Precision Audiology: Advanced Diagnostics to Individualize Treatment for Sensorineural Hearing Loss, in partnership with the University of Pittsburgh

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I'd like to welcome back Dr. Samantha Hauser. Today's course is in partnership with the University of Pittsburgh. If you haven't had a chance to catch all of our other partnership courses with upit, they're all in the course library. If you'd like to learn more about Dr.

Hauser, you can read the bio on the course registration page. But at this time, I hand the mic over to you, Dr. Hauser. Great. Thank you so much, Christy.

All right, so just to get us started with some of the basics here, these are the disclosures relevant to the presentation here, some limitations and risks, and then the learning outcomes that I hope you gather as taking the part of this course. All right, so to kick it off, I'm going to give a little bit of an overview of the things that I'll be discussing today. We're going to start off with a pretty in depth look at some of the limitations of what we currently do in diagnostic audiology and the effect that those limitations have on how we are actually able to treat hearing loss as audiologists. I want to look at the framework of precision medicine and how I think that we can apply precision medicine principles to audiology. We want to look at the approaches specifically to precision diagnostics.

And I'm going to use some examples from some of my PhD work which looks at cross species studies of diagnostics for hearing loss. Lastly, a little bit of taste of what I think might be coming down the pike. Some of the things that are both limitations to implementing this work as well as new opportunities for exciting things we will hopefully see in the future in audiology. All right, so I want to start off here with a, what I think is a pretty common clinical scenario. When I was practicing as an audiologist, I saw this all the time and it is a big reason why I decided to come back and do a PhD because I found it incredibly frustrating.

So we're going to start here with patient a. It's a 57 year old male, mild to moderate high frequency hearing loss. This person I think was a pretty classic scenario of a patient that you might see in the clinic. They were relatively interested in hearing aids, but kind of interested for to know what their

hearing loss was like. They described not being able to follow conversations, particularly if more than one person was talking.

And we did do speech and noise testing and which showed a pretty good speech and noise score, a negative one DBSNR loss. But then the next day you might see patient B here, who's just a little bit older, 62 years old, who was Very interested in hearing aids, was desperate to know more about them, how they could help him. He really struggled in a lot of situations and particularly at work. This patient is a physician, and so it was really important that he was hearing things clearly and really noted struggles in pretty much all situations. And our speech and noise testing really supported what he was reporting.

He did show a pretty significant SNR loss of 9dB here. And then I see patient C, this person just came in for a free hearing test, did not have any concerns about hearing. When we do the SSQ questionnaire, they rated every single question as no problem, problem at all, or that they could hear everything 100% perfectly and quick sense score was somewhere in the middle of the other two patients a 3dB SNR loss, which is right on the cutoff for normal. And so it drove me crazy as an audiologist that I could see three people here with mild high frequency hearing loss who reported totally different perceptions of their own hearing. And really then in terms of being able to treat these people, it made it hard to really know what's the best treatment.

And you end up going a lot just based on subject of report and how much interest people have in hearing aids in general. And so I wanted to understand, though better why these people with similar hearing tests might have such a big difference in both their outcomes with hearing aids and their perception of their own hearing loss. The other common clinical scenario that I would see was this. And I think everybody's probably seen a situation like this as well. Somebody walks into the clinic who is especially concerned about their hearing in noisy places.

But you go to do a hearing test and threshold come within the normal range. And so there's not really a whole lot that you can do for this person. Amplification really isn't the solution when they are hearing, when their hearing thresholds are within the normal range. But if you do quicksand testing and you and you measure their speech and noise score, this particular person had an 6dB SNR loss, which is significantly outside of the normal hearing range and thus does back up that there really is a problem going on here despite normal hearing. And so as an audiologist, I was really provoked by these clinical scenarios, trying to understand why people with similar audiograms have differences in their speech and noise abilities.

Why do some people with normal hearing thresholds still have trouble when they're hearing a noise? Then most importantly, is there a way that I can tailor my treatment plan to support the individual needs of these patients when all of my diagnostic measures really yield similar results? And I think a lot of this is done via clinical intuition, or I think is really what the art of audiology entails, is how we do this, tailoring, how we take into account what people report to us about their hearing and develop some sort of treatment plan based on that. And so, as a field, what I really hope that we can do, though, is begin to standardize this type of care without just relying on getting a good audiologist who's good at interpreting this type of feedback, and without relying on patients to come back multiple times and report what they're experiencing with their hearing aids. So can we help to really give some evidence to the clinical intuition that lets us know that two patients are different despite similar test results?

And I think a lot of this comes down to the way in which we diagnose hearing loss. And I think you will all agree this is quite an oversimplification of the auditory system. You have the outer ear to the middle ear to the inner ear, and then sound goes up to the brain. But despite how much of an oversimplification this is of the auditory system, this is really how we diagnose hearing loss is into these broad, gross categories of things like conductive hearing loss, where it happens in the first part of the system from the outer or middle ear, sensorineural hearing loss, which has something to do with either the sensory

part or the neural part, the inner ear of the brain. Or you can have both of those things, of course, and have some sort of mixed hearing loss.

And then we have this broad category of things that happen outside of that that we generally label as an auditory processing disorder or central auditory processing processing disorder. And so even though we really know there is so much more going on in here, unfortunately, our diagnostic tests really don't help us get a whole lot more specific than this. And what I'm going to be focusing on for the remainder of this talk is sensorineural hearing loss, in particular, the type that would originate in the inner ear itself. So components of the cochlea and what we see in all of the temporal bone histology from humans, as well as lots of research in animals, we see that there are really multiple sites of sensorineural hearing loss. So all of these components of the inner ear that make it work so beautifully can be damaged and are highly sensitive to different types of pathologies.

So you can have outer hair cell loss, inner hair cell loss, destruction of the auditory nerve fibers, or degeneration of that over time. You can have a reduction in the endococlear potential, which has to do a lot with the maintaining of the ionic balance via the stria vascularis. And of course, the inner hair cell ribbon synapses. That has gotten a lot more attention recently. And you might hear called cochlear synaptopathy when there's pathology in that region.

Those multiple sites of cochlear pathology are all vulnerable to damage. We typically think in terms of outer hair cell loss as being the predominant pathology related to sensorineural hearing loss. But all of these things are vulnerable to damage and lots of different ways, too. Ototoxic drugs can impact both the inner and outer hair cells. You can have physical injury to the system.

Infections can. Can mess up many things within the cochlea. And then, of course, noise and aging are pretty big factors that we think of as contributing to hearing loss quite a bit. In particular, aging has been related to both outer hair cell loss over time, Loss of the ribbon synapses, Degeneration of the auditory

nerve fibers, and a reduction in the endococ potential, which is the cochlear battery that powers the hair cells. And so really aging in particular, which is going to be A lot of the patients that we see in the audiology clinic are likely to have combinations of these different pathologies.

But when it comes to our diagnostic methods and the real test that we use to say whether or not someone has hearing loss or not, we use the audiogram. And so the question is, what does the audiogram detect from this range of pathologies that there could be? And what we see is that outer hair cells, of course, are detected by this. If you damage the outer hair cells, you will see an elevation in audiometric thresholds. If you damage the inner hair cells, however, you don't always see a change.

Of course, in extreme cases where you have dead regions, where a large swath of inner hair cells are lost, you may see a result of that, of course, but inner hair cells can be lost. There's some studies that are on the handouts that you get as well as that are cited at the bottom of this page. Percent of inner hair cells can be lost before you see any changes to audiometric thresholds. So this is really quite a hidden pathology. Auditory nerve fibers can be damaged without showing up on the audiogram as well.

I think a good example of this is if we start to think about things like auditory neuropathy spectrum disorder or ansd. You can have damage or misfiring of those. Those fibers without any changes to the audiogram or quite variable audiometric presentation. So changes to the stria Vascularis or a reduction in the endocochlear potential is visible on the audiogram. And this is generally sort of as a byproduct because the endocochlear potential is what powers the outer hair cells.

And if the outer hair cells aren't in the correct ionic environment to have their motility, then you're going to see an effect as far as threshold elevation there. And so one tricky piece of this though is that can you really differentiate or does the audiogram different with the endocochlear potential and a problem with the actual function of the hair cell? And that remains to be seen at this point, but seems to give us similar patterns of results. And then lastly, the inner hair cell ribbon synapse, like I said, this has been a

kind of most talked about of the hidden pathologies and has been related to something and really sparked the interest of something called hidden hearing loss, whereby we start to acknowledge that there are things within the audiogram that it is missing and not detecting. And so really we're really only getting a picture from the audiogram of what's going on with the outer hair cells themselves.

Of course, as audiologists, we have a whole test battery that we can be using. We don't always just rely on the audiogram. But I pulled out a couple of the tests that we might commonly do for an audiology workup. And if we are doing anything extra, they don't always address all parts of this. So certain things like acoustic reflexes or measuring an auditory brainste response are likely to show deficits in things like the auditory nerve fiber function.

But we're not always measuring that on every patient that comes in. Otoacoustic emissions are a common test, particularly in pediatric populations, but that's really just giving us more confirmation a lot of the time with what we're seeing on the audiogram. And so OAEs really is more associated with outer hair cells as well. Our other measures and options give us totally different information. For the most part, most of our speech testing is going to give us some information about perception, but not necessarily is it directly tied to any given pathology.

Tympanometry is of course going to tell us more about the middle ear. And we are having more and more, I think, discussion about things like genetic testing or imaging to try to get a little bit more information about the state of the person and what might be causing a given hearing loss. But at this point we don't really have concrete genetic tests or imaging that we can do that's going to identify the Exact distribution of pathologies that a given person is going to have. And that's if somebody's testing it at all, which I would argue for most of our general population that's coming in for a hearing test, we're really not measuring that. And so then the question might be, does it really even matter that we know what the specific pathology actually is?

Is that going to be changing our treatment outcomes at all? Or how does that really impact how well somebody's going to hear? And so I want to give this example from this particular paper. Again, I would, I would recommend looking to this paper a bit, and it's in the handout, I believe. But so let's imagine you have sensorineural hearing loss, or you have two individuals with sensorineural hearing loss, one type.

In this particular study, they're looking at the auditory nerve fibers from chinchillas with different types of hearing loss. And so in the animals that had a metabolic hearing loss, which this would be things that are related to the endocochlear potential and thus are mostly an outer hair cell dominated effect when you have those animals is that thresholds are elevated, of course, but there is, and there is a slight change to how the tuning curve is shaped. So you can measure a tuning curve for each auditory nerve fiber that you're recording from. What they see is that in these animals with metabolic hearing loss generally follows that shape. You see that nice little peak of the tuning curve, it generally follows the shape after exposure, the low frequency region matches up well, but the threshold is elevated.

The tip of that is at a higher level up here. And so we see, of course, like I said, elevated thresholds, but a generally normally shaped tuning curve. And so you would think in this case, audibility is really what this person needs. The threshold is the major issue. The threshold is elevated.

And so something like hearing aids that helps provide that audibility is going to help. Of course, there's also changes to the overall tuning and other factors to this. But in general, audibility is likely to help this person. On the other hand, they had some animals that had noise induced hearing loss. And noise induced hearing loss from a histological perspective has been shown to not only damage the outer hair cells, but the inner hair cells and the cochlear ribbon synapses, the auditory nerve fibers.

All of those components can be damaged with individuals that have noise induced hearing loss. And what they see is something totally different as far as the thresholds go. So the thresholds still are

elevated relative to baseline, which is in that little dotted line. There. So you do see that that tip has increased, but you'll notice a difference in the tail region of the tuning curve.

So that low frequency edge has dropped down. And what this results in is that more noise from low frequency sounds are going to be stimulating this nerve fiber. So if you can imagine that you play the particular tone that this neuron is tuned for, you would get a response to the sound that it's tuned for. But if you also play low frequency sound, like low frequency noise, that neuron is also going to fire. And so now compared to the other case, you start having more activation by low frequency noise than you would have, which then when you try to extrapolate this to what's going to happen in people, likely we're going to see poor hearing aid outcomes where audibility is really not enough to solve this.

So you can increase the audibility and match the increase in the threshold. But if you are also much more sensitive to noise than you used to be, the hearing aid is not necessarily going to help that. And we're likely to see things like poor hearing aid outcomes in those individuals. So knowing the exact distribution is really what's important, because each pathology can affect how sound is encoded in the nervous system, and different pathologies are going to damage that encoding process in different ways. I think all of these limitations really do matter from a clinical perspective in all kinds of aspects of how we treat people with hearing loss.

First, even just identifying the etiology of people with hearing loss, I saw all the time people would ask me, how did I get this hearing loss? Or what do we think is going to happen to it? And a lot of the times we're counseling on what might have caused it or how they might likely prevent it in the future. And without knowing exactly what the underlying distribution of the pathologies is, it is hard to make a guess about what really is the true cause of it. You can also think about how we might be using future therapeutics.

And so thinking about drugs that will treat hearing loss, we really want to be able to correctly identify the right etiology because those drugs target specific mechanisms of hearing loss. So you need to know who has that particular pathology. This will help us in identifying subclinical deficits. So that second case example where somebody has normal hearing but lots of speech and noise complaints, if we can really be able to detect those problems and figure out why they're there, I think that will really help us to, to better care for and counsel our patients. Same things with tinnitus.

I'm sure you've seen people with tinnitus who are really debilitated by it. But if you don't have good evidence from any of your measures that something that is wrong, it's a hard conversation to have. This is super important for how we treat hearing loss and we think about how we're gonna predict their outcomes or tailor our treatment. In particular, I think a lot about how we currently fit hearing aids we have some prescription for based on what the thresholds are for how much amplification the person should require. But beyond that it's often a lot of trial and error.

It's having the person get used to a particular sound for a bit and then getting that feedback, interpreting that feedback and then trying to make the correct change in the software. And so I think if we can reduce some of this trial and error that reduces a lot of unnecessary follow up effects visits. This also is an important thing for recommendations for follow up and I think a lot now that I'm more on the research side. You know, some of the things that are coming down the pike are how we understand hearing hearing loss and its effect on people globally. Things like understanding the effect of hearing loss and separating that out from cognition or looking at how hearing loss and cognition are related I think really matter when it comes to what our diagnostics are are for this.

How are we really able to say what the effect of aging is? If people who are aging have cochlear hearing loss and cognitive deficits, it's hard to know when that's a multi step process for how sound is getting up to the brain. If you have a disordered system that's sending the sound up to the brain, is that

really a cognitive problem or is that something more in the periphery? And I think a lot about that and I think having these better diagnostics is going to be really important for how we think about research in the future. Especially again novel therapeutics and how we're going to treat hearing loss.

Because ultimately the takeaway here is that we can really only treat or counsel or discuss with our patients things that we know that are there. Otherwise we are just mostly speculating and giving people a general idea of what could have caused their hearing loss and how we should best help them. So moving into the precision medicine framework because I think this particular problem is really well served by a lot of the ideals of precision medicine. I want to spend a little bit of time on what precision medicine is really getting, getting at in the main tenant. I think the way you can really think about it in a pretty succinct way is precision medicine means giving the right patient the right treatment at the right time.

And there's different components to each of this. So for the patient that means understanding their genetics. And I think in a lot of precision medicine in the more broad field of medicine has focused on genetics. But this also includes diagnostics that look more in more detail at anatomy and physiology. It also means taking into account the person's environment and their history.

And I think audiologists already do a good job of this and have been trying to gather all of these little pieces of information to come up with the best plan for the patient. But right now we do this in somewhat of an ad hoc way and is variable audiologist to audiologist. As far as treatments go, this could be anything ranging from surgical to pharmaceutical interventions as well as general rehabilitative strategies. Strategies if there's certain tasks that we can give a person or, or certain assistive devices, it would be great to be able to give the right treatment to the right person in that way. And then lastly is in terms of time, if we can diagnose and identify these pathologies earlier, that may help with prevention of hearing loss.

And identifying the correct pathologies also will help improve the likelihood of success, particularly on the first time that you see the patient or the first time you go to treat the patient, rather than a lot of the back and forth trial and error that we currently do. And I think there's really three parts of this. So each one of these little pieces kind of needs their own thing. And for the patient that means we need precision diagnostics. We need diagnostics that really hone in on the important key issues that are going to identify individuals from each other.

As far as treatment, we need the corresponding precision therapeutics. And there is a lot of work on this in the drug development space as well as things like gene therapy that I'm sure you've heard a little bit about. And I think on the time side, a lot of this has to do with access to care generally and making sure that people have access to going to the audiologist, to getting their hearing checked earlier and not just waiting. And to some extent this also has to do with the way that audiology is marketed less towards just when you get older, you're naturally going to go there. But can we get some baseline hearing testing and can we really make this a part of routine monitoring of the whole person's well being?

And so to contrast this, I want to look at a bit the traditional approach. So let's imagine that you have These hundred people. The way that we kind of currently think about a diagnosis is more like this, where you have people, some people have more severe versions of it, some people have less severe versions of it, but we all call it generally the same thing. And for this example, we call it sensorineural hearing loss. And we label everyone within this umbrella.

And so then when we do a particular test to say, you know, how should we treat this group? We look at the average and we take this mean kind of right down the middle and we say, what works best for people on average? And then that's the treatment that the whole group is going to get. But what I think we really need to start looking at and to kind of combine this with the initial section here. What's really

going on is not this.

It looks a lot more like this. And so there is really these subcategories of sensorineural hearing loss that are likely there perhaps people with much less severe versions have something more like cochlear synaptopathy or some of these other hidden pathologies going on underneath. Perhaps people that have much more severe pathologies like the, the red group over there, maybe they have way more both outer hair cell and inner hair cell damage. There is likely a major mix of this that's really going on. And in fact, it's probably much more complicated than what this, this picture sort of represents.

And so my goal is to not just call sensorineural hearing loss this one big umbrella term for all of these different pathologies, but to acknowledge that there are these different overlapping distributions within there that all should be targeted individually. And so when you go to treat somebody, we need to think about what specific group they are actually in. And so I think this can kind of be represented by this a bit. So if you imagine doing a treatment study, you want to know how does your new drug affect people with sensorineural hearing loss? You're going to pull from some distribution, probably somewhere around the middle.

But what you think you're going to get are all of these gray circles. And what you're actually getting is something that looks like this. Some of these people are purple, some are green, some are yellow, some are blue. And so you really have this variable group that you're actually testing on. And that's going to lead to variable outcome outcomes.

If your drug targets a specific mechanism that only works for the people in the yellow group, you're only going to see the effect for some of those people. And I guarantee that this is already happening. And so this from a couple of years Ago, Frequency Therapeutics had a big drug trial for their drug, FX322. And they were very excited about it. They had seen very promising results in one group of of people that were tested before this.

But overall, on average, they saw no difference in the effect of the drug versus the placebo group. And so when you compared average to average, really no change. But if you look at some of the individual data from the study, you had a few individuals who showed wild success with this drug. So the three I always think of, you can go to some of the papers here. The three I always think of, there was three patients that had word rec in quiet that were less than 60 dB.

And those would be people that you may be referring for a cochlear implant evaluation who took this drug and showed wild improvements in their hearing. They went from being perhaps cochlear implant candidates to having close to 100% word recognition ability. And so if you think about this drug, it maybe worked, but just for not everybody, it worked for the people that had the right mechanism that it was actually targeted. So I think that as we really try to have more precision therapeutics for hearing loss, at the same time, we need to be thinking about precision diagnostics, and how are those things going to go hand in hand? How are we going to make sure that we select the right group of people and test our drug on the people that it is actually most likely to help, so that we can see significant differences between the treatment group and the control.

All right, so let's kind of combine all of this. So we have the problem within audiology, we have the framework that precision medicine offers, and I'm going to give you this sort of definition that I think of as primary as precision audiology or precision medicine for audiology. And that really is a comprehensive characterization of hearing across multiple physiological and perceptual dimensions of hearing. We really need to be testing all of those different parts, not just one particular test that looks mostly at outer hair cell function, for example, and ultimately to provide personalized interventions for the auditory challenges that our patients come to us with. As a first step towards this, I think that the framework that I think of sensorineural hearing loss in is that sensorineural hearing loss for the average person is probably more complex.

Sensorineural hearing loss and complex is a term that's used in the the precision medicine sort of lingo for things that have multiple underlying disorders that lead to that pathology. Com they are the result of the combined effect of multiple factors. It's not just one thing Leading to exactly one problem. And they have a highly variable clinical course. And I would say that sensorineural hearing loss, as we currently categorize it, really fits all of these three things.

And so I think we should be thinking about sensorineural hearing loss as complex until we get more precise and we know more about the different types or the different subtypes of sensorineural hearing loss. So I think this is the kind of way we should be thinking about the average person that comes in with sensorineural hearing loss. And so how do we get there? And this is where I'm going to dive a bit more into the research that I've been working on. And because I think this is a big and important problem, but it's a difficult one to solve because really what we're trying to do is link the underlying cochlear pathologies with how people perceive sound.

And that's a tricky bridge to cross, particularly when we think about how we get this data. On the research side, to really know somebody's cochlear pathology, there's no good way to image the cochlea while they're still alive. We really don't have the right test to know exactly the distribution of hair cells of stria that's, that's going on in a person. But we want to be able to link and measure those things with, with their perceptual abilities. And so the way that I'm, the framework I'm using around this is that instead of measuring exactly the, the pathology that's going on with temporal bone histology, for example, we can use something like a physiological biomarker or some diagnostic test that reflects a given pathology.

We can then try to correlate those physiological biomarkers with perception. We do this little bridge here via the diagnostic to be able to link these two in people. The trick though is still on the research side of things, we need to know what the actual pathology is in an individual and how that corresponds

to the physiological biomarker. What we need is a cross species format. Without getting temporal bone histology from people and having all of this in the same human, we really need to look at different species that can be used to help us solve the problems on the different parts of this little framework.

Here in my work, I use chinchillas to look at how cochlear pathologies that are induced either by ototoxic drugs or noise exposure, how those things, things affect the physiological biomarkers that we're trying to measure. Then in humans, I can use those Exact same measurements since they're all non invasive and look at how those physiological biomarkers help us to predict outcomes like speech and noise better. Then ultimately, because I'm using the same physiological biomarkers in both the animals and the humans, we can use some modeling approaches to help us start to label and make our best estimates about what the pathology is in an individual human based on the animal data. So let's get, get into it a little bit. There's, there's three parts that I'm, I'm going to talk through as part of my research that I think are, are all relatively important aspects of this just to give you a little flavor.

So first is measurement precision. And I think of this as really an overarching issue that, that needs to be figured out for anything sort of precision diagnostics type of framework. Whether you're studying this in humans or in animals, we really need our measurements to be as precise as possible to know what exactly they are reflecting. Number two, I'm going to show you some data from two types of hidden pathologies and why. I think a multi metric approach to diagnosing hearing loss and diagnosing cochlear pathologies is really going to be the way to go.

Then lastly, I want to show you what some of these diagnostics look like in humans. We're going to come back to the three subjects that I started the talk with and look at how we can use some of these measurements and relate that to their speech invoice ability. All right, so number one here is measurement precision. And really the goal of this is to reduce irrelevant sources of noise. And I think we think about this all the time in audiology, whether we're really consciously aware of it or not.

But things like doing your hearing test in a sound booth, you know, we're trying to eliminate those irrelevant sources of noise, like other background noise that might be there. We do things like calibrate our stimuli for acoustic emissions to make sure that the, the levels are correct. We calibrate our audiometers of course, and, and we, we have all of these ways to really help us know that the measure that we're getting is something that is repeatable and something that reflects what we actually think it, it is supposed to reflect. Um, and the example I want to highlight here, one, one area that I think we could, could, we could actually really improve is calibration of sounds, particularly for things like otoacoustic emissions. And so what I have shown here is just a sort of schematic of an ear probe in a ear canal.

And so what you see is on the far right side you have the tympanic membrane, and towards the left there would be the entrance to the ear canal where the probe tip sits. And what's shown in the figure below that at, is the level of the sound that's measured at two different places in the ear canal. So you have the level of the sound in blue that's measured at the entrance to the ear canal or at the probe itself, which is where the microphone in the probe is. And then you have the sound level that is actually reaching the eardrum. And you can see that those lines do not match up.

There are places where there is about a 15dB difference between the sound level that is reaching the eardrum and the sound level that is picked up at the microphone at the entrance to the probe. And I think that this is kind of a, a funny thing that we do in audiology, where the way that we calibrate something like otoacoustic emissions is by measuring the sound level that comes back to the microphone at the probe. And so for an OAE calibration, you would get something that looks like the blue line, and then we can compensate for that when you present the stimulus. But the sound that's actually reaching the eardrum is what's, is what's in the red line. And so then you actually are getting a difference in sound and not compensating for the right levels that you actually should.

We know this problem exists and is true. It's the reason why you do real ear measurements and use a probe microphone to reach the eardrum itself. And so I think it's a, it's a good example of how we may not always really be measuring exactly what we think we are or that we're actually introducing some irrelevant sources of noise. So this type of calibration where you measure just the sound that's hitting back at the microphone is going to give you more differences when you replace the probe in the ear. So for every placement, you're going to get a slightly different response and it's going to give you more differences between individuals who may have different ear canal anatomy itself.

And so one solution for this is something that we're using in our measurements called forward pressure level as what the level of your sound is calibrated to. So rather than sound pressure level or spl, we use FPL for oae. And what's that shown is it's really our way to estimate what sound levels are hitting the eardrum, not just what's at the microphone itself. And what we see from that is there's research that, showing that you get much better test retest reliability. And some of our recent work has shown that you get better correlations with audiometric thresholds.

So if you're trying to use something like OAEs to predict hearing loss, having the best correlation possible with the audiogram is going to be important. And if we can do that by removing some of the source of variability from ear tip placement or the calibration, we can use that as a, as a better tool for doing things that we need to like newborn hearing screenings. All right, so that's on, on measurement precision and, and I think is something that is really an idea that will be carried a little bit through the, the next parts here. So next I want to focus on some of my research in, in the animal models with the chinchillas, particularly focusing on how we can separate out out two different types of hidden pathologies. And this is really going back to this new idea of hidden hearing loss, which really is the definition would be deficits despite a normal hearing audiogram.

And I have two examples of this here. So we have cochlear synaptopathy, which is the disconnect between the inner hair cell and the auditory nerve fiber. So there's the disconnect there at the synapse, the synaptopathy. And the way that we do this in the animals is that we induce a noise exposure exposure. So the animals are exposed to noise, they have a temporary threshold shift which then a couple of days later returns back to normal.

So this is very much the sort of chinchilla equivalent of going to the rock concert. You temporarily have increased hearing thresholds. You may have a little bit of tinnitus, but then a few days later that comes back to normal. That's been shown in animal models pretty repeatedly and in many different animal models that while the outer hair cells remain intact, the disconnect between the inner hair cell on the auditory nerve fiber does not recover. That's lost immediately after exposure and then does not return, leading to this cochlear synaptopathy.

The other model that I'm going to be talking about is inner hair cell dysfunction in chinchillas. This can be caused by the chemotherapy drug carboplatin. This is also used in humans. But chinchillas are special in the sense that if you give them a mild dose of carboplatin platinum, it will induce only inner hair cell dysfunction. So it's a really nice way to be able to Isolate the one particular pathology.

In addition to actually destroying some of the inner hair cells, at our dose, it destroys about 5 to 10% across the frequency range. It also damages the stereocilia. So even the hair cells that are remaining are not likely to be functioning at full capacity because the stereocilia that are required for sending that neural impulse through the inner hair cell into the auditory nerve nerve are damaged. And so in this case, we have two different mechanisms of loss and two different dysfunctions. But in both cases, they would have a normal hearing audiogram or not a whole lot of change on that.

I want to show you some of what we did here. Again, coming back to this precision physiological biomarkers. We tested a range of biomarkers that are believed to be sensitive to some of these

different pathologies. So we have abr, we're using animals, so we're going to use ABR thresholds as a proxy for the audiogram. We have DPOA eves, we have efr, which is the envelope following response.

So it's the response to a longer stimulus. And we can look at how the response of the brain stem really locks or synchronizes to that stimulus. We use a high level click ABR to look again at neural synchrony, looking at a few other measures like the middle ear muscle reflexes and some different types of otoacoustic emissions. But I'm not going to show you the data on that. There is a lot of data for this particular study, so I'm going to keep it a little bit more narrow.

We measured all of these on each individual animal, both before the exposure and then after the exposure.

Really, to answer the question of which, if any of these measures can detect which animals have the hidden pathology, we want to know, are you normal or not normal? And secondly, do any of our measures help to differentiate between the two groups? So in many cases, if your drug targets specifically cochlear synaptopathy, but you have inner hair cell damage, it's not going to help to try to repair those if the hair cell itself is dead. So knowing and being able to differentiate between these two pathologies is a super important step as far as individualizing treatment goes. And so what I'm going to show you here is a comparison of the results between animals that have totally normal hearing.

So this is, I think of this as my clinical style approach to the chinchilla work, where I have 21 chinchillas that walk into the clinic with normal hearing. I have nine chinchillas that walk into the clinic with Inner hair cell dysfunction. And eight animals I'll show you that have cochlear synaptopathy. And so here's the results from, from each of those measures. So I'll kind of walk through, through this.

So the first step, we have the audiogram. These are ABR thresholds. So closer to the bottom of that graph is better hearing. Most of our animals from, from any of our studies tend to have thresholds that

are around 30 decibels. To about 15 decibels is pretty much the normal hearing range for our animals.

You can see some that have a couple thresholds that go outside of that, but generally about 10 to 30 decibels would be the normal hearing range. What you can see is on average for these three groups, both the pathology groups and the normal hearing group, they pretty much all fit within that normal hearing range. We do start to see a slight difference at the 8kHz point with the normal hearing group somewhat in the middle. These particular animals in the synaptopathy group somewhat better at 8k, and the carboplatin group, which has the inner hair cell damage somewhat worse. So there's a little bit of separation there.

But if any of these individual animals came in or if they were people that I was doing a hearing test on, I would say all of these are essentially normal. And this is really confirmed when we look at the DPOE amplitudes. So if I was just doing OAEs, all of these animals have really highly overlapping OAE responses. You can see chinchillas give us really robust OAEs. We often have measurements, measurements up to 40dB or so, but we see a nice strong response in all three of those groups.

And there is no significant difference at any frequency here between those. So these measures that are sensitive to outer hair cell function really aren't giving us a whole lot of information about what's going on beneath the surface here. So for the envelope following response or the efr, what we have, what we're using here is a rectangular amplitude modulated stimulus stimulus. And so what this is, is it's a sharp on and off of a tone. Sounds very buzzy.

And the stimulus itself looks a lot like the, the little inset figure that you'll see here. And so you get these nice sharp peaks where the stimulus goes on and then a little bit a reduction in the response when it goes off. And those peaks, each of those is tightly correlated to the stimulus itself. And in our case it's a 1 second long stimulus that has 223Hz as frequency. So the stimulus is going to turn on and off 223 times per second.

And then what we see when we look at that in the frequency domain, so that's what's plotted in the bigger, with the big peaks themselves, is that at both the fundamental frequency at 223, you get this nice large peak in the response. And then for each of the harmonics, those first eight points there, or those next seven points eight total, you see also little response responses too. And so what we can do to get an idea of the overall magnitude of the response is we can simply sum up the height of each of those peaks to give us an overall estimate of the magnitude of the response. And so what we see here is in the black. So I'm going to start on the far right.

In the normal hearing group, they have an EFR magnitude or the sum of each of those peaks at around 0.75. And that response is greatly decreased in both the carboplatin exposed animals and the TTS exposed animals. So the both of the disordered groups show an average difference compared to the normal hearing pathology group. And so that gives us some evidence that the envelope following response in this EFR magnitude that's calculated as those peaks can help us to predict and detect who is normal and who has some sort of pathology going on related to the interhea. What it doesn't show us though is if there is a difference between the carboplatin and the TTS group.

In this case, it's able to detect that they're not normal, but there's really no difference between the two other pathology groups. Next. And the last individual measure I'll show you here is differences in the ABR response to a high level. Click. These look a little bit different than human abrs, but you can still see this nice peaky response response that happens over a pretty short time range to this high level stimulus.

And at those little triangles, what you're going to see is the wave one around a millisecond and a half or so, and wave 5, that's closer to about 5 milliseconds. And in the gray line there is going to be the normal hearing animal or this particular animal before the exposure. And then in the blue line is the animal after inner hair cell dysfunction. And you can see that there's a slight latent shift shift as well as

the overall amplitudes have decreased slightly. And so what we see when we look at all of these different groups is that again, normal hearing has a decent wave five amplitude of about one and a half.

And in both cases of the pathology group, we see a reduction closer to about 1 microvolt. And so we do see quite a decrease of this. So again, the ABR seems to be sensitive to these pathologies, but the two groups are similar, so we're not really differentiating between those. The other piece I want to draw your attention to is that what normal is can really be highly variable. So these are different animals here, but some of those animals have wave 5amplitudes that are as small or smaller than some of the other pathology groups.

And so really, this is a tough measurement because there's so much variability even within the normal hearing group, that to define one particular cutoff for normal or not normal is going to leave you always with a little bit of crossover between those groups. So it's kind of hard to have one single threshold for normal or not within a given measure. Okay, so my goal here, though, ultimately is to be able to classify the animals according to their different pathologies. And so what we have plotted here is a confusion matrix. So along the X axis here are the different colors, groups that the animals actually belong to.

And on the, the Y axis here was what was predicted. So the important part to draw your attention to, you can really just look at this diagonal from the top right to the bottom left, and any numbers that are in that particular diagonal would be correctly classified. So if I give my classifier just the ABR 8K threshold, which we did see some difference between the two groups there, it does an okay job of. Of this. It gets about 24 animals correct out of, I think the total is 31.

And so it gets it. Or I think it's 38 actually. So it gets some of them correct, but definitely misses some. And it is able to differentiate between all three groups. So it does make some prediction that some of these are carboplatin, some of these are TTs, and some of these are normal hearing.

But it's, it's good at knowing when normal is normal generally, but it's not as good about knowing when pathology is pathology. If we look at the EFR magnitude response, we'll see again, it got some of them correct. So it correctly identified 18 of the normal hearing animals, correctly identified 4 of the carboplatin animals, but it didn't label any of them as tts. And I think this is an important finding that relates to the data we just looked at where it knows that something is pathological. It can identify that it's not normal.

Normal, but it has a hard time differentiating between what type of not normal it is, because you can have pretty similar responses across those two pathologies. And so that's, that's really kind of what's happening here. And you, so you don't get any labeling of the other pathology group. It's just saying normal or not normal. If you look at the wave 5amplitudes, we see exactly the same thing.

So it's about just as good. You get about the same number of accuracy, but again, it's not good at identifying long normal versus not normal. So what's another approach that we can use to better classify this? And sorry, it's a little light here. The colors got a little swapped.

But the best accuracy of these groups was 24 correct out of 38 animals, which is an accuracy of 63%. And that was from the ABR at the 8 kilohertz threshold. So 63% is okay. That's better than half. It's better than chance, given that there's three groups, but it's not, not great.

So can we do better? And the way I would suggest is that perhaps we can combine across multiple metrics. So if we have all three of these responses, can we combine the responses to get more information on a given animal? And that seems to help quite a bit. So here I have combined the auditory brainstem response threshold, the wave 5amplitude, and then this is a slightly different measure of the envelope following response.

It's the phase locking or how. Well, it's the, the response itself is related to the stimulus. So how, how much those two things correspond. And if I give it these metrics, which of all my metrics seems to perform the best? We get many, many more correct.

And you can see that there's really this dark blue diagonal this time where it's identifying correctly almost all of the normal hearing animals. 19 out of 21 hearing here. In the carboplatin group, it correctly identified at 7 out of 9. And in the TTS group, it correctly identified 5 out of 8. And so this accuracy was 31 out of 38 animals total for an accuracy of 82%, which is much better than any of those individual measures alone.

So this gives me some evidence that I think the, the approach we need to be taking if we're trying not only to detect whether something is normal or not normal, but to subtype it and tell what type of not normal it is, we're to need more than one measure to really be able to differentiate up between these things. And this example here is just animals with Hidden pathologies. If I take into account all the range of pathologies that are, that our patients are likely to have, where it could be any number of those problems and in different amounts and at different frequencies, to really survey all possibilities there, we're going to need a lot more data, and we're going to need to look across perhaps even more metrics than this. All right, so now the question really is, how does all of this translate to humans? And can we use some of these same measures to give us more information about humans?

And so I want to come back to, to where we started with these three individuals that all have similar audiograms. The mild, moderate high frequency hearing loss. And just to remind you, the purple person said no problems at all. They had a normal quicksand score, and then the orange person had lots of difficulty and a very, a very high quicksand score. And so what happens with just the autograms?

We're sort of going to give all of them roughly the same treatment or tailor that based on what their personal report is. But can we get more information? So let's start to use some of these other

biomarkers. So the first one that I think is perhaps the most readily translatable, if you have the right headphones, is measuring the extended high frequency frequencies. So if you test frequencies above 8 kilohertz, we start to see some differences there as well.

That's a little bit more distinct than what we see in the standard audiometric frequencies. So the person who reports no problem has much better extended high frequency hearing loss than the other two do. And then if we look at some of these other metrics, so again, we have otoacoustic emissions, the outer hair cell one sort of more in. In the middle there you have the EFR to the rectangular amplitude modulated stimulus or the ram. And if you look responses at those different harmonics, you see the purple person has the highest total response compared to orange, which has the lowest total response.

That corresponds with our intuition that you have a stronger brainstem response. That's better neural encoding of sound. You should have better speech perception. That's exactly what we see in this individual. That the purple person has much less difficulty than the one in orange.

Then lastly, that we're using the wideband middle ear muscle group reflex, but in theory should hold up too for other forms of the middle ear muscle reflex. But these individuals that have similar audiograms do show vast differences in the middle ear muscle response. So they tend to have some response at higher levels. You can see some change in the absorbed power at the highest level there for everybody. But the person in orange has a much lower overall response response compared to the person in purple who has a pretty strong response overall and would have ultimately a much lower threshold.

And so these kinds of differences are correlated with our intuition about who would have the most trouble. So if the middle ear muscle reflex is mostly responding to the, the damage either from the neural system or from cochlear synaptopathy, we would expect that people that have a poor middle ear muscle reflex are going to have more difficulty. And that's exactly what we see in our response. So I, I

think this is some, some starting point on the human side to show that there's some evidence that these types of measures are getting at some of the features that the audiogram is not likely to, that are going to help us to better predict speech and noise performance ultimately for our patients. All right, so in the last couple minutes here, I just want to talk a little bit about what we're going to be seeing in the future here.

I'm going to start off with sort of the bad news and that's the bar that we need to start overcoming to really be able to implement some of these tests. And that includes things like managing our test time. The difficulty with arguing for a multimetric approach is that it's going to take longer because you have to do more measurements and so starting to think about what we can replace, what's the tests that are giving us the most value for the time that they take. There's a lot of work coming out of Matt Fitzgerald's lab at Stanford about the benefits of using a speech and noise task like the quicksin over traditional word understanding and quiet. You can get the same information as far as ear asymmetries detection, excuse me, of things like vestibular spinoma with a speech and noise test.

But you also get the added benefit of really understanding and addressing the issue that brought the person to your clinic in the first place. Regardless of the test time that we might have as audiologists in the clinic, other situations may have more time. So things like clinical trials are still going to really benefit from having this type of diagnostic approach and other types of research settings, which will help hopefully ultimately help us to better understand the changes that occur with hearing loss equipment. Things that I mentioned related to measurement precision and the forward pressure level calibrations are mostly only available in research settings currently. So having the right equipment and access to that I think is something still we're kind of waiting to happen in the clinic.

And I think a bigger problem for us and kind of the mentality we need to start thinking about is letting diagnostics go hand in hand with treatment and keeping up with diagnostics, even if the treatments

aren't all there yet, to start really pushing on that so that when the treatments are ready to go, we are too, and that we can match the diagnostics with the treatments together. And like I mentioned on the human side, and given all of the different pathologies, there's really a need for big data ultimately. And so that'll be some standardization of clinical data as well. All right, last little bit here. Some of the exciting, novel treatments that I think are really cool ways that we can see this in the future.

We are already seeing things like gene therapy and the great success that they've had with genetic issues like otoferlin deficiencies. Pharmaceutical drugs that are going to target specific mechanisms of hearing loss would really benefit from a lot of this and help us to tailor our treatments to individuals. Things like hair cell regeneration. Knowing who has the type and the particular. The particular damage that's going to require regeneration of the hair cell, I think is super important.

And I want to explain a little bit about some next generation hearing aids that are being worked on because I think it's a. It's a pretty cool approach. So rather than just using the traditional gain settings of the hearing aids, you can use a model of the peripheral auditory system and compare the normal nerve out output from your model of the auditory system to the impaired peripheral model of the system. So this would look a little bit like taking your sound, putting that through your normal model of the periphery, and then looking at what the normal nerve output would be, also then taking that sound, putting it through some personalized processing, looking at how that goes through the auditory periphery that's impaired for that individual, and then getting this impaired nerve nerve output and then comparing those two. So if there is a lack of a response in the impaired nerve output relative to the normal nerve output, you can then have some feedback that goes back to changing the personalized signal processing so that you can more closely match the output of the impaired nerve to the normal output.

And this is a cool way to really fine tune and tweak hearing aids based on what the individual's impaired periphery would be. But this does rely on knowing what that impaired auditory perfilia looks like so that you can change that in your model. You need to know if you need to damage the outer hair cells or the inner hair cells, or what combination of those things so that you really know that you're getting the right impaired nerve output because that's not something you're measuring directly. This is done by modeling. But I think is a.

Is a really cool approach in a way that we could think about how we might program hearing aids in the future is by putting these different settings in, not, not just for the audiogram, but the percentage of loss of these different pathologies and manipulating that so that we can try to match the output of the auditory nerve to what it normally should be. All right, so just to summarize here quickly, and I'm happy to answer any questions that you might have put in the Q and A during this or at the end, but I hope your main takeaways here is that sensorineural hearing loss is a complex pathology that's the result of a lot of underlying combinations of pathologies that leads to variable outcomes in our patients. Concepts from precision medicine can be used as a framework for helping us to address this issue. Multimetric approach really is going to be critical to this because there's so many different types of pathologies and we're not just trying to detect them, but to differentiate between them when they come to the clinic. We're going to need more than one measure for those things.

And lastly, that these improvements in diagnostics and our adoption of them in the audiology clinic is what's really going to open the door to new treatment strategies for our patients. Just want to take a second to acknowledge the people that have worked on this. My PhD advisors, Michael Hines and Hari Bharadwaj have really helped me to formulate all of this and Andrew Sivaprakasam, who helped me with a lot of the data collection as a fellow PhD student. And of course this work is made possible through funding from the nih, particularly our institute, the nidc. And I'm really grateful to have that funding and hope to to continue this work.

So thank you so much. I am, I'm happy to take any questions. I'm going to open up the the chat here and let's see or the Q and A.

So Alexandra says great talk. It seems like there could be substantial changes to audiology coming. How do you recommend current audiologists stay up to date on the research based being completed and advocate for being able to complete a multi metric approach in a busy clinic? I think this is such an important question and I think is something that regardless of what the research is, we struggle with this. Having access to research papers, being able to read and interpret research papers, particularly basic science I think are total challenges.

I think there's a lot of great avenues that we do have. Things like this, like audiology online, where you have access to different kinds of talks and starting those conversations. I think the. The thing related to that as well is a little bit of self advocacy and belief on the audiologist part that you absolutely can reach out to researchers as well. And so a lot of the times as a.

When I was in the clinic, I would try to read a paper. I remember a particular patient, it was a pediatric hyperacusis, this case. And I really did not know what to do for this. And I tried to research the papers for this and everything was locked down. I could not have access to any of it.

And so I just emailed the professor who wrote the paper and he sent me like 10 different things and we had this great conversation about kind of what I should do in this particular case. So not being afraid to reach out to researchers. And I'm happy to help facilitate any of that as well if there's something I can. Different conferences are of course, super useful, kind of getting out of your comfort zone. Maybe in other conferences like aas that have a little bit more of a basic science focus, I think could also be really useful.

But there's a lot, and I think audiologists need to stand on that. We really own this field and not let the change just happen to us, but to go after it and to really take ownership of it and to know that this is our domain and not just wait for the diagnostic test to be handed to us, but to start to think about these things and be ready to incorporate it when they are. Thank you so much, Dr. Hauser. That looks like the end of our queue.

Great. We have another comment from Maria. Maria just says congratulations on the excellent presentation. Thank you, Maria. Than.

Thank you. Well, Dr. Hauser, can we have you advance that final slide? This is just a reminder for our members who wish to earn CE credit to complete the multiple choice exam that'll populate shortly after the course has concluded. We'd like to take this time to thank you again for your time and your expertise, as well as the University of Pittsburgh for putting on this presentation in partnership with ao.

Have a great day, everyone. Great. Thank you for having me.