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Genetic Testing for Hereditary Breast & Ovarian Cancers: What the Guidelines Say

Dr. Simmons:
Genetic testing for hereditary breast cancer has once again been making headlines in the news and, with that, comes the re-emergence of the question as to who exactly should be tested for hereditary breast and ovarian cancer mutations.

Welcome to the Clinician's Roundtable on Reach MD. I'm Dr. Jen Simmons and with me today to shine some light on the issue is Dr. Susan Domchek. Dr. Domcheck is the Director of the McDonald Women's Cancer Risk Evaluation Center at the Hospital of the University of Pennsylvania, the Executive Director of the Basser Center, and a Basser Professor in Oncology. Dr. Domchek, thank you for joining us today.

Dr. Domchek:
It's my pleasure to be here.

Dr. Simmons:
So, to start us off, could you tell us a little bit about hereditary breast and ovarian cancer, and what the clinical indications are?

Dr. Domchek:
Of course. So, many of us have heard about two specific genes called BRCA1 and BRCA2, and there are genes which everyone has. And in the normal cell, they help repair DNA damage, so they're good. BRCA1 and BRCA2 are good. But if you're born with a bad copy or mutation in BRCA1 or BRCA2, you have significantly increased chance of developing breast or ovarian cancer. But there are cancers beyond that, as well, and particularly for BRCA2, there's increased risk of male breast cancer, prostate cancer, pancreatic cancer, and melanoma. Beyond this, there are genes other than BRCA1 or 2 that we're increasingly understanding. But BRCA 1 and 2 are the genes in which mutations are most commonly found in families with breast and ovarian cancer.

Dr. Simmons:
So what are the current genetic testing guidelines that clinicians should be aware of?

Dr. Domchek:
There are multiple different guidelines. The most commonly used is the National Comprehensive Cancer Network Guidelines. And it's important to realize that these guidelines are in a continuous state of evolution based on the risks and benefits of genetic testing. When we first started with commercial genetic testing in the late 90s, we really didn't have a very good understanding of how this information could help patients. But we've really learned a lot since that time, specifically for BCRA1 and 2. We understand that mutations in these genes have risks and we have a better sense of what those risks are. We understand what types of interventions we can do to either detect cancer early or potentially even prevent it. And excitingly in the last few years, we've understood that we can develop therapies, specific drugs, that target cancers that are related to BRCA1 and 2 mutations. For all these reasons, the risks and benefits and the considerations of who should get tested have been changing over time and, for instance, we now have a recommendation that all ovarian cancer patients get tested, that all pancreatic cancer patients get tested, all metastatic prostate cancer patients. What's been more controversial is where the guidelines should be related to breast cancer patients, because it's very much true that certain women and men with breast cancer have much higher risks of having BRCA1 and 2 mutations than others. So the National Comprehensive Cancer Center does not currently recommend genetic testing for all individuals with breast cancer, but the American Breast Surgeons does. So I think it's just trying to navigate why those differences are there, and what it means to patients is really important.

Dr. Simmons:

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How do you advise people who are seeing these breast cancer patients with regard to the discrepancy between the NCCN guidelines and the American Society of Breast Surgeons guidelines?

Dr. Domchek:
It's a great question. Again, I think a really important component of this is that there have been multiple studies that have been done that show that we are not very good about making sure that people get genetic testing who are at the highest risk of having these mutations. A study that was published earlier this year showed that only a few years ago using SEER registry databases and linking it to commercial genetic testing laboratories, we only tested 30% of individuals with ovarian cancer, for instance. And remember, we're supposed to be testing 100% of them. We also know that there are significant socioeconomic and racial disparities in terms of who gets genetic testing. So we already don't test the people at the highest risk. So when we're having these debates about where the threshold should be, I'm just trying to remind everybody, let's make sure we actually test all those people that are at the highest risk of having these mutations. It's also true that more expansive testing mostly picks up mutations in genes other than BRCA1 and 2. So if you go outside the NCCN guidelines, the likelihood that you're going to find a mutation in BRCA1 and 2 in a breast cancer patient who doesn't meet NCCN guidelines is 0.4%. So it's really about picking up mutations in other genes. And there, we don't have the same strength of evidence that we do for BRCA1 and 2 that we can use this information to help patients. There is a little bit of a philosophical debate going on right now about what is the level of evidence you need to determine that you should test everybody. And I think that there are people on both sides of this issue, and it's really complicated. Right now, genetic testing is not covered for all breast cancer patients; meaning, that your insurance won't necessarily cover the cost of genetic testing. If you are a 70-year-old woman with estrogen-receptor positive breast cancer and no family history and you're not of Jewish descent for instance, that woman right now does not have insurance coverage for genetic testing. There are cheap options available for genetic testing and it can cost as little as $250. So I think that if people want genetic testing, there are ways to get it now in a way that wasn't really available in years past when the test cost $4,000. But like everything, there are pros and cons to these types of approaches, and people can learn things about their genetics that can be challenging because now we don't just test for BRCA1 and 2, we test for bunches of genes, and all of those have different implications. So I think this is really going to be evolving in the next few years, but while it's evolving, we're really trying to focus on making sure that we don't miss those at the highest risk because the denominator of patients that we need to test there is lower than if we tested everybody. So there's just a matter of how you operationalize this in your clinic and make sure that people get the testing that they need, and that's especially important to consider.

Dr. Simmons:
I know you mentioned earlier that the BRCA genes are actionable, which is why there's such a benefit to testing. Are there other genetic mutations that are actionable?

Dr. Domchek:
Yeah. And it really depends – so there are a few, and I'll give a specific example. There's a gene called CDH1. Mutations in CDH1 are associated with breast cancer, but they're also associated with a very high risk of stomach cancer. In the past, we only did CDH1 mutation testing on individuals who had a family history of stomach cancer. But now that gene is placed on all of these panels. And what I mean by panel is instead of just testing one or two genes, you can test 25 genes at once, 80 genes at once, because the technology has made it easy to do so. So now we're testing a bunch of people for this gene, CDH1, who don't have a family history of stomach cancer. But if you're found to have a mutation in this gene, we're going to recommend that you have your stomach removed because that is the standard recommendation for individuals who have a CDH1 mutation. And you can imagine that this is challenging. So the mutations in that gene are actionable. We have something to recommend, but we're not sure if it's exactly the right thing in that situation because it's not the usual situation that we find such a mutation. There are other genes, and specifically I'll call out CHEK2 and ATM because they're the most commonly found mutations, and those genes are most commonly found after BRCA1 and 2. And for those, it's a little trickier. We have data that the mutations in these genes are associated with an increased risk of breast cancer, although it really does seem to be dependent on family history and other risk factors what the absolute risk is. Our current guidelines suggest that we should do breast MRI screening on anyone with a CHEK2 truncating mutation, for instance, because of the lifetime risk of breast cancer is over 20%. But it's worth stating that it's a guideline in the U.S., and in different countries that threshold is different and can be as high as 30% in some countries. And MRIs can have their own issues, including cost and false positives, and increasingly we're paying more attention to the retention of gadolinium, which is in the contrast dye. So we're trying to balance all these things out and yet at the same time recognize that our management guidelines for CHEK2 are based on expert opinion, which is a fancy way of saying that they're made up at the current time. And we need to continue to accumulate the data that's necessary so that we can give people more precise information.

Dr. Simmons:
I think it's clear, or more clear, to look for reasons to check for mutations in affected individuals. What about the unaffected individuals?

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What are the current recommendations in this population?

Dr. Domchek:
It's a great question. So the NCCN guidelines are pretty expansive in terms of family history recommendations. Meaning, that if you're an individual with a family history of breast or ovarian cancer, including any ovarian cancer, young breast cancer, and the guidelines are fairly long, that those individuals should be considered for testing. I think what you're alluding to is that we're not great at identifying people before they develop the cancer. And this is where we really need to partner with our gynecology colleagues and our primary care physicians about finding those individuals before they have cancer so we can do genetic testing and we can help modify the disease outcome. We can find a cancer earlier, we can prevent it altogether. And there are two ways to do that; one is identifying people in practice who have a family history and have not been tested. And another way to do it is to make sure that every time we do genetic testing and find something, we make sure to go to all those family members and offer genetic testing to those family members, as well. We call that cascade testing. And that is also really underutilized. So there's the question, why is it that some people are hesitant to undergo genetic testing? I think this is a complicated issue. Some of it relates to sometimes misinformation on cost because again if you meet genetic testing criteria, usually this is covered by your insurance and again there are these cheaper options available. One is cost. A second though, and a big problem in the United States, is that people are worried about insurance coverage in terms of if they do have a genetic susceptibility, what that might mean longterm. Let me talk about that a little bit more. There is something called the Genetic Information Non-Discrimination Act, which has been set up to prohibit the use of genetic information to be used against you in terms of your job or in terms of health insurance. Now, GINA, as it's known, does have a loophole, and it does not provide any protection against using this information for life insurance or for disability insurance. In addition, and I think people are nervous in this day and age, there is the Affordable Care Act, which prevents against using pre-existing conditions for insurance, but people I think in the U.S. do feel a little unsettled about issues related to health insurance. So again, GINA is meant to protect against health insurance, but it does have loopholes, and again it does not prohibit the use in terms of life insurance and disability insurance. But I think some people are hesitant about genetic testing, particularly if they've never had a cancer for those reasons. And then finally people don't always understand genetics very well and feel that this is information that might just worry them and not be useful to them. And there's where we do need to make it clear that, particularly for BCRA1 and 2, we can help prevent cancers and potentially save lives if individuals know that they are at risk.

Dr. Simmons:
Do you think increasing the number of genetic counselors that we have and the availability of genetic counseling may contribute to being more effective with testing in the appropriate population?

Dr. Domchek:
Yeah, I think that we have to think about ways to get genetic testing done efficiently and decrease barriers. And for different patients that may mean different things. So, as an example, we currently have a setup in place at PENN where for our pancreatic cancer patients and metastatic prostate cancer patients, these are individuals who are dealing with a serious medical condition. They are looking for therapies – they're looking for therapies to treat their cancer. They're not looking to think about other cancers; they're looking to treat this cancer. And, you know, their focus is a little bit more, you know, acute. In this case, we actually have them watch an 8-minute video, and then get their genetic testing done. And afterwards, the genetic counselor discloses it to them and reviews it all with them. But that's an example of where we've been able to test many, many more patients because we've shortened pretest education. But for other individuals, if you're 25 and have a very strong family history and are coming in for genetic testing, I would argue that that individual needs a lot more discussion about what this information might mean, what some of the possible options would be, and often even if you test negative for genetic testing, if you have a strong family history, we still need to help you manage your increased risk. So it's going to be different in the different settings, but I think we need to think about ways to extend the genetic counselor's reach and to use the genetic counselors to their maximal training, because they're highly trained, highly skilled, and we should be using them for the more complex cases.

Dr. Simmons:
So, lastly, what do you see on the horizon in the future of genetic mutation testing?

Dr. Domchek:
Well, I think there's a lot of talk about the fact that in 5, maybe 10 years, everybody will be tested for everything. It's hard for me to, as a person that helps individuals after they've gotten their genetic testing done, that feels a bit overwhelming to me. So we're really going to have to figure out, okay, who sends that test, who does the consenting, and who's helping to manage that risk, which means that we need a highly educated workforce of providers out there, including primary care doctors and gynecologists. But I think that's probably where we're heading, but we really need to do a better job of understanding how we're going to use this information to improve patient care, because that, at the end of the day, is what it's all about; using information to improve patient's health.

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Dr. Simmons:
Well, Dr. Domchek, as usual you are a wealth of information. I want to thank you for joining me today and helping to clarify these recommendations that always seem to be so rapidly changing.

Dr. Domchek:
Yes, I have a feeling they will continue to rapidly change, and I'm always happy to talk about it at any time.

Dr. Simmons:
Thank you so much.

Dr. Domchek:
Thank you.

Dr. Simmons:
I'm Dr. Jen Simmons. To access this episode and others, visit ReachMD.com where you can be part of the knowledge. Thank you for listening.

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