, their children. We don't take many blood tests that affect our entire family, could affect life insurance. So I think that it's best done in a medical context, not in a recreational context. It's interesting and worth pointing out that some of the direct-to-consumer tests such as, let's take an example, 23andMe; they do test for the three Ashkenazi Jewish BRCA mutations, which account for over 90% of the BRCA mutations in the Jewish community. Most people who are doing 23andMe, don't recognize that they're doing BRCA testing. They think they're testing to find out a little bit of information, particularly about ancestry, but maybe about some risks, medical risks, but not this kind of high impactful medical risk. And on the other hand, that BRCA testing is only relevant for somebody who's Ashkenazi Jewish. I have had other patients who are not Jewish, who do the testing and say, "Well, I've had BRCA testing. I did 23andMe." And I have to point out that they did BRCA testing, but they did a form of it that was irrelevant to anyone who's not Ashkenazi Jewish. So there's the harm in the false reassurance that they thought they had testing and they hadn't. So the bottom line is I think this should be done in a medical context. I think what you're raising is very important in cancer patients, we're trying to shift to have the oncologist test with only those who have abnormalities see the genetic counselor; that would be more efficient. And for those who test positive, their relatives can then test, and we call that a cascade testing or effect, so that's great. But you're getting at a different topic; we're talking about unaffected individuals who are seeing their gynecologist or their primary care doctor, they're not seeing a cancer doctor. Now we're asking primary care doctors or gynecologists to understand the criteria for who should be referred to have enough information and knowledge to be able to, if they're going to test themselves – they test the patient themselves, be able to get informed consent, provide the pretest counseling, or even just understand who should be referred for the testing. So I do think the next very important frontier is to educate primary care doctors and primary healthcare providers of all kind at least to recognize who should be referred for testing or who should have the testing directly.

Dr. Birnholz:
And, Dr. Tung, do you see the pendulum swinging in that direction going forward where primary care practitioners and OB/GYNs are going to be taking a fair amount of the load here, the burden of making sure that they are up to date on testing their patients, knowing who to refer, knowing who to test? The central question behind your talk.

Dr. Tung:
Sure. I think it's – the answer is yes. I am very sympathetic to all the healthcare providers and primary care physicians. They're asked to do so much. Because it's not just perhaps genetic testing about cancer, you know, it's about heart disease, it's about other diseases. So there's a lot on their plate. But I think that this is just too important, and I think, uh, it's going to need a big effort for education, and start with the low-lying fruit. Start with BRCA1 and 2 testing. And I think with a referral, then discussion about which genes should be included in these panels; that's a complicated discussion. But at least if we can get the healthcare providers to understand who to refer for the testing, then the what to be tested for can be dealt with at a different time.

Dr. Birnholz:
Fascinating. Are there any specific approaches or models that your cancer prevention center is trying to move forward with, perhaps pioneering to answer some of these really difficult questions?

Dr. Tung:
Yeah. So a couple of things. We always try to take the cumbersome and complicated NCCN guidelines and distill them to a one-sheet, easy-to-use list, and we provide that frequently to our colleagues, primary care doctors, and others to try to keep handy so that they can use that in their clinics. But I'd love to highlight another project that, uh, several colleagues and I have been part of that really gets to the heart of what you're talking about. So without going into great detail, I will tell you that it is probably appropriate for every Ashkenazi Jewish individual man or woman, probably from the age of 25 and older, to do BRCA testing. The mutations are very common in the Jewish population, and so that's – there is a large population that needs genetic testing. And these are individuals who are again seeing their primary care, their gynecologist, and not seeing a cancer doctor. So several colleagues and I started what's called the BFOR study, it's B-F-O-R. And it's trying to address increasing accessability to genetic testing, and to save that precious resource, the genetic counselor, to the outback; not up front, but the outback for those who need the counselor. Because I'll point out that in the Jewish community, although we say that the mutations are so common, 2.5% will have a mutation, 97.5% won't; they don't need the genetic counselor, they don't need all that. So this is a study being piloted in four cities, or four metropolitan areas, 4,000 individuals, men and women, for which any Ashkenazi Jewish individual can enroll. It uses an online platform to do the educational teaching with a video. Individuals sign consent online. And then they go to any Quest lab and get their blood drawn, and then they receive their results either through their healthcare provider or the study staff by email, letter, phone call, depending on the clinical situation. And those who test positive or need more counseling are referred to a genetic program, but for the vast majority, they're done. How is this different than the direct-to-consumer tests that we were just talking about? There's more education. There's a safety net of genetic experts to either help the healthcare provider or directly interact with the patient to make sure that the process is handled properly and that the information imparted is proper. Because sometimes the patient is negative; they don't have a BRCA mutation. But their family history is so strong, they need more testing. So I think it's not just a yes or now simple kind of test. I think if we can, as in the BFOR study, shift this to involve the healthcare providers and the primary care doctors, but provide our expertise as a safety net, and there to help guide the process, I think that's a mechanism by which we'll be able to test large populations that need to be tested.

Dr. Birnholz:
That sounds like a remarkable and very innovative approach to be able to increase access to testing, while at the same token not diminishing the opportunity for expertise and education to be involved from the very beginning.

Dr. Tung:
Exactly. That was the goal.

Dr. Birnholz:
Well, Dr. Tung, I could ask you a thousand more questions, but I need to protect your time, as it's very busy here.

Dr. Tung:
Thank you so much. You've asked the important ones. I'm very – I'm very impressed.

Dr. Birnholz:
I very much want to thank my guest, Dr. Nadine Tung, for joining me to talk about new insights on genetic testing for hereditary breast cancer. Dr. Tung, it was fantastic having you on the program.

Dr. Tung:
Thanks so much. Pleasure.

Dr. Birnholz:
To access this and other episodes covering innovations in breast cancer treatment, visit ReachMD.com where you can be part of the knowledge. For ReachMD, I'm Dr. Matt Birnholz. Thank you for listening.

Announcer:
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