Speaker 1:

Welcome to the Eye on the Cure Podcast, the podcast about winning the fight against retinal disease from the Foundation Fighting Blindness.

Ben Shaberman:

Welcome to the Eye on the Cure Podcast. I am your host Ben Shaberman, and I'm very pleased today to have genetic counselor Kari Branham as my guest. She's with Kellogg Eye Center at the University of Michigan in Ann Arbor, and she has more than 20 years experience in counseling inherited retinal disease patients. I think that's pretty impressive. She's also a clinical associate professor, the director of ophthalmic genetic counseling at Kellogg and Kari mentors and trains genetic counseling students, and is a co-investigator on several clinical trials. And to top it all off, she does her own research to better understand the genetic basis of IRDs, inherited retinal diseases. Welcome to the podcast Kari. It's great to have you.

Kari Branham:

Thank you Ben. Great to be here.

Ben Shaberman:

So we're of course going to talk a lot about genetic testing and a lot about genetic counseling. That's why we're here. And I'm pleased to say I've known you for many, many years, I think really since I started with the foundation more than 18 years ago. But I've never asked you what inspired you to become a genetic counselor and a genetic counselor in the inherited retinal disease space.

Kari Branham:

Well, Ben, since you asked, that means I kind of have to tell you my life story actually. So I've actually been interested in genetics going back to when I was in middle school, first learning about genetics. I kind of liked the explanation that it gave for the world around me, and I kind of knew going high school into college, I wanted to do something with genetics. I didn't know exactly what that was. I didn't hear about the field of genetic counseling until my junior year of college kind of thought, "Hey, that would be great. It sounds like something that would be very, very interesting to me." I did do some lab research when I was an undergrad and I was like, "The science is very interesting, but I just don't like spending all my time in the lab," and didn't think that was something I want to do.

So when I heard about genetic counseling, I was like, "Oh, this is great. I can still do the science. I can interact with people." Kind of the best of both worlds. When I graduated from undergrad, knowing that I wanted to go into the field of genetic counseling, but the programs were kind of competitive, so I wanted to work for a little bit before I applied to the graduate programs in genetic counseling. It just so happened that there was an opening here at the Kellogg Eye Center as a research assistant with a genetic study of AMD. So worked here for a couple of years as a research assistant, went on to grad school. And then when I had my genetic counseling degree, it just so happened that there was an opening for a genetic counselor at the Kellogg Eye Center, and the rest is history. So I always say I got into ophthalmology because of the genetics, but then I stayed for the IRDs.

Ben Shaberman:

Well, that's a really cool story, and we're so glad you're in our space. Now, are you from the Ann Arbor, Detroit area originally?

Kari Branham:

Yeah. I grew up in Michigan, grew up in Lansing, so the center of the state, went to undergrad at Western Michigan University on the west side of the state, and then have been in Ann Arbor area ever since then.

Ben Shaberman:

Very cool. So I want to spend time just talking about genetics, the counseling process, what people can expect from genetic counseling and genetic testing. But one thing I wanted to make sure people are aware of, our listeners, is that the foundation has a no cost genetic testing program for people with inherited retinal diseases. It's been around now, I want to say for six, seven years. We've had more than 18,000 people in the US order genetic tests through the program, no cost genetic tests.

The panel we use is from Blueprint Genetics, and it is your eye doctor or even primary care physician if you're so inclined that orders the test. And really the important thing is that they're able to diagnose a patient with an inherited retinal disease and then they either swab your cheek or take your spit, send it off to Blueprint. And again, they order it online. We do not order it at the Foundation Fighting Blindness. So talk to your doctor if you're interested. They can go to blueprintgenetics.com, but free genetic counseling is part of that process. And I know when we talk to patients and families about the genetic testing process, we always emphasize how important genetic counseling is. And Kari, can you tell us in more detail why genetic counseling is so important?

Kari Branham:

So genetic counselors, we kind of have that specific training. When we go to grad school, we learn not only about genetics, we learn how to educate patients, how to provide also psychosocial support. So kind of dealing with these diagnoses and getting this information, it's not always easy to understand, but we kind of have that set of skills that allow us to work with the patients, but also understand the complex genetic information. And that's actually I think where a lot of the difficulty is. It's quite easy for anybody, any healthcare professional to order that genetic testing now. But really the expertise that genetic counselors can add to that is explaining the results and doing so in a way that is sensitive that kind of helps the patients and families dealing with what is sometimes a difficult thing to deal with, help them to work through getting the diagnosis, understanding who else in the family may be at risk for the condition, that sort of thing.

Ben Shaberman:

And of course, I think what people are very excited about, once they learn what that mutated gene is, then they have a better understanding of what trials and emerging therapies might help them. I think when people first learn about or hear about genetic testing and genetic counseling, it sounds kind of ominous and they may conjure up images and inaccurate images of what that process is like. What do you find are the big misconceptions about genetic counseling and genetic testing?

Kari Branham:

Regards to genetic testing, I kind of think people don't always have a good understanding about what information they're going to get. I'll have many patients who are saying things to me, "You're going to tell me everything about my health. You'll be able to tell me my ancestry." Well, genetic testing, basically you're only going to find what you're looking for. So we're testing our patients on a retinal dystrophy panel. So when you look at genetic information, yes, you can tell lots of different things about the health, but you're only going to get back the information that you're testing for. If you're testing on

a retinal dystrophy panel, you're going to be tested on retinal dystrophy genes. We're not going to tell you everything about any aspect of your health. We're not going to tell your countries of origin. It's really kind of you're going to only find what you're looking for.

I think one of the other kind of misconceptions that will come out of that is what the meaning of the result is. As in if you get a negative test, meaning didn't identify any genetic variants that could be the cause of disease, some people say, "Okay, well that means I don't have a retinal dystrophy," when that's not at all. You can still have a retinal dystrophy, but the test is not a perfect test, so we can't always identify what the genetic cause of disease is. And the third bigger misconception that I hear about a lot is that genetic testing is not affordable or it's not accessible to me. And I think with now programs like the FFB sponsored testing programs, that's made it accessible to a lot more people. So basically if one of the previous limitations has been that the tests are pretty expensive, they're something that may or may not be covered by insurance. But then when you have things like the FFB genetic testing program, then that does allow people to have access to genetic testing at no cost. So that's kind of a big boon to the accessibility issue.

Ben Shaberman:

Certainly, and you've kind of answered this, but when people come into genetic testing and the counseling process, what are usually the big questions or concerns? Do they have worries or just confusion about what will take place?

Kari Branham:

I think the answer is yes, yes and yes. So we have lots of people who have lots of different questions and it kind of depends on what their take is. One of the big things definitely is what does this mean for other members of my family? Are there other people in the family that might be at risk for this particular condition and who else in the family should or should not have testing done? And we kind of very much look at it actually testing other family members that's really, in many cases, up to the family members if that's something that they want to know about. But that will be a big concern for the patients. Who else has a chance? This is a genetic condition and the risk for other people in the family really depends on exactly what the genetic cause of disease is in the family, but sometimes there will be a significant risk for other people, whereas sometimes it's a very minimal risk.

But that's definitely a really concerning kind of aspect. I think people they want to know a lot of times once you identify this genetic cause of disease, is there anything that I can do? And that's one of the main motivations for getting that testing done is I want to do this testing, is there anything that I can do? And so that's a lot of times what genetic counselors or other healthcare providers will talk to patients about is, okay, this is a genetic cause of disease that was identified in you and this is what we can or cannot suggest to you, as in are there clinical trials? Is there's one FDA approved treatment for patients with inherited retinal diseases? Is it the right gene for that? So we'll definitely go through all that sort of information with patients.

Ben Shaberman:

Right. And I'm sure a big question is what is the likelihood when somebody gets a test that they will get a definitive or a conclusive result current panel?

Kari Branham:

Yeah, so for the panels that we're testing on, large inherited retinal disease panel, we're able to identify the genetic cause in about 60% of patients. The remaining 40% will either be negative, meaning no

genetic changes identified or inconclusive, which means, "Hey, we found something. Not exactly sure if it's the cause of disease." That detection rate that I said 60%, that's kind of across all patients, all diagnoses, it can vary a little bit what that detection rate's going to be based on what the diagnosis is. Some of the diagnosis, for example, I would say are Usher syndrome or other syndromic conditions where there's more than one part of the body affected, that can be as high as 80, 85%. So it varies based on patient demographics and diagnoses that we're seeing.

Ben Shaberman:

Right. Got it. So a question I get frequently, whether a patient has had their mutated gene identified or not is they ask about retesting. Sometimes somebody will share a genetic testing report from a result they got 10 or 15 years ago that shows a conclusive result, here's the gene. But they think because the test is so old that they need to get retested. But generally speaking, when does retesting make sense?

Kari Branham:

So I think if the original test report was positive, and we still have evidence to suggest in the literature that the genetic cause of disease that was previously identified is still the cause of disease, then we don't generally recommend retesting. Where we think about retesting is for the negative and inconclusive test results that I just mentioned, and I don't generally think of it specifically as a timeline, as in after X number of years, you need to be retested. What we usually do is take a look at the original test, see what exactly the patient was tested for originally, what is their diagnosis, and use that information to gauge where we're at with technology and what would be an appropriate test for someone. So I don't think, while the panels that we're testing for, they've increased over time, but just as important as that is what type of testing, what variants were tested for on the gene, what genes were included on the panel of whether or not we need to retest, but generally not for the positive. More for those negative or inconclusive ones are the ones that we think about retesting being important.

Ben Shaberman:

Right. And just for our listeners to know, if you're tested through our no cost genetic testing program and you don't get a definitive result, you need to wait about three years for retesting because you can't just come back and get retested every few months because that would get a little expensive for the foundation fund. So there is a three year moratorium, and this is a big question, but maybe you can provide just some basic guidelines. When do you think family testing makes sense?

Kari Branham:

I think it depends a lot on what exactly the gene of interest within the family is. What is the inheritance pattern of it that would determine who else should be tested and when they should be tested? So we can think of something like let's say a dominant condition. In a dominant condition, the children of someone who is affected, each of them would have a 50% risk for inheriting the disease causing gene and also being affected with the condition. But there is kind of this idea in the field of genetics is not testing minor children. So if the child of the patient is an adult and they want to know if they have inherited that genetic cause of disease, then all means they should proceed with the testing if they would like to do that.

If the person at risk within the family though is a minor, a child, the general thinking in the field of genetics is not testing that child until there is some medical reason to do so or until they're an adult and can decide for themselves if they want to have that testing done. So the reason for that is really, so if your child is at risk for condition, it's not something they're likely to develop until they're adults. Some

adults may want to know if they inherited that genetic variant that's going to cause disease or could cause disease within the family, whereas other people might not want to know that. But if you test them when their minors, you're taking away their right to decide if that's something that they would like to do that testing or not, and know if they inherited that genetic variant.

Ben Shaberman:

Certainly. And I can only imagine, especially for a child or a minor to learn that you do in fact have that mutation, the emotional impact of that, I just can't imagine.

Kari Branham:

Yeah. And it gets even trickier because you definitely, you have some parents who will say something like, "Well, I'll do the testing, but we're not going to tell the child whether or not they have the genetic variant." Well, that's definitely a whole other kind of can of worms that can definitely be challenging and something that should be kind of worked through with a healthcare provider to decide when is the appropriate time to testing, what are the motivations for doing the testing and what will the communication look like within that family?

Ben Shaberman:

Right. And you obviously help with those conversations.

Kari Branham:

Absolutely. Yep.

Ben Shaberman:

So another frequently asked question I get and I'm sure you get, is about variants of unknown significance.

Kari Branham:

Yes.

Ben Shaberman:

What exactly is a variant of unknown significant, which we say in short is a VUS?

Kari Branham:

Yes. Variants of unknown significance tend to be the bane of existence for many geneticists and genetic counselors. But I'm going to give just a super quick genetics lesson to kind of help understand, explain how it is that we do the testing. When we do the genetic testing, we basically take the genetic information from the patient who's affected with disease and then we have a control or a reference sequence that we compare that to. There's always going to be differences in those two genetic sequences because we're all a little bit unique, a little bit different. But what the job of the lab does is they kind of classify any variants of unknown significance. They work to determine what is the impact of that genetic variant on the gene. And if they think that it is the cause of disease, they'll call it pathogenic or likely pathogenic. If it's just a part of the normal variation that we all have that makes us all unique but doesn't impact the gene in a way that would cause disease.

They call it benign or likely benign. And sometimes they can't fit it into either of those categories, in which case it becomes a variant of unknown significance. The evidence that's used by the lab to classify as disease causing not disease causing, they take lots of pieces of evidence. So there are normalized databases with people who aren't expected to have disease. They look for how common it is in that. They look in the literature to see how common or how often it's been reported in people who are affected with disease, they do some computer modeling of all of those pieces of evidence together are used to classify it as pathogenic or likely pathogenic. But if you can't get enough criteria to call it pathogenic or likely pathogenic, then it gets classified as variants of unknown significance, which means it could be. It's different from what we'd expect in the normal reference sequence, but we just don't have enough evidence to clearly classify it as disease-causing so pathogenic or likely pathogenic.

Ben Shaberman:

Right. And the VUS, the categorization of the variant could change over time.

Kari Branham:

Absolutely.

Ben Shaberman:

Let's say somebody has a VUS on a gene and they just want to follow up to see if it has been reclassified. Can they contact you every few years to see what's going on?

Kari Branham:

Yeah, and that's something that we definitely do. Whenever we have a patient who's coming into the clinic and we see that, "Oh, we did testing a couple of years ago, they had a variant of unknown significance," the first thing that we actually do before we consider sending off for retesting, contacting the lab to see what the classification of those variants is. Is that something that's changed over time?

We do actually also, sometimes the lab will just on their own, they'll send us an updated report on a patient that says, "Okay, this was originally a variant of unknown significance, but now we've seen the same exact variant in other people that have the same disease," and so now they reclassify it. So it's not surprising at all that I'll sometimes be able to call my patients and say, "Hey, we just got some new information from the lab that says that this is actually a variant of unknown significance." But we absolutely, before we consider additional testing that goes into the looking what was done before to see if there's new classification, if maybe we don't need to do retesting. We just need to look at those variants that were already identified.

Ben Shaberman:

Well, glad you're staying on top of these VUS's. That's important. So a few months ago I had the pleasure of moderating a panel at a conference on IRDs caused by PRPH2 mutations, and you were on that panel. And one thing that came out of that whole meeting about PRPH2 was how family members, even siblings with the same mutated gene can have such different disease presentations and disease severities. It's kind of mind-blowing how the outcomes can vary so much for the same mutated gene, and I'm using PRPH2 as an example, but it can happen with other genes as well. Why does that happen? Do we know?

Kari Branham:

That's something that always is very interesting. And PRPH2 actually, as you mentioned, it happens to be one of the genes that I find the most interesting for that very reason that you mentioned that. Why do we see all this diversity in how people can be affected and one gene affecting people in so many different ways? But as you said, that's not the only gene that is something that we will see.

And sometimes it's not even really very extreme diversity, but just maybe even severity of disease within the same family that we can see those differences. And the two main things that we think about modifier genes and environmental type factors. So modifier genes, meaning just that there could be a kind of secondary gene that's impacting the expression of how a gene is causing people to be affected, but we're not a bubble of our genes. And so kind of severity within a family can sometimes be explained by different environmental things. We know that there can be both risk factors and protective factors, things such as smoking, sun exposure that can make it so the severity of someone's disease may progress. But I think this is still an area where we have a long ways to go, understanding a lot about modifier genes, understanding why it is that we see this variable expression and something that we'll probably be studying for several years to come.

Ben Shaberman:

Right. And the foundation, I'll say we fund some research to better understand why the disease variation can occur from the same mutated gene. Well, Kari, this has been a lot of fun, very informative. We took some deep dives on certain topics, and I'm really thankful for the opportunity to do that. It's been a pleasure to just chat with you one-on-one as I've done throughout the years, but I really appreciate you doing this for the podcast, and I think this'll be of great interest and benefit to many of our listeners. So thank you.

Kari Branham:

My pleasure to be in here. I love to talk genetics, so happy to do it at any time.

Ben Shaberman:

Well, that's clear, and I'm glad you've taken your passion and applied it to the IRD world. So thank you. And as always, thanks listeners for joining the Eye on the Cure Podcast. Great to have you. And stay tuned for our next podcast.

Speaker 1:

This has been Eye on the Cure. To help us win the fight, please donate at foundationfightingblindness.org.