

Usher Syndrome Coalition | Genetic Testing, Brian Mansfield, Ph.D., Foundation Fighting Blindness

Hello, my name is Brian Mansfield. I'm the Executive Vice President for Research and the Interim Chief Scientific Officer for the Foundation Fighting Blindness. And today what I would like to tell you about is the Foundation Fighting Blindness Genetic Testing Program, and how you can get a comprehensive genetic test for your inherited retinal disease at no cost.

So what is a genetic test, and what is the value of a genetic test? A genetic test is where we take the DNA from your body, typically taken from a saliva sample or maybe a blood draw, and we look into that DNA at all of the genes and try to identify a mutation in a gene that might be the cause of your retinal disease. And knowing this can often provide comfort about the certainty, you now know what it is that's causing your disease. And that's always nice to know that there's actually a cause that you can point to.

It may confirm or refine a clinical diagnosis. And in refining a clinical diagnosis, it may suggest additional tests that your clinician may want to undertake to help understand your disease better. And I'll show you a couple of examples of that, that have come out of this testing later on in the presentation.

It may guide you to better informed decisions, because now you know the cause of the disease. And it may guide you to potential clinical trials that you may be eligible for that will at least help you focus on which studies are being presented in the literature and talked about in the media that are of particular interest to the genetic cause of your disease.

And when shared in a registry, the genetic information about your disease becomes very powerful. It can inform about prevalence of your specific gene causing the disease or even the specific mutation in your gene that causes disease. And this can motivate research. It draws researchers to that data. And it can draw industry who want to try their new technologies on specific genes, or specific variants, or mutations. They may be drawn to this because the data is out there. They can find it easily, and, therefore, you've made the barrier to their work lower.

Now the Foundation Fighting Blindness No Cost Genetic Testing Program has two programs available. It's really your clinician's choice which of those programs they're going to choose. Both of them provide the same high quality, comprehensive gene panel test. It's the best test you can get on the market at the moment. They are also both going to provide you the same level of genetic counseling.

Now when you get a genetic test result, it's not simple. It's not something like a glucose test where it's high, low, or normal. It comes with a very complicated analysis. And it really takes a genetics expert who understands the genetics of disease and also understands the clinical presentation of diseases to be able to combine that information to give you an informative outcome from your genetic test. That is the skill set genetic counselors have. And that is why we require that someone who goes through our genetic testing program also agrees to genetic counseling, so that they make the most and gain the most out of the genetic test.

Now both of these tests are not going to be charging you for the actual genetic task panel, which is a very expensive test, or for the genetic counseling. However, your clinician may choose to charge you for the clinical visit that you do when you go and ask them for the test. And the clinician may decide that they need to do some additional testing on you before they order the genetic test. If that is the case, we do not cover that cost either. We do cover the very expensive gene test, and we cover the counseling.

So the first study that we launched was called the My Retina Tracker Registry, IRB Genetic Testing Study. Quite a mouthful, really. Well, My Retina Tracker Registry, for those of you who don't know it, is the Foundation Fighting Blindness's registry for people with an inherited retinal disease. So it captures the 20 or 25 different inherited retinal diseases that are clinically diagnosed. They include Usher syndrome, but they also include retinitis pigmentosa, Stargardt disease, Best disease, Bardet Biedl syndrome, a wide variety of different diseases.

The IRB in the genetic testing study means Institutional Review Board. And this is an administrative aspect about the way we set this study up initially. Now the study was a pilot study, but it is still available to the clinicians. Only certain approved clinicians can order this test because of the way the administrative organization was set up. And only people who are members of the My Retina Tracker Registry are eligible for the test.

Now, this study ran for just over a year, and it demonstrated that there was a really large demand for testing. A lot of clinicians who heard about the test, a lot of people with inherited retinal disease who heard about the test, expressed concern that they were not able to order the test. But more importantly, from the foundation's point of view, this initial study pointed out some of the problems of running the test with the IRB administered protocol to it. And we realized there were a number of things that would really need to be changed before this program could become scalable.

So using that information, on October 2019, we launched a second program, which is called the My

Retina Tracker Program Open Access Genetic Testing. Now, as I said before, this is going to use the same gene panel tests. It's going to provide the same level of genetic counseling. But now any qualified clinician is going to be able to order the test. They don't have to be pre-approved by us. And anyone with an inherited retinal disease may be eligible to have the test.

So the key thing about this program, you do not need to be a member of the My Retina Tracker Registry. We would certainly appreciate it if after being tested you joined and shared the information with us, because that helps make the program sustainable. But you do not need to be a member of the My Retina Tracker Registry to have this test. And it will still be free.

So what's the eligibility for testing in this program? And now I'm talking specifically about the Open Access Program. You need to live in the United States or the United States territories. There are regulations that control the handling of identifiable health data around the world. And at the moment, it is not easy for us to be able to expand this to meet those criteria and offer testing to people outside the US or US territories. We're looking into it. It may come in the future. We just can't do it at the moment.

Secondly, you need to be clinically diagnosed with an inherited retinal disease. That means you need to go and see a clinician. And they need to be able to say, we believe you have an inherited retinal disease. A clinician can not use this just as a general eye disease screening.

When there's a free test around, a lot of people will say, well, why not try it and just see if I've got an inherited retinal disease where it finds my gene. Well, this program just won't work for diseases other than inherited retinal diseases. And it's a very expensive program. So to make sure we use our money most effectively, we are requiring that the clinician needs to be fairly clear you've got an inherited retinal disease. They can't just say, oh, well, let's try. I don't know what you've got, but let's have a go.

And finally, you should not have had a genetic test since 2016 that tested for more than 32 relevant genes. So if you haven't had a recent comprehensive genetic test, the chances are you're eligible for testing.

So how do you get tested? Well, the first step, of course, is you receive a diagnosis for inherited retinal disease from your clinician. And then you ask your clinician to order the test. Now it's very important to explain, you cannot order the test. The test can only be ordered by a clinician. Just as you can't order a cholesterol test or a glucose test, you cannot order this test either. It has to go through a clinician.

Now, many clinicians already are aware of this test. But if they're not, the Foundation Fighting Blindness has a web page about Open Access Genetic Testing. So you can go to the Fighting Blindness web page, and you will find there a dropdown that says Open Access Genetic Testing Program. Very specifically, the address is fightingblindness.org/open-access-genetic-testing-program, fightingblindness.org/open-access-genetic-testing-program.

There you will find some information. There is a PDF that you can download for the person who is affected by the disease that explains all about genetic testing and what is involved, and what it will tell you, and how it benefits you. And similarly, there's a PDF download there for your clinician. You can either point your clinician to that download, or you can download it yourself and print it and take it and show it to them. And it explains to the clinician what the test is, and what they need to do to go ahead and order it and ensure that there is no billing associated when they order that test.

Now at the end of the test-- and that's got a turnaround of somewhere between two to four weeks-- you will finally get a genetic counselor. We'll call you and explain the results, and also explain opportunities that this test may be providing for you. And at that time, if you would like to join My Retina Tracker Registry, the genetic counselor can help you do it over the phone online right there and then. And I hope you'll consider doing that. So very easy steps for you to do. The main thing is to make sure your clinician gets the information about how to order the test, if they don't have it, by going to our website.

So what is the outcome of the people who've been tested in our genetic testing program? So far we've had over 7,700 people have asked for genetic testing. And in testing that group of people, we have found 148 different genes that cause the diseases. And surprisingly, just six genes account for over 50% of the people who were tested. Six genes accounted for actually 53% of the people.

So let me take you through those six genes. On the screen in front of you, there is a colorful pie chart where the segments of the pie chart represent the proportion of disease explained by any one given gene. So the gene that caused the most disease in this group that we tested with the ABCA4 gene, which is typically associated with Stargardt disease. And that was responsible for 20% of the disease in the group that we tested.

The next most common gene was the USH2A a gene, which accounted for 13% of everyone we tested. And USH2A gene is known to be associated with Usher syndrome type 2A, but also a nonsyndromic form of retinitis pigmentosa. The third most common gene was the gene RPGR, which accounted for 7% of the people. RPGR is the gene that underlies X-linked retinitis pigmentosa.

The fourth gene was the gene PRPH2, accounting for 5% of people. That is a gene that causes autosomal dominant retinitis pigmentosa. The next most frequent gene was the rhodopsin gene, which, again, accounted for 5% of people. And that accounts for another form of autosomal dominant retinitis pigmentosa. And then the sixth gene was the gene EYS, which accounted for 3% of the people. And the EYS gene is associated with a form of autosomal recessive retinitis pigmentosa.

And then the other genes in the family, of course, accounted for 47%. But they all represented much less than 3% each of the total population we tested. Now, this data is very exciting. And Kari Branham, who is an assistant research scientist and a genetic counselor at the Kellogg Eye Center in Michigan, is currently preparing a manuscript for us to summarize these results and share them with the broader community.

So let me talk to you about the outcomes specifically associated with those people who are clinically diagnosed with Usher syndrome and went through the genetic testing program. Now most of those people came into the program with the type of Usher syndrome undiagnosed. So they didn't come as Usher syndrome type 1 or type 2, they came as Usher syndrome type unspecified. And genetic testing showed that 91% of those who had an initial clinical diagnosis of Usher syndrome, did in fact have Usher syndrome. But 3% of them had an atypical genotype phenotype relationship.

Now, what does that mean? Well, 3% of the people we found a gene, but we don't normally think of that gene as causing Usher syndrome. So it's atypical. It's interesting. And that would be something that your clinician would be interested in looking at, and maybe asking you to undergo further clinical testing to help confirm the Usher syndrome clinical diagnosis. This also highlights why it's important to have a genetic counselor help explain the result. Because if you had one of these atypical results, the genetic counselor would be able to explain it fully to you and put it in a context that you could understand.

3% of the people had a vision and hearing loss, but the gene was consistent with a different syndrome, a syndrome such as Alstrom syndrome, Stickler syndrome, Zellweger syndrome. And again, this is where genetic testing is informative to the clinician. With this result in hand, the clinician, again, may want to have you undertake further clinical diagnosis and testing just to be sure that the disease is Usher syndrome, or, in fact, to confirm that, while it looks like Usher syndrome, it may actually be Alstrom, Stickler, Zellweger, or other similar syndrome.

So again, this is the importance of having genetic counseling. The genetic counselor would guide you what to do, and would also be talking to your clinician about what they would suggest they do with

this result in hand.

And finally, 2% of the people who came in had mutations in genes associated with nonsyndromic disease, such as diseases such as choroideremia, autosomal recessive retinitis pigmentosa, autosomal dominant retinitis pigmentosa, and Stargardt disease. So again, you can see how the outcomes of testing are not always as straightforward as you might hope. There's often a lot of nuance to them. And this is where the genetic counselor can help guide you. And your clinician will build on that information and maybe ask for additional testing to help you.

So again, what was the genetic cause of those people who had Usher syndrome? Well, we had 264 people who had a clinical diagnosis of Usher syndrome who were tested. And we found 20 causative genes to explain the disease in those 264 people. So again, I'm showing you here a pie chart with different colored segments. The size of each segment representing the prevalence of the gene found in that population.

And the most common gene in the Usher syndrome group was the gene USH2A, which accounted for 59% of people. And that is associated, of course, with Usher syndrome type 2A. The second most common genetic cause of Usher syndrome was the gene MYO7A that accounted for 13% of people. And that is the gene that causes Usher syndrome type 1B.

The third most common gene was ADGVR1, which accounted for 9% of people. That's the gene that is associated with Usher syndrome type 2C. The next most common gene was CDH32 at 9%. That causes Usher syndrome type 1D. Next came the CLRN1 gene at 3%. That causes Usher type 3. Then the PCDH15 gene, which was at 2% of the group tested. That causes Usher syndrome type 1F.

The next prevalent gene was CEP78 at 2%. That causes cone-rod dystrophy and hearing loss. And the next gene was the USH1C gene at 2%, which, of course, is associated with Usher syndrome type 1C. And then there were 11 other genes that were each below 2% that explained 5% of the people with a clinical diagnosis of Usher syndrome. So quite a bit of variety.

Now what I would like to encourage you to consider when you have been genetically tested is to share your data. And the best way to share data is through patient registries. They help to share the data responsibly. They act as centralized sources of information, capturing your clinical diagnosis, your genetic diagnosis, and other information about your disease.

And they provide a way of connecting all of that information to researchers, to industry. They help enroll in clinical studies, focus studies. And they are a really powerful tool that save researchers and

industry a lot of time, a lot of money, a lot of effort, and, as a result, attract them to the data and to our diseases.

So for instance, many industries have a technology that they really want to prove works. And they are looking around to ask, which disease is going to be the best disease for me to use my technology to prove it will work and it can cure disease? And many times, industry has looked to retinal diseases. They are very attractive diseases for testing technology in. And we're excited by that because it means it's drawing people to look for treatments and cures for our diseases.

One of the barriers, though, is being able to find the data they need. They don't want to spend a lot of time and money phoning individual clinicians, explaining what inclusion criteria they want, explaining the exclusion criteria they want, and then hoping that the clinician has the time to go and look through the databases and identify patients who meet those criteria.

By going to a registry as a centralized source of this information, companies can drop their barrier to entering this market by just simply using that source of information to quickly scan through all that data, and then identify the patients and the clinicians associated with those patients who they can then reach out in a very focused way to. So registries are incredibly powerful and valuable. And industry and researchers really like access to them.

Key elements of a registry are that they share the de-identified data. That is, that they don't just simply hand out the name, address, email, contact information for patients. But rather, they connect independently to the patient to explain someone's interested in them, and allow the patient to determine whether they want to contact the person interested in them or not. They capture the clinical perspective of the disease, and they capture the genetic data and bring this puzzle of all these different parts together very nicely to give a complete perspective on the disease.

Now, there are two registries in our space that you might want to think about joining. Firstly of course, there's the USH Trust Registry, which is focused on all aspects of living with both hearing and vision loss. And there is the Foundation Fighting Blindness My Retina Tracker Registry, which has a similar goal as the USH Trust Registry, but is much more focused just on the retina only. It focuses on all inherited retinal diseases, including Usher syndrome.

So membership of a registry is not exclusive. Their shared missions and, also, different missions allow them to serve complementary roles. And I really encourage you to think about joining both, because both of them help accelerate research in our area. And by joining the My Retina Tracker Registry, you help to drive awareness of the value of the free genetic testing program, and that then draws

sponsors to the program who will then make it possible for us to offer this over a longer period of time.

And so to round out my talk, I'd like to just thank the partners who do support the very high costs associated with genetic testing and the running of our registry. We have those who just support our My Retina Tracker Registry. And they are the George Gund Foundation, the Foundation Fighting Blindness, of course, Eloxx Pharmaceuticals, AGTC, Sofia Sees Hope, and MeiraGTx. And a particularly strong thank you to the partners who are helping to fund this very expensive genetic testing program-- ProQR, Sofia Sees Hope, the George Gund Foundation, InformedDNA, Blueprint Genetics, and the Foundation Fighting Blindness.

Thank you very much. I hope you've enjoyed this presentation. I hope you think of using the Foundation Fighting Blindness Open Access Genetic Testing Program. And I also hope that you consider joining both the USH Trust Registry and the My Retina Tracker Registry.

And if you're interested in the USH Trust Registry, the website is usher-registry.org, usher-registry.org. And for the My Retina Tracker Registry, it is just one single word, myretinatracker.org. And if you have any questions about My Retina Tracker, please reach out by email to coordinator@myretinatracker.org. Thank you very much.