Yale CANCER CENTER answers

WNPR Connecticut Public Radio

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Adverse Events in Cancer Genetic Testing

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Welcome to Yale Cancer Center Answers with doctors Francine Foss and Lynn Wilson. Dr. Foss is a Professor of Medical Oncology and Dermatology, specializing in the treatment of lymphomas. Dr. Wilson is a Professor of Therapeutic Radiology and an expert in the use of radiation to treat lung cancers and cutaneous lymphomas. If you would like to join the conversation, you can contact the doctors directly. The address is canceranswers@yale.edu and the phone number is 1-888-234-4YCC. This week Dr. Lynn Wilson is joined by Dr. Ellen Matloff and Dr. Karina Brierley. Ellen is a Research Scientist in Genetics and Director of the Cancer Genetic Counseling Program at Yale and Karina is Cancer Genetic Counselor. Here is Lynn Wilson.

Wilson Let's start off by having you tell us a little bit about what it is you both do within the genetic counseling program?

Matloff I am the director of Cancer Genetic Counseling at Yale and Karina is one of our senior genetic counselors. We see families at risk for hereditary forms of cancer. So everything from breast cancer, ovarian cancer, colon cancer, thyroid cancer, and rare cancer syndromes like retinoblastoma or von Hippel-Lindau. We see all of those patients both with cancer and without cancer who are at risk for carrying a genetic mutation.

Wilson Karina, how long have you been doing this?

Brierley I have been with the program for 11 years now, this summer.

Wilson So, a pretty long time? Tell us a little bit about what short of background is required to be able to do this sort of work.

Brierley Genetic counselors have a masters degree in genetic counseling and there are probably about 25 or so programs in the country now and that training is both classroom work and clinical work in genetic counseling, and then obviously many people have more on the job training as well once they start a position.

Wilson But it is masters level training, so it is very advanced.

Brierley That is correct.

Wilson Ellen how long has the program been going on here at Yale?

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Matloff Approximately 17 years, which of course I started the program when I was 10, so that is why it has been going on for so long these days, but we now have one of the largest programs in the country, we will have five boards certified genetic counselors within the next few months.

Wilson That is fantastic, and as you have mentioned, there are only 25 or so programs in the country.

Matloff And those are training programs. Those are programs where people can actually go and receive a graduate degree in genetic counseling. There are probably many more clinical programs where the patients can go around the country to have genetic counseling and testing.

Wilson I see. Define for our listeners what genetic counseling and testing are and the role it plays for patients.

Brierley Genetic counseling and testing can mean a lot of things depending on the specialty, so we work in cancer genetics, but there are also programs in prenatal, pediatrics, rare adult diseases, all kinds of different diseases, but generally speaking genetic counseling is the process that surrounds the option of genetic testing, so taking detailed family histories, medical histories, discussing it with patients and their families, based on that history, whether or not finding cancer disease in their family might be hereditary, what testing is available, what testing might tell them, and then helping them once testing is ordered and interpreting their test results and using that information to make decisions about their treatment for the patient and their entire family, helping to refer family members elsewhere for testing if they live outside of our area so it is a long and complicated process.

Wilson And obviously the history of the family plays a critical role in this and trying to determine what the risk may be, but I have to imagine that you must encounter patients who either do not know much about their family history or perhaps when you learn about it, you really do not think it is significant at all, but for whatever reason people are very anxious and worried and want to have testing done. They have read articles in the newspaper, or they have heard something on television, how do you manage that situation?

Matloff That is a situation we come across every single day, and we even have patients who come and say, I am adopted and I had breast cancer at age 35, but I know nothing about my family history, and so in those cases we are forced to use the information we have in front of us, but in most families, I would say it is really interesting that once you expand the family history and give the patient the tools by which they can expand their family history, it is amazing how the story can change and

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that is important because a lot of people think that there is one genetic test for breast cancer and that you order that test and you get yes or no the way you would with a pregnancy test, but there are actually dozens and dozens of genes involved with cancer predisposition and we have learned that ordering the right test is one of the key elements and getting the right answer for the family, and we have many cases now in which the wrong test was ordered.

Wilson Ellen, especially for our listeners, talk to us a little bit about what a gene is, you mentioned that word, how does that play into this?

Matloff If we take a step back and think about the most basic unit of hereditary, it would be a gene, and so a gene is a single unit that is most often passed from parents on to children and if there is a mutation or a genetic change, a typo in that gene, then that typo or mutation can be passed down through a family. In our case, in cancer genetics, that can mean that a family member is at increased risk for a certain type of cancer, or more likely, a whole group of cancers and then that risk can be passed on to children.

Wilson And how many genes are we talking about that are in humans?

Matloff We are talking about tens of thousands of genes in a human and what we are learning is the field grows and more testing options become available. We once thought that this was fairly straight forward and fairly simple, and that there were dozens of genes involved in cancer predisposition, but as things like whole exome sequencing became available, which look at all of the genes in a person, we are learning that it is more likely hundreds of different genes involved not only in cancer predisposition, but that modify the risk in people who carry a cancer gene, there are genes that tell the patient whether or not they will respond to certain chemotherapy or certain cancer medications. There are genes that can likely predict adverse outcomes, which patients are going to respond poorly to a certain medication, maybe even have an allergic reaction and not respond at all, so it is much more complicated then I think we once imagined.

Wilson You mentioned whole exome sequencing, what is that?

Matloff The way we order genetic testing right now, I think we are going to look back on in five years and say oh my gosh, I cannot believe we used to do it that way, that is the eight-track cassette of genetic testing and what we do right now is we kind of cherry pick and just order a few different genes, for example, for hereditary colon cancer we might order one genetic test that looks at a gene involved with colon polyp development, for people who have hundreds or thousands of

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precancerous colon polyps. The way this new genetic testing will work is that people will give one blood sample and be tested for as many as 10, 20 even 30,000 different genes and instead of getting a report that is a page long, we are anticipating getting reports that are hundreds of pages long or more.

Wilson And how long do you expect it might take to do that analysis and what sort of cost are we thinking about?

Matloff That is the irony. The irony is that the cost of this testing might actually be less than it is currently costing us to cherry pick through and order a handful of genes. Sometimes when we use that method, it most likely costs between $4000 and $6000 depending on how many different genes you are ordering, but some laboratories are now saying that they can do whole exome sequencing for $2000, or even less.

Wilson So that is a significant difference. Karina, who can actually do the genetic testing and how do you recommend this be done? Is it something that a doctor can just order, a nurse, or another care giver, do we recommend that such patient see an expert such as yourself for both discussion and counseling of potential results, how should one start to go down this path?

Brierley We are obviously biased, but our preference, and based on experience from patient outcomes, would be that patients be referred if there is a concern for a hereditary cancer syndrome based on their personal or family history, and then that would be the first step, to be seen by us prior to testing. As Ellen mentioned, there are many different tests that can be ordered. It is not that there is one test, for example, for hereditary breast and ovarian cancer. There are many different genes and so for us the process starts with taking that detailed family history and medical history, assessing who the best person to test in the family is, even if the patient being referred to us is the patient being referred to determine their own risks, they may not be the best person to test in their family to get the most information for them. It may be another relative that's had cancer, so we would recommend that patients be referred to a specialist in cancer genetics with the appropriate training and background in the time to complete this detailed process of pre and post genetic counseling and testing.

Wilson And, what sort of time commitment is involved in that for a patient?

Brierley Typically for patients that are seen by our program, they are seen for one or two appointments in preparation for the process of testing, and they are each about an hour, so an hour or two hours before testing is done, and then up to an hour to go over the test results and recommendations for

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them and for their family members, so it is several hours at a minimum and then for the patients that carry hereditary mutation, we also see them for ongoing follow-up care as well.

Wilson I see, so it is very comprehensive. Can you tell us a little bit about your paper which was recently published discussing the adverse events in genetic testing?

Matloff I can remember when I came to Yale and this testing was first launched, when BRCA 1 and 2 were cloned, we were really concerned about a lot of things. We were concerned about the psychological impact of this testing on patients. If the patients learned they were at high risk to develop these cancers, would they become very depressed, would they become nonfunctional just being so worried about their cancer risks, would they kind of drop out of cancer screening and surveillance because it was so overwhelming, could they even commit suicide, these were some of the things that we considered. We were also really afraid of discrimination. Would they be discriminated against by their health insurance companies, could they be dropped, would they be discriminated against by their employers, we even worried in some religious groups where there is still match making that takes place, would these people be deemed unmarriageable that no one would marry these people, so these were kind of the social and insurance issues we really focused on and luckily those have not played out. Our patients have not lost their health insurance because of loss like HIPAA and GINA that have protected them against these things, but also insurance companies have been smart enough to realize that knowing about the patient's risk ahead of time is not only good for the patient, it saves the money, and I do not have to tell you how much it cost when a patient is diagnosed with cancer and has to go through surgery and chemotherapy and radiation, and we are taking about hundreds of thousands of dollars will cost and many of our patients are able to avoid that if they know ahead of time that they are at high risk. So, many of those fears did not play out, but one of the fears that we did not anticipate was that as genetic testing became popular that the testing companies would really market this test to the patients directly and also directly to clinicians, nurses, physicians, even technicians, who have no training at all in cancer genetics and say to them, you should order your own test, and so that is what has happened and so what our people basically discusses is the fall out from this, that what is happening when people order genetic testing without having a background in cancer genetics or genetic counseling, and the impact on the patient and the entire family and it can be fairly dire.

Wilson Well, let look forward to getting into some of the details in just a few minutes. We are going to take a short break for medical minute. Please stay tuned to learn more information about genetic testing with Ellen Matloff and Karina Brierley.

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Medical Minute *The American Cancer Society estimates that he lifetime risk of developing colorectal cancer is about 1 in 20 and that risk is slightly lower in women in then in men. Early detection is the key. When detected early, colorectal cancer is easily treated and highly curable. Men and women over the age of 50 should have regular colonoscopies to screen for this disease. Each day more patients are surviving the disease due to increased access to advanced therapies and specialized care. New treatment options and surgical techniques are giving colorectal cancer survivors more hope than they ever had before. Clinical trials are currently underway at designated comprehensive cancer centers like to one at Yale to test innovative new treatments for colorectal cancer. New options include a Chinese herbal medicine being used in combination with chemotherapy to reduce side effects of treatment and help cancer drugs work more effectively. This has been a medical minute and more information is available at yalecancercenter.org. You are listening to the WNPR Health Forum on the Connecticut Public Broadcasting Network.*

Wilson Welcome back to Yale Cancer Center Answers. This is Dr. Lynn Wilson and I am joined today by my guests Ellen Matloff and Karina Brierley. We are discussing genetic testing and the adverse events that can occur. When we left off with the break, you had started to get into some of the direction and detail of the paper that is coming out.

Brierley Yes.

Wilson Can you talk about that a little bit more?

Matloff When we realized a few years ago that this was the fall out of people ordering genetic testing who knew nothing about the field, and that this problem was becoming more and more prevalent, we decided to reach our to our colleagues nationwide via an email list for people who specialized in cancer genetic counseling and just said, we have these problems in our area, here are the kinds of cases we have seen, has anyone else seen these kinds of cases? And to our surprise we were flooded with emails and phone calls of people saying, you would not believe what happened in our area, and so this is a very difficult problem to study in a systematic way because there was no way to reach out to every single person who has had genetic testing in the entire country and figure out who ordered it and what the outcome was. You would have to have the genetic testing companies backing the study and actually many of those companies are the ones encouraging non specialists order the test, so that is just not going to happen. So, what we did instead was kind of a case report series, and we asked our colleagues to send these cases and we found that those cases were falling into several different categories.

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Wilson And were these colleagues from around the country?

Matloff All over the country.

Wilson Okay.

Brierley And so, several years ago, we published the first case series on this topic and it was controversial enough, that although we had several major journals who expressed interest in this topic, when they saw the manuscript, they would not consider it because one of the things we were saying is that one very powerful wealthy company was encouraging these people to order their own tests for financial reasons and then the attorneys for those journals said we cannot consider your manuscript. So, the first paper was published in a smaller journal, actually here in Connecticut, and received a lot of attention even though it was in a very small journal. And so now we are publishing our second series of cases, and Karina can speak to you a little about the categories that those cases have fallen into.

Wilson Please do.

Karina In the previous paper, as well as this paper, one of the main categories was the wrong test being ordered, and the results that can happen with that, so patients being given the wrong information in terms of their cancer risks and risks for their family members. Another was the correct test being ordered, but then the test results being misinterpreted. And then another category, there were a couple of different categories between the two papers of just inadequate genetic counseling, so not being given enough information or enough support and counseling, and ethical issues in terms of what is typically done in cancer genetics and that not being done.

Wilson Give me some examples of that.

Karina The most striking example of that is a new one for this newest paper, and in cancer genetics we do not order testing for minors for diseases that present only in adulthood, so for example for hereditary breast and ovarian cancer, we do not recommend testing children, because there are no interventions that can be performed at that time and there is some question as to whether there may be emotional, social, and discrimination issues in terms of children having that information before adulthood, before there is anything that they can do with that information. And in this paper there was a 7-year-old who was tested by her pediatrician, on the urging of her parents and a relative that was a physician, and then once the parents came in for genetic counseling, having the results that their daughter had tested positive for the mutation, they did not realize the impact that it would

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have on them in terms of their own cancer risks, they did not realize the impact that it could have on her daughter and that there was nothing they were going to be able to do with that information until she reached adulthood, so I would say that is probably the most striking example in terms of an ethics standpoint.

Wilson Ellen do you have other examples that you might want to share?

Matloff It is interesting. We have several colleagues from across the country who, off the record, have shared stories with us, many of them having to do with young children being tested for these adult onset diseases, even though every single national board recommends against it. There are very strict guidelines saying do not test children for these diseases. So, in addition to the case that was formally presented, a colleague told me about another case in which two young girls, I believe aged 10 and 6, were tested for a familial BRCA mutation, putting them at very high risk for breast and ovarian cancer as adults, and you can imagine for a parent to have this information, what that emotional distress is like to know that their child is going to someday be at that kind of a risk and if they share that information with the children, what that is like for a child who has not even gone through puberty yet, has not even developed breasts, to be thinking about, oh my gosh my cancer risk is so high. And also in some families where testing has not been done, the children just know that there is cancer in the family. I remember we had a 15-year-old boy, a jock type of a kid, great kid, National Honors Society, who came in and he waited until his mom left the room to say to me that he found a lump in his own breast at 15 and could boys develop breast cancer? It turned out to be nothing, it turned out to be a breast bud that was normal for his developmental age, but these are kinds of things that can happen to children who are wrongly tested for an adult onset condition.

Wilson When we talked in the first half of the show and I asked about time commitment, you were very specific about time up front and then just as important, if not more, is the time you spend after the results are available to go over all of this and to put it into perspective and follow the patient if unfortunately they may be at risk for something, and I would imagine that a good percentage of these cases that were initiated, perhaps by a physician, but a non expert genetic counselor, they get the results, you get a test and they treat it like any other blood sample, this looks a little abnormal, I will just let the patient know this result and I have got more patients to see, sort of thing and that could have pretty catastrophic implications if one is not prepared to sit down and spend the time, but I would think if people are ordering these tests and they are not experts, such as yourself, for example, I am not an expert even though I am a physician, I am not set up to appropriately counsel somebody, so I would think that the implications of positive results that may be bad enough in and of itself, but then do not have the appropriate counseling and they do not even know what to do with the information, I would think would be very damaging.

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Matloff I would say extremely damaging, and one case comes to mind of a well meaning physician who ordered such testing on a patient and then when the test results came in showing the patient did have hereditary colon cancer, the way they let the patient know was they sent the patient a copy of the test results in the mail with a sticky note from the secretary stuck to the front of it saying, you carry the colon cancer gene, your kids need to be tested someday, and that was the counseling that family got, a sticky note from the secretary, and in one paper Karina researched, we found that it is not unusual for the secretary in these medical offices to actually be doing the result ordering and reporting.

Wilson I would think that either all of, or most physicians involved who are not experts in genetic testing and counseling, are probably really just trying to do what they think in their mind is the right thing. Looking at it that way, what would you recommend going forward that physicians and health care experts think about when they are confronted by a patient or a family who is interested in this information, when they are in a position to make referrals do something different the next time, what would you recommend?

Matloff You bring up a really good point, this often occurs by well meaning physicians who are either pressured by the patient or the family, or even more likely by the testing company to order their own testing, sometimes they are given incentives, their office staff are given incentives for doing this counseling themselves and we have a particularly tragic story that I think may serve as a good example for anyone out there who is either thinking of pressuring their physician to order their testing, or for physicians and clinicians who think they should and could do it all. We have a case from the North East of a patient who had never had cancer herself, but had a strong family history of breast and ovarian cancer. She spoke to her gynecologist about it and her very well meaning gynecologist said, I will order some genetic testing for you and told the patient the good news that the test came back normal and they had nothing to worry about. Fast forward a year and a half later, the patient is diagnosed with advanced ovarian cancer. Her prognosis is poor and she is about 46 years old and at that point when she comes in for genetic counseling saying, I have had testing it was all normal, nothing was found in my family, the genetic counselor involved said, well there has been some new testing that has been added, lets go head and order that testing and was very surprised to have the testing company say, this patient was tested a year and a half ago and carries a mutation, and so they forward the test results and sure enough, a year and a half before when that patient had been tested, she was BRCA1 positive but the well meaning physician who was trying to do her patient a favor, somehow misinterpreted that test result and that patient is now dying of ovarian cancer. So even something as straight forward as a positive test result can be misinterpreted and as you well know, any time you step outside your area of expertise and you are only reading one test result a year, that is pretty difficult to do and not only are those physicians

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putting their patients at risk and the patient's family members at risk, they are putting themselves at risks, they are putting their institution at risk and look at how this one tragic case has effected this entire family, it is terribly sad.

Wilson Have you seen things change and evolve over the last couple of years, say for example between the first publication and now the new publication, or are things the same way out there?

Matloff What do you think Karina?

Karina I wish I could say that I thought things have changed. I think maybe there is a little bit more attention to it, but unfortunately the reason we are standing here today with another paper is that things have not changed enough, we were able to still collect enough cases to do a second edition and in fact we have already had another colleague reach out after we closed for publication with another case, so unfortunately I think things are still very much the same in many places.

Wilson Do you think at least in our area, since we have people like yourselves as experts, do you think less of this kind of thing goes on in the general region around here, because of the recognized expertise with folks like yourselves and what we have here at Yale? In other words, is the awareness regarding this kind of issue and what we have to offer at Yale higher in this general community? For example, if I had a patient come to me in my cancer clinic and was interested in genetic testing, I have known Ellen for a long time, so I would say I have someone I can call right now and arrange an appointment for you to see who is an international expert on this subject, but if I was in town XYZ and my center did not have this kind of expertise, as a well meaning physician I may try and get out of my comfort zone and see what I could try to figure out on my own. I would like to think I would not do that, but if I did not know how to access these resources, then I do not know. Do you think it is different in the greater New Haven area compared to a town somewhere where there is no expertise for 100 miles?

Matloff Sadly some of the worst cases reported have come from the New Haven area, and so I think the point is a good one, you would think that in an area where these resources are readily available that people would not be ordering their own genetic testing, but we found that some of them still are. The good news is that no matter where someone lives in the United States, there are now cancer genetic counseling services available, actually by phone and by Skype through some companies and they are covered by insurance, so I would say no matter where you live, there is no longer a reason to try and do this yourself if you are not qualified.

Ellen Matloff is the Director of the Cancer Genetic Counseling Program and Karina Brierley is a Cancer Genetic Counselor. If you have questions or would like add your comments, visit yalecancercenter.org, where you can also get the podcast and find written transcripts of past programs. You are listening to the WNPR Health Forum on the Connecticut Public Broadcasting Network.