WILL EISERMAN:

I would like to welcome everyone to today's webinar entitled 'Genetics and New Developments in the Screening and Testing for Healing Loss'.

I am Will Eiserman, and I am the associate director of the national Center for during assessment and management. At Utah State University. Which is funded by the Maternal and Child Health Bureau. To serve as the EHDI National Technical Resource Center.

And as a part of that, we offer periodic webinars on topics relevant to early childhood, hearing and hearing detection efforts. And today's webinar is just one of those webinars.

This webinar is being recorded. And will be available to stream on our website@infanthearing.org. In the next couple of days.

So, if anything disrupts your attention to today's webinar, know that you can access it in the next couple of days on our website. And keep that in mind, too.

In case there are folks that are not attending live today. Who you think might benefit from the information that is being shared today. So, I will turn off my screen share.

And give our presenter an opportunity to share his screen. Our presenter today is Dr. Eliot Shearer. Who is an assistant professor of otolaryngology, at Harvard Medical School. Dr. Shearer is also practicing pediatric otolaryngologist at Boston Children's Hospital.

Where he cares for hostile -- children with a wide range of ears, nose, and throat disorders. He has a special interest in the surgical management of pediatric ear disorders, including hearing loss.

Dr. Shearer is internationally recognized for his work in developing a new genetic testing platform for the diagnosis of hearing loss.

And has written many research articles and several book chapters on the subject. Dr. Shearer also studies ways to improve newborn hearing screening tests. Using technologies and ways to improve outcomes for children with Cochlear Implant.

So, without further delay, let me introduce Dr. Eliot Shearer.

ELIOT SHEARER:

Thanks for the introduction, Will. Thank you so much for having me, I am really honored to be invited to speaking to you about today. First of all, I would like to thank you all for being here and taking time out of your very busy schedule and your very important jobs to learn about genetics.

So, I would like to just say, I have no conflicts of interest. I would like to start by changing or reframing how many of us think about hearing loss. What I mean by this is that, if we think about another diagnosis, or a symptom, I mean.

If you think about someone who comes into the emergency room and they have severe chest pain. You know, you do not have to be a physician to know that they may be having a heart attack.

Now, when I was a medical student, or an intern, and if I was in an emergency room, and if I recommended that immediate leave the patient go to the Cath Lab for a cardiac catheterization for the symptom of chest pain, which is really just a symptom, I would have been laughed out of the room.

Because we all know that we need to come up with a diagnosis first. So, that means doing things like taking a history, physical exam, getting vital signs and labs. And then doing tests, like an EKG.

Because you want to make sure that you are diagnosing a heart attack before you bring the patient to the operating room. And you want to make sure it is not something like acid reflux.

Which you can treat just with an (Unknown term) , it also has a similar symptom. I realize as a ... and Cochlear Implant surgeon, that I treat patients that have a symptom. On a daily basis.

That we do not have a diagnosis for. So, what I mean by that is that, we have a symptom of hearing loss and this is, you know, a down sloping, mild to severe hearing loss you can see here. That is symmetric.

And I take patient like this to the operating room for a Cochlear Implant. Often, really, we do not have a diagnosis. So, I would like to get us to focus on, is the importance of diagnosis and reframing the way we are thinking abut hearing loss, which is a symptom of an underlying process that is different.

And this really does affect patient care. So, what I mean by that is that, if we diagnose this patient with the gene MYH14, this is a stable hearing loss, and it could look like this for the rest of your life. That reframes the conversation I have with this individual. They may decide that they want to use hearing aids instead of Cochlear Implant.

If there hearing is going to be stable for years. On the other hand, this same symptom, the same Audiogram, I could provide a diagnosis of ACTG1, which is the gene that causes quite rapidly progressive hearing loss.

And again, that may reframe our discussion around hearing aids versus Cochlear Implant. The same individual with the same hearing loss symptom could also have congenital CMV infection.

And I think everyone on this call today knows that if you are not talking to a patient who has a CMV about (Unknown term) when they are in infants, then you are not providing the most up-to-date care.

So, we know that treating children with congenital CMV with (Unknown term) can slow or sometime even reversed the hearing loss. This individual here could have the symptom of hearing lesson have a diagnosis of OTOF, or out of Ferlin hearing loss. And there are two clinical trials that are enrolling, or starting to enroll individuals for gene therapy.

So again, the diagnosis totally reframes the discussion I have with the family in clinic. As opposed to treating a symptom, we need to treat and think about the diagnosis.

So, our improved diagnostic ability has really changed dramatically over the past 15 years. And it has been brought about by new high-resolution CTs. And MRIs. Which really show the inner ear anatomy in a way we have not been able to before.

This is an example of a cochlear nerve, or (Unknown term) shown here with the white arrow. In many institutions, we are performing CMV testing on a universal basis or for individuals who have referred on a newborn hearing screening.

So, this is drastically increase the number of children with CMV that we detect. There is also tools like electrocochleography. We are able to get a better understanding of the physiology of the inner ear. Using these measures in a way that was not possible 10 years ago.

And the focus today that I will talk about is genetic testing. I will show you how this has changed dramatically over the past 15 years. And it really has altered how we care for individuals who have hearing loss. Or who are deaf or hard of hearing.

So, what this means overall is that, in my clinic, where I see the majority of children who have hearing loss. We are able to come up with diagnoses in most cases. So, this is one study from Korea that shows this very nicely. So, they had 119 children with severe to profound sensorineural hearing loss.

And they did genetic testing, CMV testing, and high-resolution imaging. They were able to identify the cause or diagnosis. In greater than two thirds of these children.

This was similar to what I see in my own practice now. And this is dramatically different than even 10 years ago. When the majority of individuals we did not have a diagnosis for. So, what I would like to propose is, we stopped thinking about and focusing on the hearing loss.

And instead, we change to looking at the deaf or hard of hearing person. And the diagnosis which could be many of really hundreds of different things.

So, they could have CMV -induced inflammatory damage to the (Unknown term) , for instance. Or the Cochlear nerve hypoplasia. Or they could have TMC1 deficiency. There is hundreds of different diagnoses that make up or that can cause the symptom of hearing loss.

And that is what leads to reduced hearing. What this really provides for us, is personalized care. Which is what we all hope to provide to individuals. So, as we know, some individuals are -- will choose hearing aids, some will go with Cochlear Implant.

We have auditory brainstem implant for individuals who are unable to use Cochlear Implant and willing. And then I told you about (Unknown term), and we will talk more about gene therapy.

We also need to alter member that in many cases, none of these treatments will be with the family chooses or the best treatment for that family. For example, the cochlear nerve hypoplasia.

So, sign language or alternative forms of communication maybe what that family chooses. My goal in my clinic is to provide the best care for the individual. And I believe that by focusing on the diagnosis and not the symptom, we are able to come up with the best answer. Of course, a team-based approach, like we do at Boston's children hospital, is really beneficial in this perspective.

That is what I -- how I wanted to frame things, before I get started with the talk. Which is about genetic testing. We will talk about sort of a who, what, why, how overview here. So, we will talk about what is genetic testing. Why should we perform it. Who should receive it and how should the clinician order it.

And what we are going -- while we do this, I will present four different patients from my practice that I have seen, that I think demonstrate the power and importance of genetic testing and genetic evaluation. For individuals who are deaf or hard of hearing.

So, what is genetic testing for hearing loss? Well, if you look at all children that have hearing loss, this sums up the causes of congenital hearing loss. So, about two thirds or 65% is considered genetic.

About 10% is an anatomic abnormality. About 20% is congenital CMV. In summer about 5% is due to (Unknown term) toxicity or trauma. Usually surrounding birth.

The genetics of hearing loss, as shown here, if we look at the genetic causes. About 80%. About one third of genetic causes are syndromic, so this means that there is other clinical features associated with hearing loss, will there is Usher syndrome, which includes hearing loss as well as progressive blindness caused by retina -- retina (Unknown term) .

… (Unknown Name). These are just the most common… About 70% is non-syndromic. This can be inherited in all different forms. The majority is inherited in a recessive fashion. Which most typically means that the parents of the child who is deaf or hard of hearing do not have hearing loss.

But, hearing loss is extremely genetically heterogeneous. So, what I mean by that is that, there is 124 different known hearing loss genes.

And this is what makes studying hearing loss and testing for hearing loss so difficult. You know, sometimes I wish that I had studied something like cystic fibrosis where there is really only one gene that can cause the majority of cases.

But, at the same time, I think this is what makes studying hearing loss so interesting.

So, if you look at a large group of deaf and hard of hearing individuals, in this case, I am showing data from more than 2400. There is not one single gene that makes up the majority of cases. So, here you can see, TJP2… Is about 20%. Stereo sell in, or STRC is the second most common cause of hearing loss, but far in a way is the most common cause of mild to moderate hearing loss, which I will be talking about later.

So, because of this extreme genetic heterogeneity, it makes testing very difficult. Truly, genetic hearing loss is complicated.

So, what we realized, 14 years ago, is that comprehensive genetic testing using massively parallel sequencing is key. So, that is a lot of words.

But, what I mean is, you cannot just test one single gene at a time for an individual. You really need to test all of the genes. So, let me back up and talk a little bit about the history of this.

So, the human genome project was completed in 2003. And some people in the call may not remember, this is what computers used to look like. These are some of the DNA sequencers that were used to complete the human genome project.

They used a technology called chain termination sequencing, which was developed in the 1970s. And it costed $8000 per million base pairs.

This meant that the human genome the initial sequence cost several billion dollars to perform the sequencing. This is what new sequencers look like. And this is from one company called alumina, that is the predominant sequencing company.

It uses something called massively parallel sequencing. And we do not have to get into all of the details, but you can see essentially sequencing that is performed on a massive scale. In parallel. Which means that, you know, at the same time.

This has dramatically reduce the cost of sequencing over the past 15 years since it has been developed. It is less than a dollar per million base pairs and we can do 80 billion base pairs in 24 hours. We realized very early that this is exactly the technology that was needed for something like genetic hearing loss, which is so complicated.

In my lab now, I have a sequencer that actually fits into the palm of your hand. This is the new sequencing technology. It actually pulls a single molecule DNA through Accor and sequences at a time. So, the new developments in sequencing technology are evolving all the time. It is really amazing!

But, what this means is that, that the thousand dollar genome is here. So, for years, people were talking about how things will change. When it cost $1000 to sequence the genome. No, we do this essentially on a daily basis. At Boston's Children's Hospital where we do genome sequencing for $1000.

You can see in the early 2000's, there was $100 million or more. So, the fallen cost is dramatic. So, this is the technology we used to perform copperheads of genetic testing for hearing loss.

In 2009 and 2010. This meant for the first time we can sequence all of the hearing loss genes all at once. This technology rapidly propagated - you can see within a few years, there were many different publications. We published several years after, using this technology for 1119 patients. Intergroup from Japan came out soon after with 1120 patients, just to show they could beat us. -- And a group.

What this means is that, this technology is is often used in hundreds of studies and thousands of patients.

There is now several different companies around the country that perform this testing. Or a similar version of this testing. This is the testing I helped develop at the University of Iowa, but you can see there are other companies here. I do not have any financial relationship with any of them. But, this company is a genetic testing for hearing loss has now become the standard of care for evaluation of child hearing loss.

All of these different tests essentially do the same thing. So, they use these new sequencing techniques. Just to give -- sequence all of the non-it syndrome a hearing last income as well as many of the syndromic hearing Lester jeans, like (Unknown Name) syndrome. Because we are better able to test for them at the same time.

We are identifying the syndromes earlier and earlier. So, why do we perform genetic testing for hearing loss? Well, really, the easiest answer is that it is the single most effective test.

So, if you look across all studies, and this is relatively even and it has been similar for the past year or so, if you order a test for an individual and hearing loss, the diagnostic yield, or also diagnostic rate, is about 40%. So, that means that in 40% of people, we come up with a diagnosis.

If -- I was raised some sites later, which showed that this is higher. So, it is more like 50 to 60%. But, if you just ordered a CT scan or an MRI, the diagnostic rate would be lower, so close to 30%. Even when I started training, we would do other testing. Like, we would get ultrasounds.

And blood tests. And these tests do not really have very much of the diagnostic yield, is very low.

The other important reason to do genetic testing is because it provides really important information for families. It provides prognostic information, so whether the during loss will stay the same or worse over time. -- The hearing loss. It also provides information on recurrent risk for patients and families. So, if they would have another child, what are the chances they would be affected? Or will their children -- when their children going to have children, but are the chances that -- that they will have hearing loss?

… We are finding really does comprise about 20% of diagnoses. And what I think maybe one of the most important income is not the most important thing, is what I find for my family is, it really empowers the patients and families.

But what I mean by this is, instead of just having a symptom, like I talked about, it provides a diagnosis. So, for instance, this is the stereo cell and gene mutation hearing loss Facebook group. And one of my patient's family started this.

And they have many members of this group now. It provides a sense of empowerment for the family so they can meet other members of their community and they can share their diagnosis.

So, I would like to talk about the first patient. So, this individual is a seven month old. It was referred on the newborn hearing screening bilaterally. And you can see an audio that we have here where it is profound hearing loss bilaterally.

And the family was really on top of things. You know, they had hearing aids since three-month-old. And by seven months, it was meeting developmental milestones. You can imagine the questions the parents would be asking. What is the cause of the hearing loss? What is the prognosis? What the recurrence risk is.

We did genetic testing. It came up with two pathogenic variations in the genes CDH23. This is the most common cause of Usher syndrome type I.

This is severe to profound hearing loss with vestibular function, which can lead to delayed motor milestones. As well as progressive vision loss due to retinitis pigmentosa.

So, these are some of the most difficult days that I have in clinic - providing this result back to a family. It is really a unique position, I have quite routinely where I am providing a diagnosis of a vision problem before it even occurs.

Because we are often ordering genetic testing, now we are often the providers who give this result back.

I will tell you that having this diagnosis of a dual sensory impairment really changes the discussion for possible treatment options. It reframes our discussion talking about Cochlear Implant, for instance. Although providing this result back to families can be very devastating, universally, when I talk to families, after they have had some time they have been so thankful to have the diagnosis.

Just because they're able to do things like teach a child braille before they start to lose vision and they can start to take vitamins, like vitamin A, and wear sunglasses to delay the onset of retinitis pigmentosa… Although this diagnosis is very hard to give, it is very important for us.

… It is 40%. And you know, sometimes I am thinking kind of negatively about that too. I was talking to one of my colleagues who is a neurologist. And I said, "my diagnostic is so low, it is 40%." And she said, "what are you talking about? That is great!"

So, we started looking into it, and these are genetic disorders, neurological disorders, that they routinely order genetic testing for. So, it is very common now to obtain genetic testing for autism. The diagnostic rate for that is about 17%.

Almost every child now with epilepsy undergoes genetic testing because there are specific treatments that are available for them. Even then, the diagnostic rate is about 24%.

And then children with intellectual disability routinely undergo genetic testing and that diagnostic rate is 28%. And now in the NICU, it is becoming more and more common to obtain rapid genetic testing. And rapid genome sequencing. To provide a diagnosis.

And this is hugely expensive because they try to get the results back within 24 to 48 hrs. In the diagnostic rate there is about 36%… What this means is that, as a provider, taking care of individuals who are deaf or hard of hearing, you all are geneticists.

It is important for all of you to understand the genetics of hearing loss as well. So, we will talk about another patient. So, this is an 18-year-old that I saw who had his congenital hearing loss. And it was, as you can see here, it was mild to moderate. With a little bit of a mixed component.

And this patient had eustachian tube dysfunction, had a bunch of tubes placed. So, her whole life, she was dealing with tubes, and straining ears. No one had brought up her underlying hearing loss that she had been struggling with. It was attributed to her tubes and her eustachian tube dysfunction. She wore hearing aids, but not all of the time.

She also struggles with ADHD. So, because we have a research study with children's, we were able to enroll her in this. And we perform genetic evaluation because she really just wanted to know what the cause of hearing loss was and what the prognosis would be. So, she is 18, she would want to know whether it would stay the same or get worse over time.

What we found was a pathogenic variation in the gene FGRF3. At the age of 18 years old, we were able to give her a diagnosis of Muenke Syndrome.

This is a syndrome that is associated with cranial (Unknown term), so abnormal, early fusion of the skull and hearing loss, as well as ADHD.

So, finally, at 18 years of age, she was provided with the diagnosis. This was hugely impactful for her because the next time that I saw her back, it was almost like she had accepted her diagnosis more and she was wearing her hearing aids.

Dylan Chan, who was at the University of San Francisco, has shown that providing a diagnosis to children increases their use of hearing aids.

For this reason, I think, it is important that we pursue this. So, the other point I will make about this patient is that, for a lot of these syndromes, there is something called a syndromic spectrum. So, what I mean by that is that, they first diagnosed, or first came up with these syndromes years ago, they probably looked at the most severely affected.

But, what we are finding, is with we perform testing of more individuals who are able to find that there is someone who has more of a mild phenotype, or a more mild, clinical features. This was very important for this individual. Even though this is not someone that you would typically think, "we should do genetic testing for." I am glad we do.

More about the prognosis and management. I just wanted to show you two different genes that have a very different prognosis. So, these are combined audiograms of different individuals with two forms of hearing loss. Techda (?) And KC and Q4. What you can see over time, is the hearing loss for it (Unknown Name) is relatively stable.

Whereas for KC and Q4, there is about a ten bold drop per decade. That we can see here. This really reframes how we think about Cochlear Implant versus hearing aids. On a day-to-day basis, if I have a genetic diagnosis, it changes the…

So, if I know the child has a stable form of hearing loss, we may be able to push a visit out to one year. Whereas otherwise, we may see the back every 4 to 6 months.

It does change my clinical practice on a day-to-day basis. Another reason why these consensus guidelines. There has been a couple of different guidelines from the international (Unknown term) otolaryngology group. And people say that genetic testing should be a part of the evaluation of children of hearing loss.

I also want to talk about Cochlear Implant outcomes. So, if you look at any group of Cochlear Implant patients, you may see something that looks like this. So, post operative word recognitions. Are on average, something like this. So, 70% for one test, Caspian Sea. 60% for another text.

What is underlying this data, is actually a huge variability and outcomes. So, there is some individuals who have a Cochlear Implant and they get 0% word recognition. And others may get 100%.

I really find this to be quite unacceptable. Because I would like to be able to cancel my families. The children that I see. Effectively, as far as how well a Cochlear Implant is going to work. So, that is a big part of my research.

Trying to understand these Cochlear Implant outcomes. So, we know that these outcomes are variable. And can we improve outcomes with a better understanding of genetics? Is the question.

So, Cochlear Implant outcomes, it is clearly complicated. So, we know there are things like the environment, so, socioeconomic status. Time without hearing. The social interactions.

These clearly play a role in Cochlear Implant outcomes. And then there is clinical variables, so things like what device is used, what surgeon… Activation in training afterwards. I would propose that, genes are likely involved, too. So, genes that could affect the sensory pathways as well as the central pathway.

So, the brain. And I really do think that a better understanding of Cochlear Implant genetics could allow us identification of poor performers preoperatively.

So, what I mean by this is that, if we think that someone is at a higher risk of not doing as well with the Cochlear Implant, we can focus the activation and training and follow-up. For those at risk patients. And then really importantly, I would like to be able to counsel my families and patients effectively.

With how I expect they are going to be doing after surgery. And then ultimately, this could also pave the way to position tailor Cochlear Implant.

So, to get into more detail about this, if you think about the auditory pathway as the schematic year, you have the hairstyle, you have the nerve, and then you have the brainstem.

The cochlear and plant electrode bypasses the hairstyle and it simulates the nerve. You would -- our hypothesis would be that, individuals who have a damaging genetic mutation or variant affecting the spiral ganglion will have a significantly worse Cochlear Implant outcomes.

What I mean by that, is that it has actually been known for a while now that if you have sensory dysfunction, so if you have a genetic variant that affects the hair cells specifically, like GGP 2 for instance, this are some of the best performers with copper implants.

Whereas we propose if you have a neural dysfunction due to genetics, if your nerve is not working as well, you may have a poor outcome. Well, there is close to 100 different genes that affect the organ (Unknown term) , or the synapse.

And there are fewer genes to affect the nondirected. Elected this a few years ago and what you can see is, when we looked at the Z score average of the individuals who had a genetic cause that was neural or a sensory cause of hearing loss that was genetic, versus things like otosclerosis and sudden hearing loss, the individuals that had a neural genetic cause of hearing loss performed worse overall than those that had a sensory genetic form of hearing loss.

I do think genetic variants that affect the auditory nerve are associated with worse Cochlear Implant outcomes.

There is a lot more work that needs to be done in this area, too. To do the study again with a greater number of patients. And this was adults. So, I want to talk about another patient. So, this is the patient you came to see me for Cochlear Implant evaluation. This is what the Audiogram looks like. So, it is sharply down sloping.

Normal to severe to profound hearing loss. This patient's word recognition scores were decreasing significantly over time. They wanted to know what the cause of the hearing loss was. And what -- whether a cochlear implant was the right treatment or whether they wanted to continue with hearing aids.

We did genetic testing, we identified pathogenic variance in the gene TMPRSS3. This is a cause of non-syndromic hearing loss. It is very controversial, but some groups have shown that individuals with this form of hearing loss have worse outcomes after two -- Cochlear Implant.

This is still - there is conflicting data, one way or another on it. But, we had a long discussion about this. Because I want to make sure that individuals are adequately counseled prior to cochlear implantation based on their diagnosis.

I should point out, though, that I am not saying that individuals with TMPRSS3 hearing loss or other genetic forms of hearing loss that may be associated with more poor Cochlear Implant outcomes should not have a Cochlear Implant, because Cochlear Implant, for individuals who want that, are the most effective available treatment for severe to profound hearing loss.

And so, my point overall is that, we should work towards better counseling based on the diagnosis.

Because after all, some individuals do very well with the Cochlear Implant. And TMPRSS3 hearing loss, for instance. But you would like to be able to counsel effectively. So, another reason why, is gene hearing for their loss. -- Gene therapy for hearing loss.

This is a rapidly evolving area right now. I will talk just for a moment about it today. And maybe in the future we will talk more about it. I have very mixed feelings about moving forward with this. Gene therapy for hearing loss.

And we can get into that another date. But, there are different methods for liking their therapy for hearing loss. So, there is replacing a gene, or suppressing the gene, or editing the gene.

And there is also the considerations like the ethics of doing gene therapy for hearing loss. Just to begin with. We do not know how well it would work, the virus can have systemic effects on the whole body. And how safe it is.

But, the point is that, any genetic therapy requires an accurate, genetic, diagnosis first. So, you cannot even think about gene therapy unless you have an accurate, genetic, diagnosis. I will say, whether you like it or not, gene therapy for hearing loss here.

So, I think most of you have heard that there is two companies now who are opening up clinical trials. For gene therapy for hearing loss. I have no financial relationship with these or either of them.

But, when company isAkouous and the other is Decibel, and the error … For OTOF… Genetic hearing loss. You can see from their website, the next targets are things like GGP 2. As I told you, it is the most common, genetic form of hearing loss.

So, this is happening now. As providers who care for children that have hearing loss, this is something that you should all at least know something about.

So, the less patient I want to talk about is this patient. So, this is their Audiogram. They have a mild to moderate symmetric sensorineural hearing loss. Again, this is maybe someone that you would not necessarily automatically say, "we have to get genetic testing for." But, this is a seven year old who did not pass their newborn hearing screening. Otherwise healthy. And is doing great with hearing aids.

But, the family wanted to know about the prognosis primarily. They are also very active in wanting to be involved in the childcare. We were able to provide them with a diagnosis of STRC hearing loss because of deletion of the stereo sound the gene. I told you, this is the second most common cause of genetic hearing loss overall.

And by far, the most common cause of mild to moderate hearing loss. Now that we are testing these individuals, we are finding this more and more frequently. That there is a long background of this gene, but it is very hard to sequence. So, until these new technologies came along, we were not able to test for it very well. Now, we are finding it is much more common then we realized before.

But, the first thing this family wanted to know after we gave them a diagnosis, this diagnosis, is whether there was a gene therapy available. You may be looking at this hearing test and say to yourself, "they were hearing aids, why would they want gene therapy?"

Again, this is where I would argue that we need to care for each family as they would like to be cared for individually. So, hearing loss in children, we show that gene therapy for STOC hearing loss is effective in mice. So, this is showing electron microscopy of the hair cells of a mouse.

You can see on the left, the hair cells that were treated. On the right, the hair cells that were, or sorry, the hairs on the left rehearsals that were untreated. On the right, herself that were treated. You can see that they are stating a nice, straight rows again. This family, every time I see them, ask about gene therapy for hearing loss. As I told you, the companies have them on the horizon. The next two years the landscapes will be changing, I think.

So, who should we be performing genetic testing for hearing loss for? The diagnostic rate varies by clinical characteristics. I told you overall, the diagnostic rate was about 40%. This is data from a few years ago now.

But, if there is a family history of hearing loss, the diagnostic rate can be higher. If the age of onset is earlier, the diagnostic rate is higher. And if it is a symmetric hearing loss, the diagnostic rate is higher as well. So, when I see a child that has congenital profound sensorineural hearing loss, in a normal -- and normal, physical exam, I tell them they have about a 60% chance of having a diagnosis from genetic testing.

Which is really remarkable. The genetic diagnosis really varies by age. So, when we look at Cochlear Implant patients, this is 100 pediatric Cochlear Implant patients. Here the diagnostic rate was about 48%. You can see all the different genes here.

So, GGB 2 is most common. If you look at adult, the diagnostic rate is lower. It is about 22%. This is for a whole number of reasons that I do not have time to talk about today. But, the genes that are affected are totally different. So, that you can see that TMPRS is three. The whingeing that I talk to you about with Cochlear Implant is the most common, genetic hearing loss. In patients who are adults.

So, it really varies based on age. We also know that genetic diagnosis varies by race and ethnicity. So, GJB 2 is most common cause of Caucasian and Asian individuals. But, it is essentially not present and noncontributory in African-Americans. So, if you were to just test for GJB 2 in African-Americans, it would not be effective.

Dylan Chet the University of San Francisco has done some amazing work looking at the genetic diagnostic rate based on the socio-demographic factors. As well as race and ethnicity. What he showed is that, Hispanics and Blacks were five times less likely to receive a genetic diagnosis as Asians and whites.

This is hugely important that we work to reduce this inequity in genetic testing. It is a focus in my lab as well as others. Around the country. So, just to show you what a diagnostic evaluation would look like for a child with sensorineural hearing loss.

They have a history of physical exam. Audio metric testing. We obtain CNV testing, and we look for specific exam findings. If we see something that is clearly syndromic, which is often very difficult in young children, we do genetic testing based on the syndrome.

… If it is bilateral, including asymmetric hearing loss, and auditory neuropathy, we start with comprehensive genetic testing. We obtain an ophthalmology evaluation. Just make sure there is not a dual sensory impairment. We get an EKG, because it is cheap and noninvasive.

And we do not want to miss any cardiac problems. And then we talk to them about imaging. In the time the -- the timeframe of this peasant weather we are thinking about a Cochlear Implant or not. If it is unilateral hearing loss, then essentially, we rely more on MRI or CT scan. This is essentially the algorithm I use on a daily basis in my clinic.

You can see genetic testing forms a cornerstone of it. However, we have started to wonder whether we should do genetic testing more for unilateral and asymmetric hearing loss. So, this is some more recent data just from last year. Showing that a diagnostic rate by symmetry, if you look at bilateral, it is about 40%. Asymmetric, it is about 20%. Unilateral hearing loss, our diagnostic rate was about 18%.

Maybe what is more important, is the number of syndromic diagnoses we make. So, for bilateral symmetric hearing loss, about 20% had syndromic diagnoses, so this is Usher syndrome or pendulum syndrome. But, it was 33% for bilateral asymmetrical hearing loss.

And actually more than half of the individuals be diagnosed who had unilateral hearing loss, had a syndromic diagnosis. So, you could argue that the unilateral hearing loss, or children, they are the ones who the diagnosis is the most important for because that is what can change our clinical care.

So, this data has really changed how I think about evaluating kids with unilateral and asymmetric hearing loss. And I do think we should be performing genetic testing for them. So, how do we perform genetic testing for hearing loss? I told you, there's many companies. There is a 1 to 3 month test turnaround time.

This can be ordered by an (Unknown term) . Many of these companies provide genetic counseling associated with it. The cost is $1000-$4000. So, that seems like a lot, and it is a lot. It will tell you that for our patients, when we looked at the last 100 patients that we evaluated, 64% of the time insurance actually covered the genetic testing.

81% of the time with private insurance. And our mass health actually covered 50%. So, this is hugely different from 10 years ago when insurance almost never cover genetic testing. Now, in the majority of

cases, beacons is covered by insurance. Because insurance companies have realized it is really integral to care for these individuals.

So, I hope that I have shown to you that by focusing on the diagnosis instead of the symptom, we are able to decide the best treatment for the individual.

I want to leave you with some future directions. So, one thing that I think about, and hopefully I will have a chance to talk to more about at another forum, is finding a therapeutic window. So, we know for things like Cochlear Implant, and I am guessing for something like gene therapy, that the therapeutic efficacy decreases over time.

And this is probably a combination of things like the spiral ganglion neurons and neural plasticity decreases over time. And then also, when you think about single-sided hearing loss, there is a side preference that develops. And what is pretty incredible, is that even at Boston children's, were we have an incredible amount of resources, our average age at diagnosis for congenital hearing loss is about 13 months.

So what I mean is, we are providing an actual diagnosis to these children. So, this is what our sort of therapeutic window looks like now.

But, in order to improve our therapeutic window for things like Cochlear Implant and in the future, gene therapy, we need to think about shifting that diagnosis earlier.

The only way we can do this, is by improving newborn hearing screening. Which I know is very important to all of you and very important to me as well.

So, the take-home points are that hearing loss is a symptom. It is not a diagnosis. And a diagnosis for individuals who are deaf and hard of hearing provides the individual family and the clinician with tons of valuable information. And it ultimately allows for personalized care.

And so, I hope you can understand that I have refrained how I think about this. And I had district and trying to get other people to think about this differently. Instead of looking at the hearing was or coming up with the diagnoses just so we can start to think about the whole child. And what is best for the child.

Instead of just their symptom. And with that, I would like to thank Doctor Kenna, my close… And everyone in my lap. Thank you all again for your attention. I really appreciate it. I am happy to take questions.

SPEAKER:

Yes, thank you, Dr. Shearer. This is Will Eiserman again. From the National Center for Hearing Assessment and Management.

And we have some questions coming in and I wanted to start off by asking you this: it seems like there are so many hot button issues. Related to what you talk about today. And it is important, I would think, that they do not get unnecessarily conflated.

There is the issue of screening children, genetically, at birth. Who have hearing loss. Because that can inform treatment. Regard us of what the treatment is. And then there is how it might inform the decision around specific treatments, like Cochlear Implant.

And then there is that even hotter button issue of whether we should be going down the path of genetic treatment.

So, can you just say a few more words to try to isolate those separate concerns so that they do not unnecessarily get conflated?

ELIOT SHEARER:

Yes, it is a great point. They are all connected. But, you can also think about them separately. So, another way to think about it is that, when we perform genetic testing, we make sure that families, first of all, want to do the genetic testing rate.

It is up to the parents, families, and individuals. That is opting into it. We never for something like this. We also want to make sure that we are providing early screening and the best possible screening. So, I did not talk about genetic screening.

And hopefully I will add another time. But, using genetics, I think we will be able to use our newborn hearing screening by detecting individuals that may have a later onset hearing less rate outside of the

newborn period. Or there things like auditory neuropathy or other things that may be missed on the current physiological screen.

So, there is a way to use genetics just for screening. When you do any screening with genetics though, you will have an individual who can opt in or opt out ever receiving results. They may have a screen that says, you failed the genetic portion, do you want to know the result or not? So, you can use genetics to just perform a screen without providing the diagnosis.

I think most families would want to know the diagnosis. Because of all of the important information it provides you. But any genetic screen would be -- need to be followed up by a full, genetic evaluation afterwards.

And then the idea of, you know, gene therapy moving forward with that. Again, that can be held totally separately and that is something that's not going to be available for many or most families.

And so, it is up to the family. Whether they want to pursue that treatment option. Just like Cochlear Implant are now. We would never force that on them. Does that answer your question, Will?

WILL EISERMAN:

Yes, thank you. I know, because I have heard you speak before, about how important it is for you to make it clear that you are about having as much information as you can when you consult with families so that they can make the best decisions that meet their families needs.

And I know that is where you are coming from and I just wanted to make sure that you had an opportunity to clarify that. Given how hot some of these other issues are.

ELIOT SHEARER:

That is exactly right. I really want to empower patients and families to make the best decisions for them. Ultimately.

WILL EISERMAN:

Here is one of the questions from our participants today: can you explain why surgeons may be implanting CIs on kids with no detectable audiological nerve? This person says, "I have seen no increase in hearing for this population."

ELIOT SHEARER:

Yes, that is a great question. You could have a whole seminar on that (Laughs). That is totally dependent on the center. And it is, you know, I can only speak for what we do at Boston children's, which is, we have an interdisciplinary group. Of audiologists, speech pathologists, surgeons, social workers, and we discuss every family and become up with, sort of, treatment options.

There are some children who have surprised us in that we - it looks like there is not much of a nerve and they can do very well. But, it is actually very rare, at our institution, that we would perform or offer a Cochlear Implant that has no nerve that we can see. Actually, we essentially do not do that. I do not want to speak for all groups, but I would not recommend that.

I know there are some people that proceed with cochlear implantation if there is no know detectable nerve. You would need to be able to cancel them really effectively as far as the risks and benefits. I hope that answers your question.

WILL EISERMAN:

Here is another question. Such interesting questions are coming in. Given that congenital CMV is so common, do you also tested those patients for genetic causes of sensorineural hearing loss? Or just assume it was CMV?

ELIOT SHEARER:

This is such a great question. This is a really important topic to me. Because exactly as you said, CMV is very common, and genetic hearing loss is very common. We have now seen several patients were being treated with (Unknown Name) for congenital CMV.

And we perform genetic testing on them. And we have actually found they have a genetic cause of hearing loss. And so, we will stop the treatment for (Unknown term). So, our protocol at children's, is any child with hearing loss, we recommend they undergo genetic testing if the family is interested. Because it does change or treatment.

Because we do not expect (Unknown Name) to help genetic hearing loss, for instance. I would say even if you think it is congenital CMV, you still need to test for genetic hearing loss, and even if you think it is genetic hearing loss, you should check for CMV. You need to demote -- both.

WILL EISERMAN:

So, CMV does not include there being another explanation.

ELIOT SHEARER:

Exactly, yes.

WILL EISERMAN:

The next question, is NTRC on the regular genetic hearing panel? Would it only connect -- attached deletions? What about mutations? This person says, "I ask because my sense both have a mutation of STRC, not deletion, it was only caught by Columbia's genomic project. It did not show up on their genetic hearing panel."

ELIOT SHEARER:

I alluded to this. This gene is very, very difficult to sequence. The new technologies we have are getting better and better at sequencing. So, we have an example of an individual who did the standard panel. And nothing was detected. We did the next level, which was Exim (?) sequencing, and nothing was detected.

And then we did one of those new DNA sequencing technologies I told you about, with… sequencing, which are very expensive. Finally, that detected an SCRC deletion. So, it is very hard to identify and it really depends on new technology.

I think we are missing some individuals who have… Or deletions. Most panels now include detection of deletion… I do not think they are capturing all of them, just because it is very difficult to do that.

WILL EISERMAN:

Yes. I do not think we will get to all of our questions, let's go for another one. This is a comment from an individual who identifies as deaf since birth. The individual says, "I am a carrier of the GJB 2 gene, my partner and children all have the gene. I just wanted to share that deafness is the only disability that has a culture and language and that I believe it would be unethical to do gene therapy to perform eugenics on deafness."

Do you have a comment about that?

ELIOT SHEARER:

Yes, again, you can spend the whole seminar talking about gene therapy, and I hope we do sometime, just so we can better educate everyone. The way that gene therapy is being talked about for hearing loss, is as a treatment. So, it is an inject -- injection in the inner ear, does not change the reproductive organs of the individual, for instance. That is a common misconceptions.

Eugenics would be something that actually erases a group of people. It is a different treatment option. How it is looking right now. Similar sort of surgery. To cochlear implantation. But without the implant.

So, I would never… I completely respect the opinion of yours.

WILL EISERMAN:

There are number of questions. Let's maybe end with this question. If you have other questions you would like to pose to Dr. Shearer, please send them to as. We will put that in, Gunner, if you could put my email in -- address. Or the helpdesk in the chat, then we can forward those questions onto Dr. Shearer.

There are a number of questions that are coming and that all have to do with the statistic that we all here. About how many children are born with permanent hearing loss to families that do not have a known history. And yet, does that necessarily mean there is a genetic component? Can you separate those two issues? So that beget a clear understanding of that.

ELIOT SHEARER:

The majority of genetic hearing loss is recessive. Which means that, in most cases, the parents do not have a hearing loss. It is the combination of the two parents, separate genes, that make the child. That makes the child different. That is a reason why we are not clones of parents, because -- it is the parents that make us.

So, I think that answers your question, well.

WILL EISERMAN:

Yes, thank you. It was not mine, it was many others. So, we are at the bottom of the hour, which means we are at our closure here. Before you all run off, Gunner is going to post a link in our chat that will take you to a quick survey and a certificate of attendance generator.

So that if you need evidence of your participation in today's webinar, you can get that there. Dr. Shearer, we would love for you to come back and talk specifically about the use of genetic screening. As a part of the newborn hearing screening protocol.

And so, we would love to get that on the books sometime soon with you. If you are open to that. Because there is a lot of practical questions about the feasibility of doing such a thing.

ELIOT SHEARER:

Yes, I would love to, thank you.

WILL EISERMAN:

Yes, thank you, everyone, for your time and attention today. This webinar has been recorded. And will be posted on infant hearing.org in the next couple of days. Keep that in mind if you need to review any of this again for your own benefit. Or if there are individuals who did not attend live today who you think might benefit from this information.

Thank you, everyone. And thank you to our captioner, and to our ASL interpreter. We really appreciate your talents, expertise, and availability, to help us make this webinar, learning opportunity, as accessible as possible. Thanks, everyone.

ELIOT SHEARER:

Thank you, thank you to the interpreter and captioner, too.

(End of Webinar)