Genetics of Pediatric Hearing Loss in the Age of Precision Medicine, in partnership with the American Academy of Audiology

Presenters: Margaret Kenna, MD, MPH, Shelby Redfield, MS CGC

Well, hello and thank you everyone for joining us on our webinar today on the genetics of Pediatric Hearing Loss in the Age of Precision Medicine. It's presented in partnership with the American Academy of Audiology. It's my pleasure to introduce our presenters today. Dr. Margaret Kenna is the Director of Clinical Research in the Department of Otolaryngology at Boston Children's Hospital. She conducts research on the causes of pediatric hearing loss, including genetics, congenital CMV and structural anomalies of the temporal bone.

Shelby Redfield is a genetic counselor in the Department of Otolaryngology and Communication Enhancement at Boston Children's Hospital and a member of the Translational Hearing Genomics Lab. She is also the Clinical Research manager for genomics research efforts within the Department of otolaryngology. Together with Dr. Elliot Shearer, Dr. Kenna and Ms. Redfield recently identified a new gen hearing loss gene and became involved in first in Human Gene Therapy for Hearing loss. You can read more about our presenters on the course page on our website. But at this time I'd like to welcome Dr. Kenna and Ms. Redfield and I turn the floor over to you.

Thank you so much, Christy. We're very happy to be here.

Welcome. I'm Tish Gaffney, the President of the American Academy of Audiology and I'm here to share important information about the organization. The Academy is dedicated to achieving recognition of audiologists as the experts in hearing and balance care and the field of audiology as an independent clinical specialty that is integral to the healthcare team. Through our partnership with Audiology Online, we're excited to offer courses like this one to help you broaden your knowledge and skills. We also offer the latest resources in practice management and evidence based clinical practice so you can grow professionally and improve patient care.

We advocate for our members in Washington and across the country to ensure that the voices of audiologists are heard and we help connect audiologists to one another through our valuable

networking opportunities like our annual convention. To learn more about the Academy, make sure to visit audiology.org thank you.

Thank you. All right, I think we'll get going. Shelby and I are going to go back and forth through various parts of this presentation and then we're happy to take questions at the end, just disclosures for presenter disclosures and content disclosures and then the limitations and risks of this particular presentation and then the learning outcomes for this presentation.

So we're going to talk about hearing loss in children, the incidence of sensorineural hearing loss. It's the most common congenital sensory impairment in the population Here in the US and abroad, one out of every 500 babies are born with some degree of permanent hearing loss. About 50 to 60% are genetic, and the remaining are environmental or structural, including congenital CMV ototypes, medications, hyperbilirum anemia, or structural changes of the inner ear. But we're really here to talk about the genetic causes. About a third are syndromic.

30% are syndromic, and about 70% are non syndromic. And the syndromic ones are much more common than we initially appreciated because we have good testing. The non syndromic ones, about three quarters, are recessive, a little less than 20% are dominant, and then about 1% are mitochondrial or X linked.

So it turns out these are. It's a very small slide, but it turns out that these are the things that are part of the newborn screen in most states in the country. And it turns out that hearing loss, which is the far right blue bar, is vastly more likely to pop up on this screen than the next most common, which is congenital hypothyroidism and some of these other things. To get onto the newborn screen, you actually have to have something for which chair is in intervention. And there's clearly an intervention for hearing loss.

So it's really important to determine an underlying etiology of the hearing loss because it has crucial implications for outcomes. It can provide prognostic information, give us an idea about whether it's going to get worse or not, how that might go. It guides treatment options and surgical planning, and certainly can affect cochlear implant outcomes and possibly outcomes of gene therapy. It may increase the uptake of treatment in families, once they know the cause, are somewhat more likely to follow through. It may determine if the hearing loss is part of a syndrome.

Some of the syndromes present initially with hearing loss, but then there are other things that may pop up later that we need to look for, and then it may determine targeted therapeutic eligibility for gene therapy.

So this is pretty much how we do this here at Boston Children's and in most places in the country. So on the left side is the screening side. All newborns in the United States and many places in the world undergo newborn hearing screen, often at the birth hospital or very soon after birth. This is a physiologic screen, auditory brainstem response testing or otoacoustic emissions. And either you don't pass or you pass.

If you do not pass or you fail, you go on to a diagnostic audiology evaluation with diagnostic auditory brain stem response testing and otoacoustic Emissions. If you're found to have no hearing loss, then it's very nice to meet you. And if it turns out you have a hearing loss, this goes on to a full evaluation, including a consultation with otolaryngology. This may include genetic testing and then analysis and interpretation. About 40% of the patients actually get a genetic diagnosis through this mechanism and about 60% don't have a clear diagnosis.

However, the average age at a diagnosis of genetic hearing loss at Boston Children's is 9.3 months. So we're going to talk a little bit about how we can speed that up.

So in the olden days, there were lots of clinical tests that were done looking for causes of genetic hearing loss because we did not have good genetic testing. But starting on in the late 90s when GJB2 was identified, it's turned out that testing for genetics is the single most effective test to identify cause of the hearing loss, followed by cat scans and MRIs and then other studies. This provides, as noted, prognostic information for patients and families, the chance of recurrence in other children or in other family members, and evaluation for syndromic causes of hearing loss, which, as I noted, are about 20% of the causes that we see. Some of these children are clearly syndromic, but many of them are not. And so it's very important to identify this early so you can find appropriate intervention.

So this is really a very nice slide based on our patients here at Boston Children's, made by my colleague and Shelby's colleague, Dr. Shearer, looking at monogenetics, so single gene causes of hearing loss. And it turns out they are by far the most common pediatric cause of sensational hearing loss. They looked at 637 R patients who underwent evaluation of Boston Children's just from before the pandemic to 2024. On this top right, about 19% of them had structural abnormalities. Cochlear nerve dysplasia, enlarged vestibular aqueduct, other findings as the primary cause, although some of these are also genetic.

And then the green circle down here is genetic causes, which are about 60% and a single gene. GGB2 and followed by strc are the two most common genes. But there are many other causes. As you can see, syndromic causes are much more common than we had anticipated.

So many professional societies endorse genetic testing for pediatric sensory hearing loss. This includes, but not limited to the American College of Medical Genetics, where it was included in their practice guideline in 2014 and then their practice resource a few years later. In 2022, where they recommend genetic testing for all children who are deaf and hard of hearing. And then the Joint Committee on infant hearing, the JCIH, included it in their 2019 position statement, included in

Principles and guidelines for early hearing Detection. The American Academy of Pediatrics also recommends this.

The American Academy of Otolaryngology, Head and Neck Surgery recommends this. So it's included in many guidelines recently. Going forward.

The thing that's tricky about congenital hearing loss or childhood onset hearing loss is it is very heterogeneous and the audiograms often look very similar, but the genes are not similar. So what we tried to do is we came up with a. Over years, there's been development of a comprehensive genetic test for hearing loss where you can test, at this point, hundreds of genes at once. In 1998, we could test for one gene. Now we can routinely test for somewhere between 150 and 300 genes.

These panels include most non syndromic hearing loss genes, and they also include many of the hearing loss syndromes. So, as you can see, this is based on work done at the University of Iowa by Dr. Shear and his colleagues. A big hunk of this is GJB2. It's also called connexin 26, followed by stereocillin and then followed by the SLC26A4 gene, which is associated with enlarged vestibular aqueduct. And then going around here.

One of the things I think that has been surprising to us is how common, as noted, the syndromic genes are. Myosin 7A is the gene for Usher syndrome type 1, which is listed as a rare disease. And although rare, it's not nearly as rare as we used to think. It is one of the things that presents with hearing loss, and then over time, the vision changes.

Thanks, Dr. Kenna. I'm going to now speak more specifically on some of these non syndromic genetic sensorineural hearing loss genes before turning it back to Dr. Kenna to dive a bit more into the syndromic conditions and genes. So we reviewed this exact slide already at the beginning, But I think it's worth kind of hammering home the point that when you're doing an evaluation for pediatric genetic

hearing loss, you really need to take a comprehensive approach. I think years ago, before I was in this role, people might have started with the most common or the gene that they were sort of most suspicious about based on an audiogram. But diagnostically, that doesn't really seem serve our patients because there's just really so many genes that can be in play.

So we do take this broad approach for testing them all at once. The majority of pediatric sensorineural hearing loss and in this case non syndromic sensorineural hearing loss, it follows a recessive inheritance pattern. We have two copies of every single gene. And it's very common for the parents of a child with sensorineural hearing loss to be carriers of one individual non working copy of a gene or, or a gene that sort of harbors a mutation and having a 25% chance of passing that non working gene on to have a child affected with sensorineural hearing loss. And so this makes up, you know, around 70 to 80% of the cases that we see and explains why a majority of our patients don't have a significant family history of hearing loss.

When we ask about family history, there are certainly cases of dominant hearing loss genes as well. Even in this non syndromic world where, where you know, parent may be affected or very, very mildly affected, we see a lot of variability in terms of clinical presentation. So sometimes we have parents who are sort of showing have a genetic form of hearing loss but have subclinical like never had suspicious, suspected of having hearing loss or even been diagnosed, but that may present differently in their child. They can pass their non working hearing loss gene onto a child who has a much better different hearing loss presentation than them. So we see these two patterns recessive more often than dominant.

Dr. Kenna alluded to GJB2, the gene or connexin 26, the protein that this gene encodes as being kind of, no matter where you look or what paper you read, the most common cause of genetic hearing loss. This is a recessive gene. It's also referred to as DFNB1 or Recessive Deafness Type 1 because it was

the first hearing loss gene ever discovered and it was described in 1997, so not all that long ago in the grand scheme of things. This is a gene that encodes a protein that's crucial to kind of ion homeostasis in the inner ear and it's expressed in the supporting cells in the cochlea. And it makes up really depending on the population that you're studying or the paper that you're reading, between 25 and 50% of all genetic diagnoses.

There are some really interesting sort of population or ancestry specific mut in the GJB2 gene that are very common. 35del G being an example of a mutation that is kind of associated with a severe presentation where kids who have, you know, homozygous or both copies of Their gene affected with this mutation are usually, not always, but usually born with a severe to profound hearing loss as opposed to this V37I mutation, which is associated with a very mild form of hearing loss. So the degree, as I was just suggesting, the degree depends a lot on the specifics. So knowing the gene isn't necessarily enough. You need to do a little research on the specific mutations that are identified in that gene.

And we do a lot of determining prognosis for our patients based on their specific genes, genetics, and we call that a genotype phenotype correlation where you can really get very granular on what to expect. This gene sort of is notoriously variable. Some families, some children will have stable hearing over time, others can be variable. So we do the best that we can to assess prognosis for these families. And I think, you know, sometimes we can't resolve all the uncertainty because of these just super wide ranges of what we can expect even when we dig into the mutations a little bit further.

So here's an example and these are sort of remade audiograms of very real cases from our patients where we have two siblings who both have this mutation. I was just talking about the 35 Del G variant. They have it on both copies of their gene, meaning both of their parents were carriers for this exact same gene. We have an older sibling who's presenting in this fear to profound range early on. She's 10

years old now, but has had this profound hearing loss essentially since birth.

And relatively recently we met a new sibling who's now 15 months old but is still presenting with hearing loss in the sort of mild to moderate range. We anticipate some progression for this younger sibling, but you can see the variability exists for patients with the exact same genetic testing result within the exact same family, sort of. In contrast, if we take that same patient we just looked at who has the 35 Del G variant, this more severe variant has a profound hearing loss from birth. And compare that to a patient, another real patient of ours who's three years old, who has this sort of interesting looking W shaped audiogram with hearing loss in the mild to moderate range. They have a much more mild mutation on both of their two copies of this gene.

Another very common one called M34T. We see vastly different audiograms even for kids with the exact same gene.

Here's a case example for you, just a little bit of just emphasizing the GGP2 gene and the interesting things that come along. Because if you have a pediatric audiology practice, this is probably the gene you'll be most likely to see but a three year old female patient presenting with concerns for hearing for the first time at three years old. She passed a newborn hearing screen and subsequent OAE screens with the pediatrician. She had speech and language that were developing pretty typically until age two and a half years old, at which time she experienced sort of regression of, of speech and language skills and parents had developed concerns for her hearing. She had behavioral audiology testing that was inconclusive and the family or you know, she wasn't able to get a good, a good behavioral test.

And family did a sedated ABR for this three year old. This revealed a B bilateral moderate to severe sensorineural hearing loss. This is what her audiogram looked like. And we performed a hearing loss comprehensive panel and we found that she was in fact positive for this 35 Del G variant that can be usually severe to profound from birth, but we also know it is progressive and that is sort of what we

hypothesized was the case for this patient. This indicated risk for further progression and the family was considering a cochlear implant.

It also indicated risk for future children as this couple was planning to have more kids and they wanted to get a better sense of what the recurrence was, was for hearing loss in their future children so that they wouldn't be taken by sort of such surprise and that they could get the diagnosis at an earlier age for their future children if that ended up being the case. Moving along to another example, we want to spend some time speaking about stereocillin and Casper 2 and non syndromic sensorineural hearing loss. With decreased male fertility, this is the second most common cause of genetic hearing loss. So worth taking a couple of moments just to review. This condition was formally referred to as deafness infertility syndrome.

But we kind of have amended how we speak about this because it's actually really two separate conditions. Hearing loss being one condition associated with the stereocillin gene and CatSper 2 being a totally separate condition in males related to decreased infertility. In males related to the CatSper2 gene. The reason that they're often spoken about together is because these genes happen to sit right next to each other on the chromosomes. And some places in our chromosomes or some places in our genes are really vulnerable to breakages and basically having little pieces snipped out and being glued back together again, if you can imagine it that way.

So many patients are actually sort of fully missing both copies of these two genes. In all children who are missing both copies of the STRC or stereocillin gene, they will have a mild to moderate sensorineural hearing loss that tends to be pretty stable. We see some very slow, gradual progression over the course of many years for these patients. But males that are missing two copies of this CatSper2 gene will likely need assistive reproductive technologies in order to conceive biological children. We can also see these two conditions separate from each other.

So if you're again have a pediatric audiology practice, this is a condition that you would be likely to encounter. And now I will pass it back over to Dr. Kenna to dig into some syndromic forms of hearing loss. Thank you, Shelby. So I think when I was first in training, we didn't, we thought syndromic hearing loss was rare. We didn't have genetic testing, we didn't really know how to look for it.

But we did know that there were some hearing loss syndromes, that is, that were associated with other things, systemic things that we needed to pay attention to. And so many of these things involve renal abnormalities, Craniofacial changes, Neurologic concerns, Ophthalmologic changes, Pulmonary issues, pigmentary issues, Genitourinary issues, Thyroid dysfunction, and cardiac anomalies. And sometimes it's just one of these, and sometimes there may be a whole array of these in association with the syndrome where hearing loss is just a single part. So a good example of that is charge syndrome or charge association, which is associated with hearing loss, but also renal, craniofacial, neurologic, ophthalmologic, pigmentary, gu, and cardiac issues. So in that case, it's a multi systemic involvement.

Common forms of syndromic hearing loss may present as mimics, Meaning that they may present in early childhood or in infancy with their hearing loss. But some of the other syndromic things, we just don't see them until we go looking for them. So an excellent example of that is usher syndrome. There are nine recognized genetic forms of usher syndrome, but the babies, by and large, do not pass a newborn hearing screen. And by and large, the hearing loss presents at or shortly after birth.

So the babies look fine. And at this age, we actually don't know what they have. They have hearing loss, but we all know that usher syndrome presents eventually with progressive loss of vision, Sometimes called retinitis pigmentosa, in childhood or adolescence, depending on the gene. Variable vestibular dysfunction. The type 1 usher syndrome folks often are very late walkers and their balance is quite abnormal.

But USH 2 and 3, not so much. It turns out this is a relatively common syndrome. But we didn't really know that until we started testing for it because they present with hearing loss. But the ophthalmologic findings don't show up until often the patients are old enough that they're no longer in a pediatric practice. So we used to think this wasn't very common.

There are three main subtypes and there are many genes involved. It's autosomal recessive inheritance pattern for these genes and it has very crucial management implications. So for example, if you knew the child had usher syndrome type 1, where they tend to have a bilateral severe to profound hearing loss at birth, we know those children are also likely to start losing their vision in childhood. And so if the family chooses American Sign Language or some type of manual communication as their preference, we know in the long run that will be very challenging for the family. And so we would talk to them certainly about hearing aids, but also about cochlear implants.

The other reason to do genetic testing is you want to sort the syndromic from the non syndromic. So when they come through the door and they have their hearing tested, the hearing may look the same. And so just by looking at the child and looking at the audiogram, you actually usually don't know what they have. So on the left is a patient with GGB2, which Shelby just described as the most common non syndromic form of hearing loss. And this is a patient of mine who presented with a bilateral severe to profound hearing loss.

They got cochlear implants, they did great. Here's a patient on the right who presented with a very similar audiogram. But this patient has type one Usher syndrome. And so this has obviously very big implications not just for the hearing, but for other systemic. In this case, both their vestibular system and their ophthalmologic system and their retinal functional will be involved, but they have the same audiogram.

So it turns out there are other common forms of syndromic hearing loss that mimic non syndromic hearing loss that are not Usher syndrome. So an example of that is something called Dravel and Lange Nielsen syndrome. These patients present with a bilateral severe to profound hearing loss. But this also causes is a life threatening heart condition called Long QT syndrome. And if you look up especially the old literature on Jerval Lang Nielsen Long qt, you see that one of the symptoms is sudden death.

Obviously it's also a final symptom. So we'd like to actually find the patients before they have sudden death because there are interventions that you can do to prevent that. So because of this, especially before we had genetic testing, many olaryngologists would order an EKG for all babies who have profound hearing loss. And in many cases, we still do that. If for some reason genetic testing isn't available, the insurance won't cover it, or the child has to go to the operating room before we know what they actually have.

Because there are things that you have to do to prevent them from having sudden death. And that's entirely possible. So this is a mimic. There are many others that present that are syndromic forms of hearing loss. Some of them present, like Wardenburg syndrome.

If the patient walks through the door and has a white forelock, different color eyes, or they have early gray hair, they have vitiligo, they have white spots in their skin, well, then you think, aha, they have Waardenburg syndrome. But it turns out there are seven genes for Waardenburg syndrome, and many of those do not present with all of those syndromic features. So it may be the hearing loss only. Alport syndrome patients will is excellent, primarily, Although there are other forms of this. And the patients who have this may develop renal failure, pendrid syndrome, they may develop thyroid dysfunction, Perot syndrome.

There's several genes actually, especially in girls. This actually may cause infertility. So it's important to know about these. And sometimes the only way you're going to figure it out is by doing genetic testing.

However, you can't do genetic testing without genetic counseling. So that's my cue, or at least you shouldn't. That's my cue to jump in again then, and take over talking a little bit about what genetic counseling, at least in my practice, looks like. And of course, address a little bit about how audiologists can either support the genetic testing process or support their patients who've gone through or are going through the genetic testing, testing, and counseling process. So I love this figure.

I love to kind of put it all on one screen. What it means to be a genetic counselor and what it means to help families through a genetic testing process. I always sort of start my sessions by saying to patients, you know, it's not like ordering a cholesterol test that will just tell you if your cholesterol is high or low. There's so much more that goes into this. It's the most highly personal data that we have.

You know, our genetics, it's what makes us us. And my job is to navigate all of these different factors and walk families through the process. I'd say at the core, my job is as an educator. Many families who walk through my door have never heard the word, you know, well, maybe that's a bit of an exaggeration, but they may have never heard the term genetics or DNA before. May not be a part of their culture or even their language or their education.

Some of the families that I meet with have PhDs in genetics. And so my, my role is to tail that education to where the family is and where they're, where they're at, bring everybody up to speed, be on the same page, and then focus in on the hearing loss, specific considerations when it comes to hearing loss, you know, all those benefits and limitations of what testing can bring. I do a lot of psychosocial counseling and supporting of families who, you know, maybe just got the big news that their child is born deaf or hard of hearing and now are learning that there may be other implications. They could have something like Usher syndrome or Wardenburg syndrome or any many of many other examples. And so it's a lot to navigate, especially in the newborn period.

I help families think about what kind of management they may need going forward clinically and of course, other, you know, topics that I wish I didn't have to deal with, like insurance coverage and how we're going to get this testing done. But there's a lot of logistics and it's kind of a big lift to get genetic testing done, especially, especially for kids with like unilateral hearing loss or who may not, not perfectly fit the kind of the bill for what, what testing should be covered. So I really help families walk through this whole process. From my perspective as a genetic counselor, it's really important to have a pre test conversation with families. So it's essentially the consent for the process and it's involved, it's risks, it's benefits, it's emotions, it's logistics, it's all of that.

So I have a relatively lengthy initial meeting or session with families, 30 minutes to an hour, just to review all the background information. My job is to essentially deal with all of this in the middle here, the actual testing process, ordering the appropriate test for the family based on symptoms, presentation, history. Usually it's that large comprehensive hearing loss panel that Dr. Kenna described, but not always. And so we need to think about choosing the right test that fits the patient, making sure we can get that ordered, get the appropriate sample type, and then interpret the results. I always say to my families, your genetic testing results are going to pop up immediately on your portal, but they may look like they're written in an alien language and unfortunately, the genetic testing companies include some very technical terms on the reports.

So it's our job to get these complex reports back and interpret them in the context of our specific patient. And so we have again, a lengthy and important post test counseling session. Here are your results. Here's absolutely everything that we know about it. Here's what you need to know about it.

Here's what you need to do. We'll connect you to healthcare providers that you may need to speak to to keep this going. Any appropriate referrals. We also love when we have the opportunity to connect people to a community of people with the same diagnosis. There's very strong family patient

foundations out there.

For example, for Usher syndrome, we're very connected to that community and then of course for many other diagnoses as well. So we try to create sort of a holistic experience for our patients as best we can. And for me, the core tenet of my practice, and I think most genetic counselors would agree, is just knowing your patient and then meeting them where they're at at every stage here. Well, here's what the genetic testing reports look like. I just told you that they're really complicated, but it's not impossible.

It just takes a little background education to learn how to interpret these. And this is a mock what it's very similar to what our patients actually reports look like. This patient here is receiving a diagnosis of GGB2 related hearing loss. And my favorite box, and I point this out to audiologists, every genetic testing report will have a box that just says result. Most of the time it says positive, negative or uncertain clinical significance.

And I think if you can do anything to support your patients, it would just be to look at this little result box. If you have access to their genetic testing report, get a sense of whether they got a diagnosis from their genetic testing or not. And if they did, maybe take a few moments just to review that gene, read the genetics note, read the genetic counseling note, if there is one, or do the best you can to do research on your own to get a sense of what like the audiologic implications of that specific gene are. Hopefully the genetics team has laid that out clearly in, in their note. But I think it's not the norm for the genetics team to have a subspecialty practice in hearing.

They're of saying all comers to their pediatric genetic process clinics. So perhaps taking a moment to review what the audiologic implications of this gene may be for your patient to help think about management, timing, follow up, or just extra counseling that you can Give within that context, bringing in your specialty is always a benefit. And so these are the things that I focus on. I've reviewed some of this already so I'll try not to repeat any of it. But again these are the sort of three possible results that we

see on genetic testing.

Results positive those depending on the findings sometimes are the most simple conversations we have. It's GJV2. We know a lot about it. We know that it's going to be maybe progressive, but we can manage that. We know there's no other health implications.

It's kind of clear. And so I review all of these things on the left in terms of follow up that may be needed. Negative sometimes that is. Those are the more difficult conversations. We thought we might find something we didn't and now we don't have that clear prognostic pathway forward.

We don't know exactly what the future here may look like. And so those can be more difficult conversations for families. Certainly they're often relieved that nothing such as Usher syndrome or something kind of of syndromic where there's important medical implications came up. You know that that can, there can be relief there. But negative and uncertain results are, are usually some of the more difficult results to, to give back to families.

But of course we review the gene, the prognosis of hearing inheritance pattern. That's a big question especially for new parents who've just had a baby and maybe their first kid and they're thinking of having more. What, what implications are there? Or maybe there's older children. Could this impact them even though we haven't appreciate.

So always I facilitate follow up genetic testing where appropriate and where desired for parents to determine what their genetic background sort of looks like specifically if they're carriers or what have you and testing for siblings as well. And I've certainly worked with families where we've gone very far up the family tree and we're offering genetic testing for people's second cousin once removed. We really try to support families in a holistic way who want to do genetic testing.

So I'll move on from this slide now. So I, I've already shared a bit of this, but I just want to emphasize it because you know, that's what we're here today or to make this connection between genetics, pediatrics, genetics for hearing loss and audiology practice and what that can really look like. I'd say being able to lay a little bit of the groundwork or educate families on maybe some of what you've learned today, potential benefits of genetic testing. You Know, not getting into the details, not even needing to mention a single gene. But maybe you just diagnosed a child with hearing loss, and you can present, like, you know, genetic testings out there.

It may give you information on prognosis. It may give you information on what to expect for the future. Is that something you're interested in? Helping to make a connection to genetic professionals either in your, your center or your area, getting familiar with the resources that you have kind of close at your fingertips, or maybe further afield. Where can I refer?

You may need to do a little digging, depending on what kind of center you work at. But there's more resources out there than you might know about, including some online genetic testing companies, genetic counseling companies that actually have great reputations for certified medical professionals. Maybe that's something that families can access. If you don't have direct access to genetic counselors or geneticists at your hospital or institution, and then I have found, working with audiologists at Boston Children's Hospital, they really like to invest a little bit of time just to understand the specifics of the patient's diagnosis to support these families. I think it's all part of that core tenet of meeting families kind of where they are at.

So that's the end of the genetic testing. Excuse me, the genetic counseling session. But the name of our talk is, you know, genetic testing in the age of Precision medicine. So what does that really mean? And so what we've presented is all kind of standard of care, the kind of typical genetic counseling experience, genetic testing experience at our center.

So what happens if we go through that whole process and we don't find it? What else is available? Or maybe we do find something really interesting and we want to keep working and what, you know, what options are beyond just, okay, a genetic diagnosis. And now we know we're going to talk about that at the moment. So we have this is a.

Or the chart that we were looking at before. We see many children who, all the signs are there that they have a genetic hearing loss, they have a bilateral congenital symmetric sensorineural hearing loss, and a sibling with the same. We do the whole genetic test and nothing comes up. Well, genetic testing and our understanding of genetics is an evolution. When we started doing this testing in 1997, we tested patients for one gene.

Now in 2025, we're testing them for 300 genes, but there are 20,000 genes there. And believe it or not, most of them, we still have no clue what they're doing. So when we, in the context of hearing or in terms of Clinical context in general, other indications. So this gene panel, when we order a gene panel test, typically we'll find about two to five genetic variants or variations of interest for our patient. That's sometimes good enough.

But we only find answers for 40% of our patients patients. So sometimes we will think, can we go bigger? Exome sequencing is a way of sequencing all of the coding regions of the genes, so not quite the whole genome, but all of the most information rich areas of the genome. And now instead of looking at two to five variants, we've got about 100,000 variants on our hands that we need to interpret. And let's say we don't find anything notable within that exome.

Let's go bigger. We can do genome sequencing, sequence every single gene, every single bit of a DNA the patient has that we have access to. And now we're talking about 5 million variants that we need to sort through and understand. So it's a really exciting challenge. We have a study that Dr. Kinne runs and that I work on and manage and all of our studies have fun names, so forgive us, but this is the

bilateral and unilateral genetic hearing loss study.

So we call it the Bagel study for short. This allows us to enroll any patient that has an undiagnosed sensorineural hearing loss as well as their parents, perform either exo or genome sequencing, sort of depending on some of the clinical history, and return results directly to families. So it goes through this big research process. We have, as you can imagine, a kind of complex variant assessment and filtering system. We can winnow it down often to one variant of interest from those 5 million that we got.

And then we're lucky enough to have the budget to be able to take our research testing and turn it into to kind of clinical high quality test results that we can return back to our families and kind of circle it back into clinical care. So just to give you a sense, these are the genes that we find through Bagel. The Bagel study, I won't go into too many details here other than to emphasize that there's many, many very rare conditions that we were sort of never expecting to find for our patients when we set out on this endeavor of doing exome injection genome sequencing for our patients. So here's a case example that might help demonstrate the power of doing broader genomic testing in a research setting for our patients. So we were seeing a nine month old male patient who referred bilaterally on their newborn hearing screen.

They had an ABR suggestive of severe to profound hearing loss and absent OA that a history and physical exam that were essentially unremarkable. And they underwent genetic testing through our practice that was totally negative, nothing reported at all. This patient got scheduled for bilateral cochlear implantation and in the meantime enrolled in one of our research studies to try to dig into it a little bit and see if we can understand more. So they had exome sequencing that actually revealed a sort of rare form of Noonan syndrome caused by the PTPN11 gene, a mutation in the PTPN. This was a de novo mutation, so a random sporadic mutation that occurred just for our patient and wasn't found in parents.

And this gene's actually not really included on any hearing loss panels because it is not. Hearing loss is not typically the presenting syndrome symptom for this condition. So often children are born with complex cardiac, complex cardiac defects, other symptoms that are much more pronounced and they would be referred to, to a cardiologist for Noonan syndrome genetic testing or just cardiac genetic testing in general. This was totally missed. And we actually found this with our hearing loss panel.

We only found it by doing our broad genetic sequencing. And it had crucial implications because this patient was actually scheduled for cochlear implant surgery already, but really needed a cardiac evaluation and hematology evaluation due to bleeding risks and concerns prior to that surgery. Surgery.

We also found, you know, I think when you read a lot of the literature that's out there, you see that, you know, genetic hearing loss really is for bilateral symmetric kids. And there's a lot of data on this, a lot of, of, of data in this one figure. So I won't spend too long speaking about it, other than to emphasize the points that we've been doing genetic testing for kids with unilateral and asymmetric hearing loss for a long time and find positive results. We are often finding syndromic results that were super subtle. They escaped our notice.

We didn't think the child had a syndrome, but they did have a unilateral hearing loss. We sequenced them and sure enough, there's syndromic findings with really important management implications. So we, you know, Dr. K and I support genetic testing for any child with sensorineural hearing loss of any kind of presentation.

And I just wanted to take a moment. I sort of emphasized the sort of rare things that we can find by doing genomic sequencing, emphasize that we find diagnoses for patients we weren't necessarily expecting to, and we can even identify brand new hearing loss genes. And so we found we had a patient with A mild to moderate congenital hearing loss of unknown etiology. She enrolled in our

research study and we found some interesting variants in this gene with a very long name. It's called PKHD1L1.

It wasn't known to be associated with hearing loss, but for sort of reasons that I won't get into, we were really curious or interested in these variants. So we reached out to collaborators and sure enough, we found collaborators all over the world that had patients with genetic variants in the same gene. And we were able to put together this really nice paper with a lot of evidence that PKHD 101 is actually a novel hearing loss gene. And we hope that eventually it will be added to the hearing loss panel tests. So all that goes.

There's a lot that goes into this and that goes into adding to our knowledge of hearing loss genes is I think of it as like an apple tree where maybe we've accessed a lot of the lowest hanging fruit. And we use our research and we use genomic tools to delve into it it as deeply as we can. We're sort of climbing the tree to understand more about genetic variation for which there's not a lot known right now in the terms of the hearing loss space, not a lot understood. And we're kind of chipping away at understanding all of that. And I'd love to now pass it back over to Dr. Kennedy to continue our conversation on some of our research.

So just in our last few minutes, thank you, Shelby. Shelby, the things we want to do is we want to find out the diagnosis as soon as we can, if there is genetic diagnosis, so we can intervene if there's intervention to be offered to the family, either for the hearing loss or if they have cardiac or hematologic or other other things that we find. So several years ago, we had participated in a study at one of the local hospitals looking at newborn screening, genetic newborn screening in a brand new baby. We learned a lot from that study. And now we have a new study called TOAST.

Dr. Shearer, my colleague, is the PI for this. All of our studies, bagel, coffee, chives, toast and pastry are all breakfast foods. So it's very important to know that this one is actually looking at babies who all

newborns, as noted, have a physiologic screen, which we talked about either ABR or occasionally OAEs. They don't pass the screen. They come to see us at Boston Children's and either we collect saliva or blood to do genetic testing on babies.

Some of these babies are only a week or two old. And eventually this will also include CMB screening. Currently, the average age of diagnosis for something genetic in Our institution is 9.3 months of age. And that's with all the support and teamwork that we have. The goal is to try to be less than three months.

And so this new toe study, I think now has about 70 patients in it, and we're really excited about finding things early. The idea is to turn this around as fast as possible. And if it turns out to be really useful and cost effective and speedy, this is something we'd want to incorporate for all babies who are presenting with possible hearing loss at the time of birth.

As Shelby mentioned, we can actually also diagnose genetic hearing loss now before the babies are born, or at least the spirit. And so we've been working with our maternal fetal care center here at Children's. When mothers and sometimes fathers have either antenatal or so before they get pregnant, genetic testing, or once they get pregnant, they do genetic testing for the mothers and the fathers, and they may find that they have hearing loss genes, and therefore the baby has the possibility of also developing hearing loss. So we've actually been meeting with these babies, babies before they're born, along obviously with their parents. Most of these are recessive hearing loss screens, or sometimes there's a family history.

And with this, we've actually been able to diagnose. We're up to about 30 families now. Some of these children are diagnosed in utero, some of them are diagnosed after they're born. And then we meet them once they're born and they become our patients. Patients in many cases.

But we're also able to reassure the families about what we know about the genes. And as Shelby said, we can talk to the families. We know this is how it's going to go with this particular set of genes. These are the interventions available to your child. And basically we can also provide reassurance that in most cases the children are going to do just fine because they've had an early diagnosis.

So now we know potentially the genetics of many of these, for many of these patients. So now what do we do? We, we do early and accurate genetic diagnosis, which now may enable gene therapy. So if we can diagnose the fetus, a newborn, a child in adult, and people who are older, as I get older, I don't want to feel elderly, but older patients. But we know that also the inner ear structures, especially things like the spiral ganglion, neurons, are probably at their best.

Like many things when you're young and over Time, time, they begin to fade away. And so the therapeutic window for many of these genes would be earlier on in life to have a, the highest possibility of a therapeutic efficacy.

The strategies for gene therapy are many, and I'm sure many of you have read about these. You can correct the gene, you can replace the gene, you can modify the gene, you can silence the gene, you can restore absent function, you can override abnormal function, and you can inhibit abnormal gene function. And a lot of the approach for gene therapy has to do with the gene, the type of mutation where in the genome it is, how it's affecting the patient and so forth. So not all gene therapy approaches are actually useful for every gene or every mutation. And so you actually may end up doing one thing for one particular crispr.

And once CRISPR became like on the front page of the New York Times and Time magazine and cnn, the patients began to come to us and say, well, can't you just do crispr? Sort of like, can't you just take Tylenol or Advil or, you know, anything? And the answer to that is not yet, but this is a good idea. There are some, many genetic therapies for things that are not hearing loss. For example, CasGV, which is

the brand name for a intervention for sickle cell disease, is available and very effective, FDA approved.

And we have patients at Boston Children's who have had this. Probably the first one was Loxturna, which is for something called Leber's congenital amaurosis. It's caused by particular variants in the RPE65 retinal photoreceptors. This has been available now for about 10 years. And this is actually genes attached to a viral vessel vector, as opposed to CASP, which is a CRISPR Cas9 mechanism where you go and you chop out part of the gene and you replace it.

You can also skip exons. Some of these genes, they're like train cars. Some of them have 60 or 80 exons, the part that makes the protein. And you can actually block some of that with oligocense nucleotides. A good example of that is spinraza, which is for spinal muscular atrophy, in this case type 2.

But there are also stem cells, the possibility of carrying things in there with nanoparticles, either using small particles to replace things or to inhibit things, exosomes. And you can change the cells either inside the patient or you could take them out, change them and give them back. And these are just some of the techniques that people are considering or actual use. So we are involved here at children's and many other institutions with a gene therapy, the first gene therapy in humans for hearing loss. And the gene is called otoferlin.

It actually is a relatively rare gene and of all these 2,000 plus patients, it's in here somewhere. So it's a very uncommon gene. It causes a hearing loss called auditory dyssynchrony. And some of the and those positions often present with a bilateral severe to profound hearing loss. The drug delivery in this particular case is by a viral vector.

But any type of drug delivery to cure hearing loss or at least stabilize the hearing, you want to obviously preserve the hearing the patient already has. If possible, you want to avoid extensive surgery which in

itself can cause further change in the hearing. Hearing you may deliver through the middle ear through the round window, either directly through the round window with a small insertion, but maybe that someday there'll be things we can put in there on a gelatin sponge. Thermosensitive gels, digestion of the round window with collagenase microperforations. All these ideas have been tried in the laboratory and you could also potentially send them along in, along a cochlear implant electrode around array.

There are a lot of challenges however to gene therapy. There are multiple types of mutations. There are obviously a lot of genes, they're deletions, exon expansion. So there's a lot of different things that would have to be worked out. Of course, not all hearing loss genes have been identified.

There are multiple protein expressions. An example of that is harmonin, which is one of the proteins involved in Usher syndrome to the stereocilla. And it can other, other versions are at the hair cell synapses. There can be off target effects, you don't know how durable they are. And it's very expensive, localized.

So should we do this? Deafness isn't life threatening. Who will have access? When do you diagnose the patient? There are many populations that are understudied, including patients of Hispanic background, African Americans, Native American Americans, smaller or more isolated populations.

And when do you do this? Do you do it? And we identify the baby's pre implantation in utero, in the delivery room, in the clinic. So all of these things need to be carefully considered before we really launch into this in a major way. So in summary, genetic diagnosis of pediatric hearing loss enables precision medicine diagnosis and can inform care.

Audiologists, at least for us, are a crucial part of supporting the family. By understanding the audiologic implications in this case of a reticular gene or genetic presentation New technologies and testing strategies such as carrier screening, genome and exome sequencing, and gene therapy are bringing

innovation in the area of pediatric sensory neural hearing loss. Thank you very much. This is very much of a team effort. We could not do this without all of these people listed.

And there are lots of people who aren't listening listed. And then finally, we want to thank the American Academy of Audiology for inviting us to participate in this presentation. And thank you very much.

And please remember to cleat your exam. Thank you. Okay, the first question that came in, which is a great one, is how often do you see children with Connexin 26 or GJB2 hearing loss have unilateral hearing loss hearing loss? Do you want to take that one, Dr. Kenna? Sure.

So the. The first patients identified with Connexin 26 related hearing loss all had bilateral hearing loss. And in fact, they. Almost all of them really had a bilateral profound hearing loss. But as testing went on, we found out that although most of them have bilateral hearing loss, not all of them.

And we have patients in our patient population who have a unilateral hearing loss and who have pathogenic variants in the GGB2 genes. So I think it's not common, maybe 3 or 4%, but it does happen. And so you don't want to ignore those patients. And as Shelby's slide showed, our unilateral hearing loss patients, probably about 10 or 15% of the time, have a genetic cause of hearing loss. About half of those are syndromic, but the other half are things like GJB2.

So thank you for asking that question. Absolutely. The next question is from Dialek, who's a audiology student from New York, who asked, I'm curious, since our advances in genetics, have some of these major genes been included on genetic testing panels for newborn screening? That is general newborn screening, not newborn hearing screening? I can take that question.

It's actually much more difficult and it's a very heavy lift to actually have any conditions added to the newborn screen. So not the hearing screening, but the newborn screen that they do from that a little

prick of the baby's heels and they get a dried blood spot. Some of the limitations there to doing actual genetic testing on the newborn screen are sample sort of amount. You get a very limited amount of DNA. And in fact, right now, none of the newborn screening is actually genetic testing.

It is biochemical testing for conditions that may have a genetic origin or may not. But it's not direct genetic testing. There are pretty.

There are just like a whole Panel, a whole wide organization of people who have to assemble and decide what conditions are sort of actionable and common enough to add them to the newborn screen. But I can tell you that there are many, many, many researchers working on large scale studies, studies of like up to, you know, a couple, maybe up to a hundred thousand newborns trying to do newborn genomic screening for any pediatric condition. So it's all in the research space now. So we're moving towards a newborn genetic screen, but we're not quite there yet. And our post study that Dr. Kinne described is a way of hopefully moving kind of closer or supporting the idea of new newborn genetic hearing loss screening.

So focusing on the hearing loss there. Yeah, there are some places that report doing this. There's some studies that have reported from China where they've just looked at a handful of genes. There's one of the provinces in Canada that uses it in conjunction with their CMV screen. So again, it's just a handful of genes.

And so I think as Shelby said, in addition to finding the genesis, which we know how to do in many cases, you also have to figure out who's going to take care of those patients, what are the interventions going to be? It has to be equal and equitable access. And do you test for all the genes or just some of the genes? So I think there's. It's coming for sure it's coming.

I think we just have to see how fast it's coming.

All right, well, thank you very much for those excellent questions and for the additional discussion. So I'd like to thank Dr. Kanae and Shelby for this excellent presentation and for sharing their time and expertise with us. And thank you everyone who participated in today's course. As Dr. Kenna said, please do remember to take the the exam. It'll be available on your pending courses page in the next 10 to 15 minutes and please do remember to complete it in the next week.

We also look forward to your feedback on the course evaluations which helps us to improve our courses and bring topics that are of interest to you in the future future. So please do send us your thoughts on that. This concludes today's webinar. Thank you again for attending and we hope to see you again in future courses. Have a great rest of your day.