Genetic Testing of Hereditary Cancer

Narrator:

Welcome to Project Oncology on ReachMD. This is the Prova Education activity: **Genetic Testing of Hereditary Cancer**. This CME activity is supported by an independent medical education grant from Invitae. Your host is Dr. Brian McDonough. Dr. McDonough welcomes Dr. M. William Audeh, Associate Clinical Professor of Medicine at Cedars-Sinai Medical Center and UCLA School of Medicine, and Medical Director of the Wasserman Breast Cancer Risk Reduction Program in Los Angeles. Dr. Audeh is a consultant for Amgen. Dr. McDonough has nothing to disclose.

After listening to this educational activity, participants should be better able to explain the genetic basis for hereditary cancer and describe its key characteristics, describe the criteria for which genetic testing is considered appropriate, identify individuals that warrant referral for further genetic risk evaluation, appreciate the range of genetic tests currently available, and how to interpret them in clinical practice.

Dr. McDonough:

Approximately 14 million new cancer cases were diagnosed worldwide in a single year, according to a recent Globocan data for 2012. Of these, an estimated 3-10% of new cancer cases can be considered to be hereditary tumors. The recent emergence of genetic panels helps individuals at risk for hereditary cancers to better assess potential preventative options. In this interview, Dr. Audeh explains the genetic basis for hereditary cancer, their key characteristics, and describes criteria in which genetic testing is considered appropriate.

Dr. Audeh, first of all, welcome to the program.

Dr. Audeh:

Thank you very much.

Dr. McDonough:

There's increasing interest in genetic testing for a variety of conditions. Specific to our discussion today, could you explain the genetic basis of hereditary cancers?

Dr. Audeh:

Yes. I think the complexity of cancer, it really derives from the genetic basis of all cancers, and we know that a certain proportion of them are due to inherited genetic factors which ultimately lead to the development of cancer, primarily in adulthood. When we look at the function of the genes that have been associated with hereditary cancers, many of them are actually genes involved in DNA repair, which is logical since losing effective DNA repair may allow mutations to develop in a particular tissue that ultimately leads to cancer. So most such genes are due to DNA repair defects, but there are genes that have other functions that are mutated and will lead to cancer in a different pathway.

Dr. McDonough:

Are there key characteristics common to many hereditary cancers, and what are the hereditary cancer syndromes?

Dr. Audeh:

Well, there are many hereditary cancer syndromes; although, I think there are, perhaps, 3 or 4 that most every physician should have some familiarity with. I think the key characteristics are several. One, of course, is seeing multiple members within the same family having not only a single type of cancer but perhaps many different cancers. Another

would be the early onset of the disease. We have statistics that indicate most cancers are diseases of aging, and when a breast or a colon or an ovarian cancer appears in someone younger than the average age, that should certainly cause someone to consider a hereditary cancer.

Dr. McDonough:

You more or less have addressed this, but I think it's important to look at in what way is hereditary cancer different from an increased familial incidence of certain cancers, because that's a big issue we deal with in practice?

Dr. Audeh:

One of the problems is that it's not always easy to separate the effect of environment and lifestyle factors from the role the genes play in causing cancer. We tend to think of the hereditary cancers as having a higher likelihood of appearing in people who carry them, otherwise known as high penetrance. However, the difference really in a hereditary cancer versus a familial cancer may be a combination of gene and environment. For example, you may see a family with a high frequency of cancer because of the location in which they lived and grew up, and so there may be a greater effect, let's say, of exposure as opposed to inherited genetics.

Dr. McDonough:

How does one identify individuals with a family medical history that warrants evaluation or a referral for further genetic risk evaluation? What criteria are appropriate?

Dr. Audeh:

When it comes to a family medical history, I think it's very important to take a family history that extends for at least 3 generations because there are instances in which genes

that cause cancer can be carried silently and not expressed, and so one needs to look beyond first-degree relatives. Another factor is certainly even with women's cancers, such as breast and ovarian cancer, one still needs to ask about both sides of the family because the genes that are associated with breast and ovarian cancer, the BRCA genes, for example, can be inherited through either parent because these are autosomal genes; they're not sex-linked genes. So I think the most important message I can give is to take at least a 3-generation pedigree and to evaluate the family in that way.

One of the mistakes that is often made in ruling out a possible familial or hereditary factor is when the family tree is small. If a parent, for example, is an only child or the father only has brothers, family history is going to be negative for breast cancer, but yet, the gene could still be there. So that's one of the factors that needs to be taken into account.

Dr. McDonough:
If you're just tuning in, you're listening to Project Oncology CME on ReachMD. I'm your host, Dr. Brian McDonough, and I'm speaking with Dr. M William Audeh, and we are speaking about genetic testing of hereditary cancer.

Dr. Audeh, I have some more questions. What range of genetic tests are currently available for hereditary breast cancer, colon cancer and others, and how are they typically performed?

Dr. Audeh:
Well, there are now many laboratories around the country, in the United States, and in many other parts of the world as well that are offering genetic testing for hereditary breast, colon, ovarian cancer and others. Any method by which a sample of DNA can be obtained is adequate for these tests depending on the lab. So most laboratories will perform a test on

a tube of blood, removing the white blood cells and analyzing their DNA; but there are many labs that can also use a buccal smear or just a scraping from the inside of the mouth, because you can often get enough cells that way to analyze the DNA. Most of the tests perform sequencing of the genes to search for a mutation, but in certain cases there are some commonly-known and identified mutations which are so frequent that the test may simply look specifically for the most frequently seen mutations and be more focused in that way.

Most of the genetic testing available now will yield an answer within 2 to 3 weeks. The number of labs now that are offering genetic testing has increased to the point where I think the cost of genetic testing is starting to come down because of the competition between laboratories.

Dr. McDonough:

Interesting. You know, once results of the test are received, how do you interpret what those results mean with regard to future risk and explain them to your patient, and in what ways do genetic counselors aid in the process?

Dr. Audeh:

To answer the last part of that question first, genetic counselors have always been the first line of experts in explaining the genetics of any disease and had spent much of the time, I think, in the history of medical genetics focusing on pediatric syndromes and prenatal diagnosis and that kind of thing. Cancer genetics is a relatively new area, and so the role that genetic counselors play often overlaps with the role that medical oncologists are playing when it comes to interpreting the results and advising patients and their families about the meaning of these tests.

In general, though, whether it's a genetic counselor or a medical oncologist or any other health professional, I think it's important to explain something about heredity and the manner in which genes are inherited and then focus specifically on the implications of the gene in question. So the way the test is interpreted is really, if a mutation is recognized in the gene which is thought to produce a dysfunction in that gene, either inactivating it all together or causing it to malfunction, then that is clearly going to be a gene associated with a certain risk of cancer, at least in the area of cancer-related genes.

The statistics are quite extensive in terms of genes such as BRCA1 and 2 or the colorectal Lynch syndrome-associated genes regarding the risk of cancer in people who carry them. The other common diseases that are detected in terms of their risk, ovarian cancer, of course, is associated with BRCA1 and 2 in the so-called hereditary breast and ovarian cancer syndrome; while in the Lynch syndrome, colorectal cancer is the primary cancer, but there are many others that are associated with those genes such as endometrial cancer in women and other gastrointestinal cancers. So beyond identifying the mutation, there is also the importance of understanding which cancers the mutation places that patient at risk for.

Dr. McDonough:

Dr. Audeh, if a decision is made that there is risk sufficient to consider a preventive action plan, what might that include? And as you answer, does it always need to be drastic as we've heard in recent news stories?

Dr. Audeh:

The decision to take a preventive action I think is a combination of both medical evidence and personal preference, because in every instance we are really talking about taking an action to prevent something that may or may not happen but for which we think there's a

high likelihood that it may happen. With most of the hereditary cancer syndromes that we can detect by laboratory tests today in the clinic, the likelihood of developing a cancer is not 100 percent. It's far less than that. And so the decision begins with asking: How high is the risk of this particular cancer? With hereditary breast and ovarian cancer with a particular mutation in BRCA1 or 2, how high is my risk for breast cancer or ovarian cancer? Once you establish how high the risk is, then it becomes the physician's, I think, responsibility to lay out how much the risk can be reduced by various preventive actions. We know, of course, that the most drastic step is a surgery to remove the organ that could develop the cancer. That's going to be the most effective way to reduce the risk of cancer, but it's also the most drastic. Many people do not wish to go to that extreme and wish instead to still do something preventive but not requiring surgery. In a hormone-dependent cancer—like many breast cancers are being dependent on the estrogen hormone—we have extensive information indicating that one can reduce the risk of breast cancer, even those that are related to genetic predisposition, by taking some kind of anti-estrogen therapy, mainly a pill, and that will reduce the risk of breast cancer by about 50%. So while it isn't as much of a risk reduction as surgical removal of the breasts and a mastectomy, it is still a step in preventive action. And so the extent to which people wish to go for prevention I think is a very personal decision, and our role as healthcare professionals is really to lay out what we know.

In the case of other cancers or cancers where we don't have a preventive therapy, one could still consider increased surveillance and screening as a way to at least detect a cancer at its earliest possible stage. So what you're really preventing there is not the development of the cancer, but you're preventing, perhaps, the need for more aggressive therapy when you can catch something so early and perhaps all one needs to do is simply remove the cancer.

Dr. McDonough:

Dr. Audeh, could you tell me how the landscape of genetic testing has changed?

Dr. Audeh:

It has changed a great deal in the 20 or so years that I've been doing genetic testing. Genetic testing has always been, and still is for the most part, a way of identifying individuals at increased risk of cancer so that they can undertake prevention or screening. Very often, however, the question is only raised when someone has developed a cancer and the question is: Was this cancer due to an inherited factor?

What has really changed the landscape, besides the fact that there are now multiple laboratories offering genetic testing, is what we do with the information. It is no longer just information to determine the risk of another cancer in the future. It is now becoming essential information for making treatment decisions, and that is a huge change. The most telling example I think is in the area of the BRCA genes—BRCA1 and 2—which are responsible for the hereditary breast and ovarian cancer syndrome that many people use to make decisions about whether to do preventive surgery or increased surveillance.

Within the last several years, drugs have been developed which actually take advantage of the abnormality that mutation in BRCA1 and 2 can cause in the development of the cancer, so that it is now essential to know if someone is diagnosed with breast or ovarian cancer whether they carry one of these genes, because that may allow them to receive a highly targeted drug which works specifically against the effect of that gene. And I think that that's a story that's going to be repeated with virtually every one of the major cancer syndromes that we are aware of.

I've had the privilege of working with many of these patients and some of these

medications, and a young woman who had a very strong family history of breast cancer was ultimately diagnosed with breast cancer and was found to carry a BRCA gene; and for her, we were able to offer her access to a drug that may help improve her chances to overcome this cancer because it's a targeted therapy that we could only use based upon the genetic knowledge that we acquired with genetic testing.

Dr. McDonough:

Dr. Audeh, I wanted to ask you one last question—it's my favorite question in the world—and that is: Is there anything that we didn't discuss that you felt is really important to bring up at the end of this?

Dr. Audeh:

The thing that we found that's been very surprising to many people in this field is the range of cancers that can arise when we find a gene that seems to be predisposing to cancer development; because although we have syndromes that we identify such as the hereditary breast and ovarian cancer syndrome associated with BRCA1 and BRCA2, it turns out that those are not the only cancers that those genes can cause. In fact, for carriers of BRCA2 mutations, there is also a risk of pancreatic cancer and prostate cancer in men. There's even a small risk of melanoma skin cancer. So when we try to identify cancer-causing genes, I think the one message I can give is to not be too restricted in your thinking, because the way these genes interact with other genes and with the environment may explain why some people develop a breast cancer while others develop a pancreatic cancer. And identifying people who are at increased risk really should put them in the path of enhanced screening and awareness, because being armed with that knowledge I think is the best thing we can do to help them.

Dr. McDonough:

Well, Dr. M. William Audeh, I want to thank you for joining us and discussing this. I think it was a really great conversation. I appreciate your time, and I think many of our listeners will as well.

Dr. Audeh:

Thank you.

Dr. McDonough:

Thanks again for joining us. I'm your host, Dr. Brian McDonough. Thank you for listening.

Narrator:

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