Ménière's Disease Symposium
ARO MidWinter Meeting | February 21, 2025

TRANSCRIPT IN FULL

- We are going to start in about four minutes. Can you just put some captions up on the screen just so we can make sure it's good. Thank you. Yep. All right, we're good.

- Hi everyone. Ooh, that's really strong. We're going to get started here in just a minute. So can I ask the the first session speakers to come and join me on the podium? And we're also going to hear from one of our sponsors of this fantastic event to kick us off. So we're going to get started in just a minute. Thank you.

- Heather. Hi Heather.

- We good to go? Yeah. Good afternoon everyone. My name's Timothy Higdon and I'm the president and CEO of Hearing Health Foundation. And I want to welcome you to the Ménière's Disease Symposium. This is a program that has been in planning and thought for quite a while and we're really thrilled to have all of you here. I want to take a moment to thank our sponsors. Spiral Therapeutics and Scott Dorsey have sponsored the the symposium. Our co-hosts are the American Hearing Research Foundation, Cures Within Reach, and the Vestibular Disorders Association, and we've been working together for I think about nine months to pull this together. I also want to take a moment to thank a couple of our Ménière's disease major donors that have really supported the research. Cary Kopczynski, who's here, the Salice Family Foundation, and Karen Coley. And I also want to acknowledge a couple of the HHF board members who are here, Paul Orlin, Judy Dubno, and Cary Kopczynski. So there are two sessions this afternoon and a reception that will be in the back afterwards. Everyone should have gotten a drink ticket for that. And at the end of this of symposium, there'll be a QR code where we'll ask you to, well, the QR code's right here. Please fill out the survey and let us know what you think. So without further ado, we'll get the symposium started. And thank you so much for coming.

- Hi everyone, my name is Clare Thibodeaux. I am the Vice President of Scientific Affairs at Cures Within Reach. We are so excited to be with you here today. I think we're going to have a really great symposium to talk about Ménière's disease from clinical applications to research. And to get us started, we're going to be hearing from a Ménière's disease patient. Cures Within Reach began funding research in this space in about 2018, and we've really seen that this is an area that needs a lot more research, that needs a lot more attention. And we're really pleased to see everyone here who shares that belief and is as interested in solving Ménière's disease as we are. Again, I want to thank Hearing Health Foundation and the American Hearing Research Foundation for really being the driving force behind this, behind this symposium today. So we are all here because we want to help patients who have Ménière's disease who suffer from this condition. So I think it's only fitting that we begin our symposium today by hearing from a patient, Heather Davies, and hearing her experience and perspective. Heather?

- Thank you.

- Imagine the sweet chatter of your 3-year-old daughter's voice penetrating your ears with such painful intensity. You have to wear earmuffs just so you can tolerate being close to her. Imagine your hearing begins to fluctuate in one of your ears and in the roaring hissing tinnitus in both, knowing all too well what comes next. The uninvited visitor vertigo. Within moments of thought you're on your knees gently guiding yourself onto your stomach and finally resting yourself, your face on the hardwood floor, one hand outstretched in front of you as if to stop the never the sensation of a never-ending fall. Your eyes fixated on one spot today. It's a spot far underneath the entertainment center. Your eyes fixated on this without breaking your gaze. You move your hand backward and breathe a sigh of relief. Your daughter's found her way to you after all, this is a game she's played daily for nearly six months. Your back stretched arm cradles her against your waist and she's content playing with her Olaf, stuffies and dinosaur on your back. As you breathe a sigh of relief, she's unaware of the torment you're experiencing as a wave of nausea comes over you, you're exhaling slowly, not blinking, not moving, praying the vertigo passes quickly and takes tinnitus with it. As you remain calm, slow breaths you, questions pass your mind, is the stove off? Is the baby gate locked? The spinning's faster now and you're just praying to God that it stops your eyes still fixated on that one spot on the wall as you fight back tears. No, not the tears. You start your mantra. I'm safe. I'm steady. Inhaling now you breathe in, calm, exhaling. I release fear over and over to remain in a place of peace knowing that this will pass. Imagine this lasting for two hours, four hours, sometimes six hours or longer. I don't have to imagine this insane reality because I lived it nearly six months in 2016 and '17. My name's Heather Davies and this is just one of many stories that I have living with Ménière's disease. Today I am an ambassador at VeDA and host of the Ménière's Muse podcast where vestibular warriors come on and share their very honest stories living with Ménière's disease, obstacles they've overcome and ones they continue to live with on a daily basis. I was living a very full life when Ménière's burst into my world. I was stepping into my 18th year working as a psych nurse, running fitness groups while also caring for my 15-year-old son and 3-year-old daughter. I had no white space on my calendar and yeah, I was burning the candle at both ends. I began experiencing some numbness and tingling on this on my head that went down my face and I just pushed it off as stress. I'll deal with it. And it continued to happen and I promised my mother if it happened again, I would go to the emergency room. Well, it happened again after many tests, they came back and told me I had a brain tumor, which that's all I heard after that. Brain tumor. Although I was initially fixated on the meningioma being the cause of my symptoms, I just knew it was the root. It turns out it was just an incidental finding. So off we went to figure out what was going on with my body. We visited over a dozen doctors, various specialties, but it wasn't until I went to a multidisciplinary clinic where I was finally diagnosed with Ménière's disease and vestibular migraine. So once the beta blockers and diuretics began lessening the vertigo, I attempted to return to work with accommodations. I was unable to drive, so I had to be escorted to my patients' homes and I worked as a psych nurse. So I gave a lot of long-acting injectables. I began to question myself, second guess and triple guess myself, to the point it simply wasn't worth the risk for my patients. So I stepped away from nursing and I lost myself completely. I lost complete confidence in myself. I didn't know how to be anybody that wasn't a nurse. Been doing it for so long, I lost my complete identity in between doctor's appointments, I would spend my

day cooped up in a dark room, sorry, I apologize, I didn't get many visitors. And I had a visitor one day, a friend came into the darkness and she sat on the side of my bed and she said, I don't know what's going on with you. I'd like to understand, but it seems like you've given up, so maybe you should start dreaming another dream. Those words hit me so hard. So as I watched her leave, pulling the door closed behind her, those words hit me hard. Dream another dream. I never thought of the dreams that my husband and I built together never happening until very moment. So that thought never crossed my mind. I never thought of this disease taking our dreams from us. Her words landed like a gut punch and it, but it also shifted something inside me raw and unyielding. And it made me want to figure out how to live my best life with this disease. So, so the journey started and I was determined to live my best life regardless. Our dream was to wait till my son graduated, buy a sailboat, sell our home, 90% of our belongings and set sail. So in the wake of my friend's statement, I realized I had to figure out and make that happen. So the the journey began, it was one of deep self-reflection, taking a step outside of myself and looking at the bigger picture, how I was living my life and how I could make the best of what I was dealt. I was working a full schedule with barely getting five hours of sleep a night. I rarely listened to my body, so I had to figure out how to trust myself again. And so the reinventing began. I began to mourn my previous life while learning to navigate a new one. It is one with less rigid schedules and a more of a go with the flow mindset. It's balancing hope for the best while also planning for the worst. And I still do that today. I began making changes spiritually, physically, mentally, and nutritionally. And I started to regain control of my life. If I have a bad day, I will go outside and if it's doffing off our bow or birds singing or simply the sun on my face, and I remember those little glimmers of hope and that life is still good despite the symptoms. There are so many Ménièrians with heartbreaking stories in the time that I've been diagnosed. One in our community has taken her life and two others have attempted theirs. And these are just friends that I know of. And but these two ladies are now with the support they've received in the vestibular community are strong voices. And I must say that one of the most powerful aspects of navigating life with Ménière's is the sense of community that you get from all involved. I had the privilege of collaborating on a project called Dear Ménière's. I don't know if any of you have heard of this book. There are hundreds of letters here to Ménière's and there are photos of artwork that all Ménière's patients have contributed to this book. All proceeds do support Ménière's research. It is, it is raw, real, and heartfelt. It is not for the weak. It is a beautiful book, but there's a lot of emotion inside of this. Early in my journey, I was searching for reassurance. What I needed to know was hope. I needed hope in order to move on. And while walking one day and listening to a podcast, I wondered if I could do this. I wondered if I could create a space for vestibular voices, for people to share their stories, obstacles they've overcome and once they continue to live with. And that's when the Ménière's Muse podcast was when it started. A lot of the guests have left corporate jobs to find themselves, to coaching vestibular warriors to live a normal, as normal life as they can. Others have created apps for the community, but it's through that share, that shared vulnerability, laughter, and tears that we're able to move forward and chart a course toward hope for ourselves. Listeners are finding strength in knowing they're not alone. And that's what a lot of us need is to know that we aren't alone. And to that, to hold onto hope. I've expressed many times in the podcast that Ménière's has been both a blessing and a curse for me. A curse being the physical and emotional pain, the loss of my independence, the impacts on my relationships, and of course my career and the

uncertainty of it all. A blessing which cannot be found in the depths of the darkness through greater self-awareness, stronger connection, advocacy, and and the purpose and supporting others. A common thing among vestibular warriors are those tiny blessings, those little glimmers that you can find every single day, whether you're having a good day or not. Just the tiny little ones that make it all, all worth it. This is not of course to minimize the bad days, but when I was diagnosed with MD and VM, my world quite literally turned upside down. I lost my balance, my sense of control, and often my hope. But along the way, I also discovered a resilience I didn't know I had. I found a community of people who helped me navigate this uncertain journey. This illness is undoubtedly a curse. It's relentless, unpredictable, and isolating. But in the darkness I did find light. It pushed me to connect with others, to advocate for awareness, and to find meaning in those small victories. It became a catalyst for my personal growth and deep empathy. The research, the research that you do, the treatments you develop and the hope you give is part of that light for people like me. Your efforts remind us that while we may be navigating an unsteady path, we are not alone in seeking solutions. Your work isn't just about curing symptoms, it's about giving hope. And I hope each of you realize that every patient you see, every study you complete, every small advance in understanding brings us closer to a life where we can embrace the blessings over this curse. So I stand here today as proof that while chronic illness takes, it also teaches. And with your continued dedication, I believe we can turn the tide creating a future where blessings far outweigh the curse. For everyone navigating this journey, I thank you for your dedication and for being a part of this journey with us. Thank you.

- So we have a couple minutes for questions. If there's anybody in the audience that has any questions for Heather today, we have mics in the center. Please feel free to to go to the one of the mics if you have any questions either for Heather or for any of our other presenters.

- I have a question.

- Do I have to push something? I think so. Yeah. No, it's not working. It's working. Heather, one of my patients gave me that book. It's actually a pretty good book and it has a lot of good testimonials in it. I have a question for you. What symptom was the most affected most your quality of life? And is it the hearing the balance, both? And if you were to choose one to get rid of, which one would it be?

- Honestly. Honestly, once the vertigo, the vertigo of course, but the hyperacusis is my most debilitating. Having a 3-year-old now 11 where I couldn't, I was unable to tolerate being close to her. That was the hardest. And aside from the vertigo, yeah, the hearing loss I can deal with, you know, but it's, it's really all a matter of perspective. I really believe that. I know that my, my hearing is going, it's just something I'm going to have to deal with. And, but on a day-to-day basis, if I were to ask for one thing to be gone, because my vertigo's not constant anymore, is the hyperacusis.

- Thank you. I think, I think we have a question in the back.

- Thanks, Heather. I have a question for the audience. There was 211 people here that were signed up. Anybody here raise, raise their hand to say whether they have Ménière's disease or not?

- I didn't understand. Yeah, I didn't hear it. Couldn't quite understand that question.

- The question is, is that how many people in the room have actually got Ménière's disease?

- Oh, who have Ménière's disease.

- Heather, I think that's a very, very brave thing to do and I would like to thank you for that.

- Thank you. And I can't hear but okay. Who has Ménière's disease? Yeah, sorry. Yeah, it's, the question was who here has Ménière's disease? Any other questions for Heather before we move on?

- Oh, thank you.

- Well Heather thank you very much for sharing that story, your experience. Very powerful and I think a great way to frame the rest of our discussion today. So next up we have Robin Bigelow, who's going to talk about the, Dr. Robin Bigelow, on the history of Ménière's disease to give us some historical perspective.

- That's very good. Thank you. Good afternoon everybody. Thank you for inviting me to speak here and thank you for sharing your heartfelt story. It's a important reminder of why we're all coming together today and what we're working towards trying to help people suffering. And today I'm going to be talking about the history of Ménière's disease, looking at different surgical management strategies for Ménière's disease that have been tried in the past 150 years. I have no relevant financial disclosures. The objectives, I'm going to talk about some historical accounts of individuals who may have had Ménière's disease, a brief history of Prosper Ménière and reviewing a kind of timeline of different surgical therapies that have been trialed for Ménière's disease. A couple early descriptions of Ménière's disease. This first one is about Martin Luther, who was famous for the 95 Theses in 1527. He described having roaring tinnitus in the left ear and a state of sickness and collapse, followed after a night's rest. All the symptoms subsided except the tinnitus. Similar attacks with increase of the tinnitus and vertigo ceased him at irregular intervals and distressed him extremely. He thought that the devil was chasing him and he was so frustrated. He was known to throw his inkwell across the room. Sounds like a possible description of Ménière's disease. Another notable historical figure possibly had Ménière's disease is Jonathan Swift, a famous author from the 18th century. He said, I got my giddiness, then I got my deafness. And these two friends, one or another have visited me every year since. And being old acquaintances have now thought fit to come together. Descriptions of vertigo have been present in medical literature as far back as medical literature exists in Egypt and Greece and Rome. Dizziness and vertigo have been thought to be due to a seizure or stroke related to changes in blood flow in the brain. Previously that was until

Prosper Ménière came around. He was born in 1799 in France and after medical school was eventually appointed as the director of the Institute for Deaf Mutes in Paris despite having no prior training in otology. He died in 1862, just one year after his famous contribution to otology. He was a bit of a Renaissance man and had many interests outside of otology and medicine. He published multiple papers about orchids and was a lover of the opera and literature and also published on the historical understanding of medicine from Greek and Latin poets. His landmark presentation for which he's famous for was in 1861. He presented to the Imperial Academy of Medicine. He argued that vertigo and hearing were linked to each other and could result from inner ear disease. This was a dramatic departure from the previous understanding of vertigo as related to problems in the brain. As evidence he described several cases of vertigo and hearing loss happening after penetrating ear trauma. There was a young girl who had vertigo prior to passing away. And on autopsy they found blood in her labyrinth and in her ear, but none in her brain. He described a symptom complex, which is now known as Ménière's disease, and saw a number of patients who experienced fluctuations in hearing loss, tinnitus and dizzy spells. And he described how after the hearing was gone and the fluctuations decreased, patients no longer seem to experience vertigo, which is similar to how we think about Ménière's disease often burning out. This quote will lead us into the next section talking about treatment for Ménière's disease. The number of treatments available for a condition is inversely proportional to the success of those treatments. I first heard that from Derald Brackmann, a giant in our field, and I think it's appropriate in Ménière's disease. We have over the past 150 years tried many different things and currently there are many different treatment options available and none of them are especially successful in everybody. So what did people get in the time of Prosper Ménière? Medical treatments included quinine, dyspeptic treatments and iodine of potassium, as well as taking Turkish baths or being exposed to sulfur water. Procedural treatments included bleeding or leeches, a seton to the neck to produce pus to balance the humors or moxa, which is an ancient Chinese remedy of burning cotton and placing it close to the skin to balance heat and cold. Menière himself didn't much believe in these treatments and said it was to paraphrase kind of a travesty. And often the treatment was worse than the disease. Looking at the medical literature moving forward, one of the first major textbooks principles in practice of medicine by William Osler in 1900, not many changes, he still recommended iodine, potassium, salicylates and quinine. Another textbook from the early 1900s by Edward Dench recommended bloodletting. Considerable blood should be abstracted from the mastoid region by means of a wet cup. Bloodletting is permissible when the attack is of unusual severity. Wet cupping is making a cut in the skin and then putting a negative pressure cup to draw blood out. A number of early surgical attempts at Ménière's disease are summarized here. Parry divided the eighth nerve intracranial by a middle cranial fossa approach, often leading to facial paralysis and several mortalities. Crockett removed the stapes, which led to deafness. Milligan and Lake opened the semicircular canals and instilled an antiseptic and early attempted a labyrinthectomy. Babinski, famous for the Babinski reflex among many other advances in neurology, advocated for lumbar puncture and said it was moderately successful. Jenkins would decompress the horizontal semicircular canal and similarly said it was moderately successful. Another text from the time, 1914, by Ballenger recommended pneumomassage or suction of air in the ear canal. This relieves pressure upon the footplate and can be performed by placing a rubber tube from the mouth into the ear canal and sucking and blowing intermittently. This idea

lasted for many decades and actually led to the development of the Meniett device, which was used several decades ago and fell out of favor. And another textbook, Dr. Ballin recommended cold compresses, sponge baths and early mention of the importance of diet in managing Ménière's disease. He recommended avoiding alcohol, tea, and coffee. He injected potassium iodine into the tympanic cavity through a eustachian tube catheter and electric treatment to the head. Electricity was used for a number of different medical treatments at the time, and it was kind of in vogue and used in most medical disciplines. They would instill low current electricity across the head and it was said to be moderately successful. Portmann in 1926 had the first description of an endolymphatic sac surgery. Here's some diagrams from the original publication demonstrating a mastectomy being performed with a gouge. The surgical steps are similar to how endolymphatic sac surgery were performed for until today with decompression of the sigmoid and posterior fossa plate. And Portmann advocated for opening the endolymphatic sac with a needle. Walter Dandy, who was a famous neurosurgeon who had many contributions to the field, he advocated for eighth nerve section for intractable Ménière's disease. This was successful in treating vertigo episodes and hearing could be preserved in many cases. Bilateral nerve section led to Dandy syndrome where bilateral vestibular hypofunction, which can be fairly debilitating. And in his first 400 cases there was only one reported death. Interestingly, in his texts he described doing a suboccipital approach under just local anesthesia in the majority of cases, a little different from today. A number of other destructive procedures were proposed for treating Ménière's disease. Wright did a transtympanic, trans-oval window injection of alcohol. Mollison injected alcohol directly into the labyrinth. Cawthorn did a transmastoid labyrinthectomy. Goodyear opened the horizontal canal and scraped and cauterized the membrane and they did a similar procedure using electrocautery to neutralize the inner ear function. An interesting paper from 1948 advocated for division of stellate ganglion and sympathetic truck as well as the vertebral artery. The authors said, while it may be risky and potentially cause a stroke, the risks were low because most Ménière's patients were young and healthy. The other authors at the time disagreed with him. And the sympathetic neurectomy was popular for a number of years, but the medical literature appropriately did not support his advocation for a vertebral artery ligation. Several doctors in 1951 were doing the first tympanic injections. Currently we do tympanic injections of corticosteroids or gentamycin for treatment of Ménière's disease. Back then they were injecting cocaine, tetracaine and alcohol. They described patients getting severe dizziness 20 minutes after the injection. Medical literature was not as rigorous in its standards back then. I wanted to put the direct quote and picture of the results section of their paper here. It says, of the 37 patients selected for injection, good results were obtained in the majority and that's it. A frontal lobotomy was in vogue. In the middle of the 20th century, there's a case series of 20 patients who had tinnitus, many of whom were reported to have Ménière's disease. Frontal lobotomy is a procedure to destroy the prefrontal cortex. There was one death, eight people improved and 11 had no change in their tinnitus. There was a nice quote from this that I'll summarize where the authors described, the patient said the tinnitus was no better and she had behavioral problems and inhibition problems, but she was happy because it didn't bother her that much anymore. And the husband was happy because she didn't bother him much anymore. This is a nice diagram from Bryan Ward's paper describing several endolymphatic surgeries that were done in the 1960s. I encourage anybody interested to look it up, there are some interesting and clever ways that physicians at the time

tried to manage the dilated endolymphatic space that we know is responsible or at least a part of Ménière's disease. In 1962, William House described the endolymphatic shunt. This is the modification of Portmann's endolymphatic sac surgery before where the similar surgical steps were performed. And instead of just opening the endolymphatic sac, a foreign body was placed into the endolymphatic space to keep it open. He published on this a number of times and described good success. So how does Ménière's disease relate to the moon? Alan Shepard was the national hero when he was the first American who was sent to space. Unfortunately, two years later, he developed Ménière's disease and he suffered greatly. Medical therapy including diuretics and niacin were ineffective. He did his research and heard about Dr. William House and in 1968 had a shunt procedure done. Six months later he said he had no more symptoms and he ended up flying to the moon with Apollo 11 several years later. That concludes my very brief history of some of the surgical treatments for Ménière's disease. There are many more. If you're interested we can dive deep into the history. I think it's very interesting to look at where we've been in the past in treating this challenging problem. It puts in perspective, people back then were doing their best. Currently, we are doing our best. Fifty years from now we're going to look back at this time and think, why couldn't we do better?

- So we do have some time for for questions. Any anybody in the audience, if you have a question, please step to one of the mics. Or any of the fellow speakers up here please feel free to use your mics here for any questions.

- Everyone, so what are we doing today that you're going to include in this talk in 20 years?

- I mean, do we know will gentamycin work? If you ablate the inner ear that works, do we know how well oral steroids or intratympanic steroids work in a systematic way? I think anecdotally they certainly do. Same for diuretics or dietary change, I think anecdotally in individual cases, some people respond to certain things very well. But ideally if in you know in 20 years in 50 years we'll have a better understanding of Ménière's and we'll have Ménière's type A, B, C, and D and we can appropriately put people into the right category at the onset and figure out what treatment would work for Ménière's A versus Ménière's B.

- Any other questions? Thank you Dr. Bigelow. So now we have Dr. Habib Rizk who's going to talk to us now about maybe some more modern treatment options. Thank you.

- Good afternoon everyone. I'm happy to be here and talking to an audience that wants to listen about Ménière's disease. So I was tasked to talk about the current clinical care and standard treatments that we use and address the topic of potential unmet clinical needs. These are my disclosures. This is the outline of my talk. I'm going to review quickly the Bárány and American Academy criteria for many years. I'm going to talk briefly about the migraine overlap. We're going to discuss some of the care gaps and the standard and off-label treatment. And finally I'm going to talk about clinical trials and what we can do better to improve our research and find cures for this disorder. In 2015 the international classification of vestibular disorders changed a little bit and simplified the the diagnostic criteria for definite Ménière's disease, we know we now we use the following criteria of having more than two spontaneous episodes of vertigo lasting

between 20 minutes and 12 hours with fluctuating otologic symptoms within 24 hours of the episode, as well as an audiogram showing a mid- to low-frequency hearing loss in two consecutive frequencies. The 2020 Academic, American Academy criteria kind of followed the same format. They simplified a little bit of the very strict audiometric thresholds that were discussed within the Bárány consensus document and they issued two statements, one about using this current more modern criteria to diagnose the disease. But also statement three, which sounds self-evident, is obtaining an audiometric testing before making the diagnosis. And that speaks to how many patients sometimes carry that diagnosis and they've never had an audiogram. The other question that is asked, is there a role for imaging in the diagnosis of Ménière's disease? And in the guideline document it was an option to obtain imaging, an MRI. And while certainly an MRI of the internal auditory canal is an option in typical cases, something needs to be said about the advent of MRI hydrops and I'll leave it to my next speaker to talk about that. That could potentially close a gap in the diagnosis. When we look at what we currently do in clinic, most of what we do is has absolutely no evidence. I mean the guideline, recommend dietary and lifestyle modifications because it's a tool that has been shown to work with some patients. We don't have the evidence to support it, including with a very recent Cochrane database that was published in 2023. The same goes for the pharmacotherapy we use, whether it's diuretic or betahistine. The guideline issued an option for those treatments to be used even though we have a low quality evidence of the effect of betahistine on vertigo. And the most recent systematic review published with the Cochrane website in 2023 also showed that there's absolutely no evidence for oral pharmacotherapy. And it doesn't mean that it doesn't work, it means we haven't done the studies to prove it. And any clinician who treats Ménière's sees patients who improve. And it's hardly, it's kind of statistically impossible that all of this is just placebo effect if you follow patients long enough. So there's no evidence for the most basic of our interventions. And one other gap that we need to close is what is the outcome measure we need to use to follow and and to follow treatment success for future trials. More recently with the advent of the migraine overlap and the correlation with Ménière's disease, we started kind of, it's kind of an eye opener for a lot of clinicians about how prevalent migraine is in this crowd, even though it's been reported since 1861. And that seminal, our article from the Berlin otologic group, showed that Ménière's attacks can be accompanied by at least one migraine as symptom in almost half of the cases. So the guidelines issued by the American Academy committee was to assess for vestibular migraine as a recommendation. And you know, for this crowd it sounds evident, but I have ENT in my state that say we don't believe in the existence of vestibular migraine, you have Ménière's disease for example. So there, there's a lot of knowledge gaps that we need to bridge to understand that these are two potentially interrelated disorders and we need to make our best to do our best to differentiate them. So it's unlikely that this is just a coincidence. And there's potentially a causal link in certain types of Ménière's disease with migraine. And some patients fit clear diagnostic criteria for one or the other or both. And also if you follow patients long enough, some patients initially fulfill criteria for vestibular migraine and then a few years later, if you're still following them, they can develop a hearing loss in the low frequencies and you might need to change your diagnosis or add many years to the diagnosis. And this is not surprising when you look at the physiology of the endolymph, there's a lot of ion channels in there that are targeted by migraine medication. Most of the migraine prophylactic medications, the old school migraine medications, are sodium or calcium

channel blockers, which exist in in big density within the inner ear. There's also steroid receptors and beta adrenergic receptors within the inner ear as well as aquaporin receptors. And all of those can be found in migraine medications. And the migraine reaction, the autoinflammatory migraine reaction can affect the endolymph theoretically. This interesting paper was published by Dr. Lopez-Escamez's group and kind of started talking about those Ménière's subclassification that Dr. Bigelow was alluding to. And there's like five endophenotypes of Ménière's disease. The classic one, which fulfills the criteria that we talked about that has absolutely no gray area with it. There's the type 2 which we call delayed hydrops following a surgery or trauma or those other patients who had a sudden hearing loss. And then 20 years later they start having episodic recurrent vertigo. And there's type 3, 4, and 5 which seems to be more interrelated, the familial type, type 4, which has some sort of migraine history, not vestibular migraine, so a migraine history, migraine headaches, visual auras, satellite to the Ménière's disease diagnosis. And type 5, these are the patients who have some sort of autoimmune disorder. And more recently the the same group looked at vestibular migraine endophenotypes and identified five clusters. One with longer duration of vertigo attacks, one with absent migraine headaches and cochlear symptoms. And then group three and four they have cochlear symptoms during the vertigo attack or cochlear symptoms and headaches during the vertigo attack, which are almost impossible to differentiate from a probable Ménière's disease diagnosis. And only if there's an audiogram that shows the low to mid-frequency hearing loss can you say this is Ménière's disease. And the fifth group is patients who have classic migraine headaches and no cochlear symptoms during the vertigo spell. And the hypothesis is that vestibular migraine can present with peripheral symptoms and it could affect the labyrinthine artery causing a vasospasm of the labyrinthine artery which can lead to otologic symptoms or can strictly affect the brainstem, which can lead to those more central signs without otologic symptoms. And the question remains if we can differentiate the two pathologies. Are there any inflammatory biomarkers? Can we use imaging to differentiate between the two? These are some of the biggest care gaps that we have currently and there's a lot of groups looking to solve this. We know that certain types of cytokines are more represented in Ménière's disease, like interleukin-1 beta is highly prevalent. The group from Dr. Vambutas has looked at immune-mediated inner ear disease, which is almost, sometime, I mean bilateral Ménière's disease can be difficult to differentiate from autoimmune inner ear disease with vestibular symptoms. And they found higher levels of TNF alpha and interleukin-1. Our group published recently on a pilot study looking at cytokines differences between vestibular migraine and Ménière's disease, definite Ménière's disease. And we found higher levels of TNF alpha and interferon gamma and lower levels of ENA 78, which is an eosinophilic marker and this is at the resting state before any antigen stimulation. So there's a lot of progress to be made in this field so that we can understand what type of response and that if we solve this, not only can we create better diagnostic tools and biomarkers, but potentially therapeutic targets. So in clinic when you have migraine or vestibular migraine in addition to Ménière's disease, it's important to treat both. I would never proceed with any ablative procedure if there's any migraine feature that has not been treated or addressed. Many patients find that their attacks of Ménière's disease can be triggered by the same foods or dietary elements that trigger a migraine. So I put everybody on both a migraine diet and a low salt diet. Also for some patients sometimes the vertigo settles down but they still continue to have otologic symptoms. But whether it's

fluctuating tinnitus, or a fullness, hyperacusis, and these could be related to a type of neuropathy and can be due to a migraine response. So I would always consider migraine treatment for patients who have no more vertigo but continued otologic symptoms. The last part of that of what I want to talk about is what are we doing wrong from a clinical trial standpoint and why haven't we been able to identify yet any successful treatment, with all the trials that have been done in the past decade? We looked at 15 studies with various interventions, whether it's betahistine, the shunt surgery, the intratympanic dexamethasone injections. And we found that there's a lot of inconsistent reporting of the outcomes. There's a non-standardized reporting of outcomes and we found a high level of placebo effect. 52% of patients treated with the placebo had a reduction in vertigo symptoms for as long as two years. There was less prevalent effect on the hearing outcomes and it's kind of self-evident that the placebo effect affects mostly the subjective outcome measures. Placebo effect is more prevalent at short-term vertigo control, whether it's due to disease remission or the fluctuating nature of the disease remains to be seen. And other factors that can affect the placebo effect include patient characteristics, physician-patient relationship and the treatment expectations. We did our own study, a single center randomized double-blind study looking at venlafaxine, which is a serotonin norepinephrine reuptake inhibitor, to look at whether it can work on Ménière's disease using its ability to work on the aquaporin receptors. That was the theoretical concept behind it. This project was supported by the American Hearing Research Foundation and Cures Within Reach Foundation and we started that study, we recruited our first patient two weeks before Covid hit. So that study was supposed to take a year and a half. It took three and a half years to complete. But what is also interesting, we had a lot of lessons were learned from this study. First of all, our power analysis was for the sample size was based on a routine 20% placebo effect you see in most literature. If we had done it on a 50% placebo effect that we, you know, acknowledged with that systematic review in 2023, we would have had to double, at least double the sample size. We screened over the two and a half years of recruitment 182 subjects for eligibility and entered them into a four week eligibility window where they had to do a low salt diet and track their symptoms and had to have at least two episodes before getting into the trial. Some of the patients improved on the low salt diet once you had them, you know, do a good low salt diet, identify their triggers, they were able to manage their symptoms and they didn't feel the need, even though these were patients that were struggling by the time they got to the clinic, some subjects did not want to consider the trial because they did not want to risk getting the placebo even though it was a crossover design. And I'm glad we have a patient representative on the panel and because we have to always encourage those patients to consider since we don't have a cure or a standard treatment that works and everything is basically 50-50 in a way, even what we do in clinic, I tell patients this is a treatment that may work on you, it's 50-50 and going into a trial, if it's available you have a 50-50 chance of getting the placebo versus getting the the treatment. The duration of the study was five and a half months trying to account for some of the fluctuating nature. And both the placebo and the venlafaxine group had improvement of outcome measures, which was definitive vertigo days and DHI compared to baseline with more than 50% reduction in the number of episodes per month. Now looking post hoc at the study, some patients are still on the medication and refuse to come off of it. We prescribed it to them off-label after the study ended. But the question that remains is why aren't we able to find any treatment that has a good signal statistically that can be promising and it's has probably

something to do with the way we're designing those clinical trials and for Ménière's disease it might, we may not be able to do the classic double-blind randomized trial. First of all, it we might have to identify and study separately the multiple phenotypes. A Ménière's patient with migraine can be studied in a different subgroup than Ménière's disease class 1 or delayed hydrops or post-traumatic Ménière's disease. And given that this is a relatively rare disorder, that begs the question about recruitment and accrual of subjects and the need for multi-site clinical trials, longer follow up, which can lead to more attrition rate. But this is also another point where we need multi-site collaboration, standardizing the outcome measures to facilitate comparison between studies, trying to use objective measures to identify a true vertigo attack of Ménière's disease using remote recording rather than just relying on the patient saying they're dizzy because they can be dizzy without it being a true Ménière's attack. Objective identification of fluctuating hearing loss using smartphone applications and considering a a different design than the double blind, which is has been done in psychiatry and depression. The STAR*D design where a patient selects a list of acceptable medications that we use in real clinical setting, all patients start with the same medication and after a typical clinical follow up, if there are side effects or no response, the patient is randomized to a second tier medication with either complete switch or add addition therapy. So an example, and I'm finishing up on my talk of a tiered protocol for Ménière's disease, all participants could be started on a low salt diet and a diuretic. If improvement of symptom at month three, which we would do usually in clinic, you can continue a 12 month follow up if the symptoms, if the patients fail, you can randomize subjects to step two, you can switch to betahistine with escalating titration or add betahistine with escalation titration versus going to steroids or migraine preventive treatments. The STAR*D design for depression was open label and non-placebo control. We can even consider designs that include a placebo controlled arm. So in rare non-fatal diseases with no cure, clinical trial interventions are considered an equipoise compared to standard of care treatment. And I usually. it is ethical for the clinician to actively encourage patients to participate in the trial. And I explain to them that what we currently do is a 50-50 chance anyway. Once we design trials, better stratify patients, better improve funding, which sounds tone deaf by the day, you know, when I did the trial nothing was happening from an NIH standpoint. Standardize outcome measures, we may have a shot at solving this. Please consider applying for your grants to the ANS VeDA grant that looks at topics aimed at improving clinical outcomes for patients with vestibular disorders. The deadline is coming up soon. Consider sending your patients to those registry studies and I'm happy to answer any questions.

- Thank you. Any questions for Dr. Rizk?

- That was great. So that was a great talk on one of my biggest issues with a lot of these patients is compliance. So for instance, dietary compliance, they tell us, oh I think I'm following a low salt diet. But we really don't have a way of monitoring what do you do in your clinic and how do you really enforce that they're actually doing what they're supposed to be doing.

- This is a tough one. There are some patients from the get-go, you know they're going to do well because they are very well regimented, disciplined and I mean I encourage them to use the apps. MyFitnessPal is one that I've actively encouraged patients to download. Even the

non-paying feature has a way to track sodium and has barcode scanning. But I think we actually need to do a study, a simple study starting with this, doing a study looking at, is a low salt diet actually necessary and what is the threshold? Because patients often ask us, what target should I get to? And it's kind of human nature. If you don't have a target to aim for from a salt-wise, they're not going to know what they're going to do and they're not going to track them, you know, very well. So I don't have a real way to do it other than rely on their own characteristics. I encourage the use of the apps though.

- Yes. You mentioned fluctuating hearing loss that we should monitor that, but what about detecting a nystagmus during attacks? I think this can be very useful also in terms of having the right diagnosis that the patients actually have nystagmus diagnosed during attacks.

- Yes. I think we should rely on objective recording of, so in a clinical trial design we should rely on recording of the episodes if we can with, you know, we have, everybody has an iPhone these days.

- Yeah.

- To look at the nystagmus and I don't know, I mean probably many of you have, I've had patients have a Ménière's attack in my clinic as I was talking to them and it goes from zero to a hundred and it's pretty impressive and unmistakable.

- But it rarely happens that.

- It rarely happens. Yeah. But if we are designing trials, I think we should do objective recording if we want to increase our, you know, our chances of success.

- Thank you for your wonderful talk. I have a question on do you, are you aware of if there, if there are any wearable devices that can provide a more objective evaluation of the episode of the vertigo?

- I know that there's many companies looking at providing a wearable device, but I mean usually, you know, with the iPhone, if they are able to, I mean Heather can speak to this, the vertigo attacks can be very debilitating. But sometimes if you have somebody that can record the eye movements, that can work. But there's a lot of companies working on something that can be placed around the head that can record the eye movements.

- Dr. Rizk, a question about, some of the patients I see have this sense that they can't get their hearing aids correct. That they feel like they kind of go through a lot of different trials of hearing aids. Is that something that you find goes into symptom management? Like if they feel like they really have the right ones, they do a lot better? Or how does that play in?

- I mean diplacusis happens with Ménière's disease, to the the fact that it's a cochlear pathology and they can feel like they have this distortion of the sound. What I tell patients is sometimes I

encourage them actively, especially if they have a severe hearing loss that fluctuates into a better range, to get those AmpCROS devices that can be fitted into a regular hearing aid versus a CROS hearing aid at times. Audiologists don't like them much, but for the Ménière's patients they work and they can allow them to switch between modes depending on how they're doing on a specific day.

- Just following on, when you were talking about frontal glasses with iPhones at the Bárány last year, there are a number of companies that are doing that. They're very cheap, you can find them online. There's been six or seven different companies that have used the technology of the iPhone. They put on a little, a little kind of a microscope to the end to make sure they can focus on the eye. And it's just, and there are some people that have some custom 3D printed machines that then just fit it to the actual patient. And so online there are quite a few people that are doing that.

- And they're available for the US market, you're saying?

- I think so because I've bought them for people when I've, when I've visited these conferences, and there are some people that will ship all over the world. So they are available.

- Thank you. Thanks.

- Well thank you Dr. Rizk. That was a very excellent talk. Really appreciate your insights especially about clinical trial design. To talk to us a little bit more about migraine and Ménière's disease. We have Dr. Jeff Sharon.

- Thanks. It's a pleasure to be here. Can everyone hear me okay? Yeah, there's kind of like an echo up here and I couldn't tell if you all can hear. Okay. So I'll dive in. Habib thanks, that was a perfect segue for what I wanted to talk about in terms of the vestibular migraine and migraine in general and Ménière's disease. I do have some disclosures. I'll talk about some data from an investigator initiated study that was paid for by Eli Lilly. And then I am a paid employee of Spiral Therapeutics, which does Ménière's research. So migraine is shockingly common. You all know someone in your life who has migraine. It affects 10 to 15% of people worldwide, which is an astonishing number. One to 4% of the population has chronic migraine. Migraine is the most common cause of disability for those in their working years. The scale of migraine cannot be underappreciated or underestimated. What isn't discussed as much is that the earliest migraine manifestation is not a headache. And we all think of migraine is synonymous with a bad headache. But when a 2-year-old suffers from migraine, they get vertigo and migraine and vertigo are therefore biologically linked, likely in in profound ways. And some of the talk today will be, I'm not going to have definitive answers. We're going to, I'm going to have some thoughts in terms of ways to think about how they could be related and whether or not it is worthwhile to explore the link between migraine and basically I'll say every other ear disease. But for today's talk we'll focus on Ménière's disease. And there you see some fancy animations. So migraine and other vestibular diseases, it's so bizarre to me that it's connected, but it is when you start looking at the connections between migraine and every other disease I as a

neurologist treat, you find connections. Dr. Rizk mentioned that more than half of patients with Ménière's disease meet criteria for migraine. Migraines associated with a twofold increased risk of BPPV. And when we repeated that study at UCSF, we found that it was associated with earlier in life BPPV. So you would get BPPV five years earlier if you had a migraine history than if you didn't. And 50% of patients with idiopathic bilateral vestibular loss have a history of migraine. So, go figure. So clearly there's something going on here. I cannot believe this is all a coincidence. I guess I do believe that migraine affects the inner ear in ways that we don't understand, but ways that we need to understand to advance the field. This was a paper we came up with a number of years ago and we tried to map out the diagnostic landscape of vestibular disorders. And what you see is a lot of overlapping circles. This is not the case with some other things I treat, you know, when I see a brain tumor on an MRI, if we diagnose it as a vestibular schwannoma, it is therefore not meningioma. Those circles don't overlap. But here, when you look at vestibular disorders and you could see Ménière's in particular, there's large overlaps with migraine, with BPPV, with bilateral vestibular loss. So we're seeing a complex web of interrelationships between vestibular entities and we have to accept that in order to properly investigate them. So I guess I'm saying I view migraine as the elephant in the room that is basically involved with every symptom and disease that ear specialists treat. And even when it's not directly involved in pathophysiology, it still seems to be involved with outcomes and response to treatment, as is the case with superior semicircular dehiscence syndrome. So let's talk about CGRP. Why do we want to talk about that? Because it's a potential link and it's something we've been studying, so I want to add it into the discussion. So what is CGRP, calcitonin gene related peptide? No need to remember that, we all just call it CGRP. It is a neuroinflammatory peptide that is now thought to be part of how a migraine happens. So it's found throughout the peripheral and central nervous system. It's released by the trigeminovascular system and it is found and expressed, what's not as well known, in the vestibular periphery. So here I have a slide from a paper from Anne Luebke's lab in Rochester showing a mouse utricle where you see CGRP expression. And interestingly, the location would suggest an involvement with the efferent vestibular system, which is an intriguing thought. So how do we know it's related to migraine? Well, a series of experiments years ago, Lars Edvinsson and others infused CGRP into migraine nerve and caused a migraine. So that's a pretty good argument that CGRP is related to migraine. Another argument is that there's now two large classes of medicines that block CGRP and have proven efficacy in treating migraine. Those medications are monoclonal antibodies and also gepants. So gepants are pills that you take and the monoclonal antibodies are injected and usually last a month or so and both are used to treat migraine headache. Neither one is often a cure but they are very often a successful treatment and for many patients a game-changer. Interestingly though, CGRP in addition to its relationships to migraine is related to vestibular dysfunction. So Dr. Anne Luebke has shown that CGRP knockout mice have balance difficulty and lower VOR gain. And I'll show that here. So here's some experiments they did with these CGRP knockout mice and you could see clear alterations of VOR gain not affecting the phase. So clearly some relationship between vestibular response to stimuli and CGRP and also impaired balance. So these mice have to balance on the rotor rod and after the training trials, the CGRP knockout mice have impaired balance. So this is very intriguing to me that CGRP appears to be connected to vestibular, proper vestibular function. So we did a trial that we finished up last year called the

INVESTMENT trial. It was a pilot sized trial looking at one of the CGRP blocking drugs. And that drug was galcanezumab, which is sold under the name Emgality. And this was a double-blind randomized placebo-controlled trial funded by Eli Lilly, but it was an investigator-initiated study from me and we had a one month baseline period, three months of treatment, with a one-to-one randomization between drug and placebo. And what we're showing here is the DDD count that stands for definitive dizzy days. So every day in the trial you got a text message. The text message said, rate your dizziness over the last 24 hours as none, mild, moderate, or severe. And moderate or above was counted as a definitive dizzy day. So the average person at the start of the trial had 18 of these definitive dizzy days. So relatively high disease burden, but that's who signs up for clinical trials. And by the third month of treatment there was a difference between the placebo and the control group and the treatment group. So the treatment group dropped to 6.6 days and the placebo group was 12.5 days. So nice separation between the two, but clearly either a placebo effect or a regression to the mean effect as Habib was alluding to. The dizziness handicap inventory also had a nice separation between the two groups with those getting treated, dropping 22 points. Habib's published on the MCID for this scale and this study just beat that. Okay, so let me lay out the argument. The argument is Ménière's disease related to migraine. So we'll go through could it be. So number one, epidemiologically we've talked about the fact that more than half of patients with Ménière's disease meet criteria for migraine, more than you'd expect by chance. And in a cohort of 147 patients, Neff showed that one quarter of patients met criteria for both diagnoses. A second line of argument would be the phenotype. So 45% of Ménière's patients always experience a migraine symptom with vertigo attacks. So meaning an aura or migraine headache or photophobia not considered to be traditionally Ménière's symptoms. There are so many shared features between the two diseases, aural fullness, episodic vertigo, the triggers, the typical triggers like allergy, stress, tinnitus, hearing loss, sensitivity to barometric pressure. Hamid Djalilian did an interesting study where he looked at the laterality of migraine headaches in those who had migraine and Ménière's disease and found that they were correlated. So if you had more left sided headaches, your Ménière's disease, if you had both, where it's more likely to be on the left side. And endolymphatic hydrops can be present in vestibular, in migraine, not very commonly found though. Is there a pathophysiologic link? Can we come up with a study? Well there's an oft-quoted study from Zoltan Vass from 2004 where he looked at these blood vessels. So these blood vessels that are innervated by the trigeminal nerve and they do go out to the inner ear. So he was looking at the SMA or spiral modular artery and he was activating the trigeminal vascular system and he caused plasma extravasation. So that's what you're seeing in the images there. C is the control and A and B are the treatment arms. So you can cause plasma extravasation with stimulation of the trigeminal vascular system. So that is a plausible link between the two diseases. So I'll read what he said in this paper 20 years ago. He said the findings suggests that stimulation of paravascular afferent nerves may result in permeability changes in the basilar and cochlear vascular bed and may contribute to the mechanisms of vertebro-basilar type of headache through the release of Substance P, which is another neuroinflammatory peptide similar to CGRP and the stimulation of the TPVR1, which is the receptor, respectively. We propose that vertigo, tinnitus and hearing deficits associated with migraine may arise from perturbations of capsaicin-sensitive trigeminal sensory ganglion neurons projecting to the cochlea. So there you have it. Here's an interesting study from

Yoon-Hee Cha and Bob Baloh showing that when you had Ménière's disease and migraine, you were likely to have your Ménière's disease earlier in life compared to just migraine alone, you were likely to have it later in life. But they didn't see differences in hearing thresholds between those two groups. Another interesting study from the same group looked at the complex web of genetics and found a number of families that were affected by both migraine and Ménière's disease and they color coded. The migraine is shaded in the top left, the Ménière's disease in the bottom right, and you can see here that the relationships between the two are quite complex with some family members just having migraine, some just having Ménière's disease, some having episodic vertigo or aural which was the other two shades and some having all of the above. So more evidence for their interrelationships. Here's an interesting one and nice to follow Robin's account on this. This was a historical recount by Hamid Djalilian discovering Ménière's disease and its association with migraine headaches. So he has two quotes from Ménière himself, and I'll read the second one. I do not hesitate to regard these migraines as dependent on a lesion of the inner ear. They're accompanied by noises by vertigo, by gradual diminution of hearing. So it, it's actually likely that Ménière himself thought that migraines were related to the symptoms cluster that he described. I'm running out of time so I'm going to go quick. Does treating migraine work for Ménière's disease? This is probably the million dollar question, right? You give a whole talk and the answer at the end is, so what, what's the practical implication of this? I think the practical implication of this is should we be investigating migraine drugs as a treatment for Ménière's disease? Dr. Rizk looked at Effexor, actually looking for, as he noted, based on some theories with aquaporins, but did not find a difference between treatment versus placebo. And Effexor is considered a migraine treatment as well. Stefan Hegemann recently put out a report of treating six migraine Ménière's patients with rimegepant, which is a gepants and noted Ménière's symptom resolution in all of them. My personal experience with that hasn't been quite as good, but it is certainly we do see some effects. And then Hamid Djalilian treated Ménière's patients with nortriptyline, verapamil, or topiramate, so traditional migraine medications, and did see quality of life improvement thereby arguing that there was some treatment effects. All right, so I'll finish with this one. This is for Miles Atkinson in 1961 and he said the fact of the association of migraine with Ménière's disease is no new observation. Ménière himself referred to it, but it has not received the recognition which would appear to be its due. These are the patients who are really out of luck who continue to have migraine attacks after acquiring Ménière's attacks, one alternating with the other. Such a person lives in a very special hell. And with that I will conclude. I put up a screenshot for those interested in this topic. Mike Teixido has a wonderful talk on the House YouTube channel, which is a great channel full of wonderful free content. It provides a deeper dive into this topic. So I recommend that if you're interested. My conclusions are that migraine and Ménière's are likely linked and that further study of migraine medications for Ménière's disease is warranted. Thank you all.

- Thank you Dr. Sharon. Any questions for Dr. Sharon?

- Thank you for very interesting talk. I'm so interested about the relationship about between CGRP and migraine. So are there any report that, what kind of stimulation activate the CGRP neuron in the vestibular organ?

- The question was about the relationship between CGRP and the vestibular periphery and, and how you activate the CGRP receptor. Well, presumably it's the CGRP release, meaning from the trigeminal vascular system that is the ligand that activates the receptor. I think we have to do a couple things to advance this mechanism. One of them is probably, we have to show that the CGRP receptor is expressed in human tissue. The studies that the slides I showed are animal tissue and then we need to better understand the effects of CGRP on the inner ear. Thank you.

- Thank you.

- I remember Amgen and Novartis did a large scale CGRP antagonist trial. I don't know if among those patients, you know, people looked at whether the migraine patient has, you know, Ménière's disease and whether there are actually therapeutic effect in those patients. You mentioned sort of like 40-50% migraine patients actually have Ménière's disease right?

- The other way around.

- Oh, the other way around.

- Yeah.

- But, but there is a correlation. So it would be interesting to look at those subpopulation with Ménière's and see if that drug really in those large scale trial, it's actually the trial is done, right?

- Yes. I really like your question because I had the exact same thought. So I have asked, when I was trying to get money to do this vestibular migraine trial, my original thought is let me just approach the drug companies and ask them for their clinical trial data from their pivotal trials and see if they gather data on dizziness as an outcome measure. And then I could save myself a couple years and figure out do their drugs work for at least vestibular migraine. I don't know that they quantified people enough to know whether or not they had Ménière's disease and they were not collecting that data. There's an issue with just how the neurology world views the relationship of vertigo and migraine. And so it was reported in some trials as an adverse event if someone developed dizziness or vertigo, but in none of the trials was it collected as an outcome measure. So I think it was a miss on be on the part of the people who did these large trials to get that sort of data.

- Okay. Thank you.

- All right, well thank you very much Dr. Sharon. So we've heard a lot so far about clinical trials using drugs and their effects. We're going to switch gears a little bit now and Dr. Amy Juliano is going to speak to us about imaging and MRIs in Ménière's disease.

- Thank you so much Dr. Thibodeaux and good afternoon everyone. I want to thank especially Dr. Divya Chari and the organizing committee for the invitation to speak and it's great to be here among this company. So I'm a radiologist and I'm a head and neck radiologist practicing at Mass

Eye and Ear. And my special interest is in temporal bone imaging. So I will speak a little bit today about imaging in the context of Ménière's disease and I'll focus on the inner ear and of course endolymphatic hydrops. So here's the outline of my talk. I will talk about imaging anatomy, we'll talk about Ménière's disease and hydrops, a bit about evolution and MRI techniques. And then what do we talk about in radiology reports when we interpret a scan of a patient with Ménière's disease? First a bit about inner ear imaging anatomy. So here's the bony labyrinth, I'm sure here we're all familiar with this complex structure and for radiologists when we do cross-sectional imaging interpretation, we look at slices. So we slice this up to contiguous sections along the body part. So here's the CT scan. CT, basically the theory is like x-rays, how much does the substance in the body block the oncoming x-ray photons? So it's all about the substance density. The denser something is the more photons it blocks, it looks a certain way. And when something is very not dense, it does not block a lot of photons and the substance looks a different way. So here we see bone, very dense blocks, a lot of the oncoming x-rays. It looks white and we call that dense. Air, it's very not dense so that looks black. So this is a CT of a left temporal bone. So on imaging left is right, right is left. And so here we can see the cochlea, bit of the vestibule. Now we scroll up to a next slice. We see a bit still of the basal turn of the cochlea and now we see the vestibule. And then the next slice we see semicircular canal. That's CT. MRI works differently. And that's all about particle physics. How does a substance's physical particles act, their spin inside a magnetic field? So it has nothing to do with density, but it has to do with physical properties. We do different pulse sequences. So we accentuate different parts and substances look different. So this is a T1-weighted MRI image. And you'll see here the back of the head is towards the back. The tip of the nose is in front. The patient is lying down. We can see the pinna on either side. So in a T1-weighted sequence, fluid is dark. So we see the CSF here, that's dark. A bit of the cochlea. Fat is bright, see the subcutaneous fat. And if we give intravenous contrast, the contrast is bright. So wherever contrast gets to along the bloodstream, like to a tumor, we can see it lights up. For example, here is actually a little glomus tympanicum paraganglioma. So that's a T1-weighted sequence. A T2-weighted sequence looks a bit like this, but this is not any old regular T2. This is a heavily T2-weighted MR sequence. And on this, fluid is super bright. So you can see all the fluid in the cochlea, the CSF super bright, everything else is dark. So you really accentuate the appearance of fluid. And if we zoom in, we can see here now fluid in the cochlea, fluid in the vestibule, a bit in the semicircular canals outlining the cochlear nerve. We can see the modiolus dark, interscalar septum dark. So that's MRI. Now we open up the bony labyrinth. It's not a solid chunk of bone, it's not hollow and empty, it is sort of hollow. But there's another maze inside this bony maze. And inside is this maze that's lined with a membranous wall, and that is the membranous labyrinth. So here's a diagram courtesy of Elsevier. And you'll see here in blue is the fluid inside the membranous labyrinth. Between the bony labyrinth and the membranous labyrinth is a different fluid. That's the white stuff, that's perilymph, and that's between the bony and the membranous labyrinth. We can talk about the different parts of this membranous labyrinth. There's the utricle. Here is the saccule, and here is the cochlear duct going around inside the cochlea. Now how big are these structures? So let's look at a histologic slide. Here's the cochlea and look at the blue. That's the endolymph, that's tiny. That's the cochlear duct. And normally the majority of the fluid inside of cochlea is perilymph. A very little bit is endolymph. Let's look at more. So here again we have the cochlea, that's the internal auditory canal. Here's the vestibule in here. We see saccule,

utricle, the blue blobs, right? Endolymph blue. Tiny. The majority is white and the majority is perilymph. That's how it's usually normally. Now what about in Ménière's? In Ménière's disease there is hydrops. So these blue parts with the endolymph are big. So now we can say, all right, that's big, that's hydrops. Now we're not saying Ménière's necessarily causes hydrops or is the only thing that leads to hydrops. And we're not saying that hydrops causes Ménière's, but we're seeing, at least at this point in early 2025, we can say in a Ménière's disease patient, we can see hydrops. And at the very least it's an epiphenomenon. It's something that happens in Ménière's. Aha. So for imagers, the question is can we see the endolymph and distinguish it from perilymph? Because if we can, now we can diagnose hydrops, we can see it. And if a Ménière's patient comes for scan or there's high clinical suspicion of Ménière's and on imaging I say, well I see hydrops, that's going to help to confirm the diagnosis. So can we see the endolymph as distinct from the perilymph? Let's take a look. Here's the CT. Remember, bone is white, air is black. Everything in between, muscle, fluid, you know fat, different gradations of gray, but not enough for us to tell between different types of fluid inside. What about MRI? The heavily T2-weighted sequence where we see fluid, now all the fluid is bright, we cannot tell between endolymph and perilymph, it's all the same super bright. So how are we going to do this? Well, it's been discovered. Remember I talked about how the intravenous contrast looks bright on T1. Well it turns out if you wait long enough, the contrast permeates from the bloodstream into the perilymph but not into the endolymph. So if you wait long enough and you do a delayed post-contrast, we'll find the perilymph now lights up but not the endolymph. So now we can distinguish between those two. And now we can see hydrops. So here's a patient with a big cochlear duct, a big saccule, a big utricle, that's endolymphatic hydrops. And we can more specifically say cochlear hydrops, saccular hydrops, utricular hydrops, or as a whole vestibular hydrops. But we can now see it. And that is huge because for the first time now we have tangible visible objective signs of hydrops in the setting of Ménière's. Here's a patient, left ear that's to the right, and right ear. Over here you can see the difference between the two. Big cochlear duct, big saccule, big utricle. That's hydrops in the right ear but not the left. So how did this come about? The first time this was discovered was back in 2005 a group Zou et al. They were authors from Finland, from Sweden and from China. They collaborated and they looked at guinea pigs and they also scanned humans. They introduced contrast agent directly onto the round window membrane. They also injected through the vein. And they found that if you wait the perilymph lights up with contrast. So this was the beginning of the era of imaging of hydrops. Two years later, Nakashima Naganawa in Japan, a big group that did a lot of work in mine imaging, they started doing this clinically. In humans there's a sequence, you may have heard of this, 3D FLAIR, fluid-attenuated inversion recovery. It's feasible to visualize endolymphatic hydrops. And in the beginning they inject it through the drum and contrast permeates through the round window membrane, you can see as bright perilymph and the little dark areas are endolymph. But you only get benefit of one ear, otherwise you have to inject both drums and you have to wait a long while. And in subsequent years, in the last two decades, lots of research going on. This is just a sampling of the papers. There are so many more just showing the evolution went from intratympanic injection to intravenous injection, different imaging techniques. But these all tend to be very long scans. Good, so now we can see this and what am I going to say on an imaging report? Well first of all, of course I'm looking at the size of the cochlear duct, saccule, utricle. And in particular this is the saccule that's big on the right side.

Saccular hydrops correlates with Ménière's symptoms. The other thing that's been discovered, and this is not specific to Ménière's, but if the perilymph takes up a lot of gadolinium, there's something wonky with the blood-perilymph barrier. And that is a sign of sensorineural hearing loss. So the greater the degree of perilymph enhancement, there is sensorineural hearing loss. And that's another parameter we can talk about. So when I'm reading a report, imaging, what I'm going to say in my report is the size of all the different lymphatic, endolymphatic structures, and the degree of enhancement. Great. That's the story of imaging, right? No. We have gone beyond that now. What else can we talk about? Well it turns out that there has been discovery as to the mechanism of Ménière's disease and we'll hear more about this later on. So it turns out that not all Ménière's patients are the same. There's something going on with the endolymphatic duct and sac. Something is wrong with it. But what's wrong with it, what's been discovered is that some patients have an endolymphatic sac that never developed properly and some patients had it developed properly but then the lining degenerated. So these are the two endotype phenotypes of Ménière's disease, the hypoplastic form, and the degenerative form, the two different endotype phenotypes. So here's a landmark paper by Bächinger et al and David is here in the audience along with Andreas Eckhard. And they in this landmark paper described the two different endolymphatic sac pathologies within Ménière's patient population, the hypoplastic ones and the degenerative ones. Now can I say this in my radiology report? Actually no, because I cannot see the endolymphatic sac unless it's huge, then sometimes I can diagnose that. But when it's small or normal, I can't see it. So what use is it for me as a radiologist? Well it turns out that in this paper there's a second big point and the second big point is that the vestibular aqueduct can give you information. The vestibular aqueduct houses the endolymphatic duct and sac. And it turns out that the morphology of the vestibular aqueduct tells you something about the situation of the endolymphatic sac inside. And it turns out the vestibular aqueduct looks a certain way when the endolymphatic sac never formed. And the vestibular aqueduct looks a different way when the endolymphatic sac and duct are fully formed. So now on imaging I can see the vestibular aqueduct for the most part, especially on CT. And if I look at it I can say, hmm, I think the endolymphatic sac never developed or developed properly. But if the patient has Ménière's the lining degenerated. So let's take a look at this. We're going to tell the Ménière's disease endotype on imaging. So this is a right temporal bone and I'm scrolling up and down. And so you can see here the pinna, the patient is lying down, back of the head towards the back. So I'm going to scroll. So here you see the lateral semicircular canal. Here you see the vestibule and here comes the vestibular aqueduct, it comes out, it bends. And here's the back part that goes towards the posterior fossa and that's how it usually looks. The main part of the vestibular aqueduct is kind of sideways, kind of horizontal. That's how it normally looks. So I want to show this cadaveric specimen that we scanned of a temporal bone. This is the right temporal bone because it shows so beautifully the whole course of the vestibular aqueduct. Do you see this front part that's going to go towards the vestibule? Now that always comes out of the vestibule at a fixed angle and that was shown by David and Andreas and their team. It always comes out at the same angle but not the back part. This in a normal adult looks like a hockey stick. The part that hits the puck comes out of the vestibule always at a fixed angle. The handle of the hockey stick is the part that goes towards the back. This angle between the part that hits the puck and the part that your hands hold onto has been coined in their landmark paper in 2019 as the ATVA, angular trajectory of the vestibular

aqueduct. And it turns out that in fetuses this part of the handle is actually kind of short and straight. It doesn't really bend that much. So the ATVA is very close to 180 degrees and in fact they found over 140 degrees in fetuses. In a normal adult it bends so it's closer to 90 degrees. In fact, they found less than 120 degrees. So now we know if the angle is a certain way, well it tells us about the endolymphatic sac in a fetus. It's not yet completely developed. So if it's a long, short straight vestibular aqueduct with a large angle, that implies a hypoplastic or underdeveloped endolymphatic sac. Whereas in a grownup fully developed, so if we see the normal angle, that's a fully developed endolymphatic sac. But now if you tell me actually these are both grownups with Ménière's disease, well then I'm going to say you know what? This one was never developed properly. That's going to be the hypoplastic endotype of Ménière's disease. And if you tell me this other patient on the right is also Ménière's patient, well I'm going to say yeah they had it formed properly but the lining degenerated. So now I can tell the different endotype phenotype on imaging and that has prognostic implications. So we're using ATVA as a surrogate to tell the status of the endolymphatic sac and endotyping the patient into the subset of Ménière's disease. But it turns out it's not so easy to see the vestibular aqueduct. They're often very small on imaging and on MRI really hard to see. But it turns out that the bone thickness is correlated. And this has also been published by David and Andreas's team. So if the endolymphatic sac never formed properly, it turns out the entire temporal bone kind of is a bit underdeveloped. Mastoid may not be pneumatized so much, and the bone behind the semicircular canals tend to be thin. So now it's tough to measure the angle, but it's not hard to see the bone thickness. It's thin here, hypoplastic endotype. It's thick here, degenerative endotype. So now we can use the retrolabyrinthine bone thickness as a surrogate of the ATVA. So by looking at the bone thickness, I have a good idea if the patient belongs to the hypoplastic endotype or the degenerative endotype. The story is a little bit more complicated than that but look at this purple box here. Anytime it's a fetal ATVA, there is no thick bone. So if I see someone with thick bone, I have basically ruled out the hypoplastic endotype. So we published this last fall showing that we can add that to our radiology report which has prognostic implications for the patient. So when I report what do I talk about? The size of the endolymphatic structures, cochlear, saccule, utricle. I talk about the degree of perilymph enhancement because it matches sensorineural hearing loss. And if I can I talk about the ATVA but better seen on CT, or the retrolabyrinthine bone thickness, which you can see on CT or MRI. So in summary, MRI is now allowing us to see hydrops. That's a tangible visible finding and it's changing the landscape. We have additional anatomic features to help us subtype the Ménière's disease. So we can give some prognostic implications for the patient, which we'll hear about later this afternoon. What's happening in the future? Well we can improve imaging techniques, faster scan time, higher spatial resolution. Radiomics is a big deal, things that cannot be seen by the naked eye. Maybe AI can help us figure out differences in texture. And anything else is what I think the beauty of meetings like this is for, where researchers gather together and we find the next horizon. So Andrea shared with me the slide that I really wanted to show you. I'm really honored to be a part of our group that we meet together every week to talk about what we can do for Ménière's disease and Ménière's disease patients. I thank you so much.

- All right, we have time for one or two questions for Dr. Juliano. If anybody in the audience has a question.

- That was fascinating, does every Ménière's patient now get a temporal bone CT at your institution?

- I would like that to be the case. I think they do get the MRI with the hydrops protocol and once in a while they do in addition get the CT so we can help better with the endotyping. But ever since we've been able to show the retrolabyrinthine bone thickness is a good surrogate, we can kind of get a good idea and that's a routine part of our radiology report.

- That was a really great talk. I'm wondering if you could comment a little bit about the logistics of scanning MRI at, you know, just after contrast and three to four hours later, and how you were able to incorporate that into your routine clinical care.

- Yeah, so when we first started doing this, we would have the patient get scanned, get the intravenous contrast, get a couple more images and then they go, they can go to their clinic visit in otology, they can go shopping, they can go to the cafeteria, then they come back four hours later and we do that scan. Lately we've stopped doing the initial part. So when they come they just get the injection and they leave, kind of like a nuclear medicine scan almost. Then when they come back all the imaging is done at a delayed post-contrast. So that does require clinicians to figure out that they don't actually need the IAC protocol. They're just really here to look at the hydrops. But in fact we do do sequences like the heavily T2-weighted sequence so we can rule out vestibular schwannoma, we can rule out some other things.

- How specific is the finding of endolymphatic hydrops for Ménière's disease? For instance, if we let's say scan a lot of patients with just asymmetric hearing loss, how many of them would have in endolymphatic hydrops?

- I think that would be hard to answer because we don't get like the requests for patients that they don't really have a high suspicion for Ménière's. I would say that I always read my scans without looking at the clinical history because I don't want to be biased. So I never pull up the chart to see which ear, whether is this just a rule out, are they, you know, do they think it's actually a vestibular migraine? I never look. And I would say for the most part when I look at it and then I look up the chart, it jives. So it does seem to be very much matching the clinical impression. Whether healthy patients would sometimes have it, it's harder to say because we don't really have many patients who don't have high suspicions for Ménière's come for the scan. I would say the contralateral ear though might be a good sign of it unless that's the herald of the beginning and that often would be negative. We don't see bilateral, for example, all the time. It's more often it's asymmetric, it may be unilateral. So I don't doubt that it's valid.

- I see one question in the back and then we'll move on after that.

- Yeah, continuing from that same line of thought, quite a while ago Steve Rauch showed abnormal VEMPS contralateral to Ménière's ears. And so my question is how often do you see hydrops in the contralateral ear in people with unilateral Ménière's disease?

- So I would say saccular hydrops not common at all. Cochlear duct prominence, we often see it even in patients who are not quite symptomatic. And I think that the cochlear duct can be a bit prominent without there being symptoms. And I don't know if that heralds the beginning of maybe the rest of it having some enlargement, but the saccular hydrops, no I would say.

- That's puzzling because you would expect for the VEMP abnormalities to be present, that they have saccular hydrops.

- Yeah, I do think that it would be a bit asymmetric. But then again if I see that the chart does say there is, there are symptoms, there's clinical testing on that side, that actually to me might be a positive that would jive with the read. So yeah.

- All right, thank you Dr. Juliano. So that concludes the presentations we have in this clinical portion. We're going to have a a moderated panel discussion now. So the speakers who are not on the panel, thank you very much for your presentations. You're welcome to join the audience and we'll bring up the moderator and and the rest of the panel.

- Well good afternoon everyone. So this is a very fairly short panel discussion about patients. I'm John Oghalai, I'm from USC and then we've got Habib and Jeff who spoke earlier. And then we're adding in Dr. Bill Slattery from House Ear Institute. And this is just going to be some practical patient scenarios and I'm just going to kind of pose questions to the panel members and see, you know, how they would work up the patient. How would they treat the patient, what are their thoughts? So here's our first patient, patient number one, a 32-year-old female. She owns a a store. She's had fluctuating right ear fullness and hearing loss for six months. She's had three episodes of severe vertigo and kind of has some mild dizziness the rest of the time. And I've got her audiogram here and word recognition scores. Jeff, do you want to just maybe start off, maybe interpret the audiogram and and tell me what you're thinking?

- Sure. So your audiogram shows normal hearing thresholds in your left ear and then the right ear has a low frequency sensorineural hearing loss. This patient's 32 and has some concerning symptoms for Ménière's disease. I always try to distinguish if they're having any of the characteristic triad of Ménière's symptoms at the time of the vertigo. So is there aural fullness, is there tinnitus, and is there hearing loss with the vertigo? Because I feel like that strengthens the connection and then we do, you know my history, I exposed all that in my talks. I'm always curious if there's a migraine history, if there's any other otologic conditions, if there's any other medical problems as well to try to further characterize what's going on.

- Yeah and none of these are trick questions. You don't have to worry. Yeah, sometimes at our medical conference there'll be like a surprise tumor will pop up or something. We're not doing that here. Okay. Habib, what would be your next step in working up this patient?

- This is a fairly classical patient where I wouldn't get an MRI from the get-go. It looks like an asymmetric low frequency hearing loss. So I would straight ahead and talk to the patient about

Ménière's, explain that this is my highest suspicion, I'll put them on a low salt diet and a migraine diet and give them medication to manage the severe vertigo attack. Usually I give them a first aid kit, promethazine and Valium to have on hand, and bring them back after a few weeks with a diary that you know to see what is the number of their episodes and discuss next steps depending on how severe their disease is. If the hearing loss hasn't, that audiogram for example was obtained from, they usually fluctuate and then come back to baseline within 24-48 hours. I don't do anything. But if their hearing doesn't recover to baseline more than 48 hours after fluctuation, I suggest steroids as well.

- Do you do oral steroids or intertympanic or both or either?

- I would start with oral steroids and on when they return, if I repeat the hearing test and they're still low and/or they're having multiple episodes of vertigo more than one a week, usually I consider steroids. Okay.

- But for this patient on initial presentation it would be a diet, low salt diet, and a diuretic.

- And diuretic, if they're not on it, I would discuss it with them. Mostly the diet I would say mostly

- Mostly the diet. Okay, very good. Bill, would you have any other thoughts on this patient or do anything?

- So a couple things. One is I always like to characterize are they what I call classic Ménière's disease. And the way I define that is, you know, vertigo episode four to eight hours, the symptoms occur at the same time of the vertigo episode. It's resolved by the next day and then they're back to normal. That's I call classic. Because then you get this what I call atypical Ménière's disease. And I, I go back to, you know like George Gates used to say, you know, Ménière's disease should be called Ménière's syndrome because as was pointed out, you know you talked about five different categories, there's probably more than five that we just don't know yet. And so, you know, that's why I like to characterize this as classic or not. Anybody that has unilateral symptoms, I always get an MRI scan, that's just part of our standard evaluation. Patients who come in with vertigo spells, I will do the similar migraine diet, low salt diet, but I also will put them on diuretics because I figure I really want to know if this helps stop the vertigo spells. They've had three episodes over the last six months. We'll start it for a month, reevaluate four to six weeks later. If they have no spells I'll continue the diuretics for four months total and then I'll have them come off at that point in time.

- Hmm, very good. Any other comments on this patient?

- Back to the history we know we focused on migraine and history, but the other thing we, I don't know we kind of touched on, was allergy. At least in our practice Jennifer Derebery, you know, had a lot of Ménière's patients and found that, you know, the incidence of allergies and we'll touch on that with autoimmune as well. Is that immune? Is it autoimmune? But there's a significant number of these patients who have allergies and if you get the allergies under

control, sometimes just allergy management will control their Ménière's disease. So is that immune-mediated Ménière's disease? It is a different variant. Again, these are some of the things we still don't know.

- What about the role of stress, other illness, on this kind of thing? Has that played a role? Have any of you seen that impact this kind of a patient situation?

- Many patients report that stressful events or poor sleep can also trigger an attack. We also notice weather changes in some patients. Barometric pressure changes seem to be very triggering events mostly in the vestibular migraine crowd but also in Ménière's patients with migraine features.

- And just to comment since you brought that up, it just reminds me, Jennifer Derebery would always talk about the barometric pressure means that there's fungal allergies that plays a role. I don't know if that's true or not. I know

- So in South Carolina there's fungus all year round but I also looked it up once, and a fun fact, Charleston has the highest variability of barometric pressure in the entire continental U.S. Whenever there's hurricane season in Charleston, my Ménière's patients are the only ones who don't evacuate. They're in my clinic to get a steroid shot or something.

- Wow. Yeah. The barometric pressure. I'm so curious about because how is it sensed, you know, some long haul birds who like migrate around the whole globe have an organ in their inner ear called the paratympanic organ that directly can sense barometric pressure and that's how they stay at a constant altitude and it's unclear to me, maybe someone knows how, how a human would sense barometric pressure changes. But we do hear that frequently as a complaint.

- I'm currently doing a study with Amir Kheradmand at Johns Hopkins and we're recording mostly vestibular migraine patients but in my center we're also enrolling many patients and we're tracking through an app their geographical location and then mapping it to barometric pressure. So we don't even know if it's a true correlation yet. We're trying to figure out if it's barometric pressure, temperature, humidity, or pollen count or all of the above. So I guess we're going to know in the next few years.

- Right. And I think there was a similar study within the NHS in the UK that found some weak correlations. I'll also add, I guess regarding stress, not with Ménière's disease but with vestibular migraine. I'm in San Francisco so we did a very San Francisco study which was, we did a study of mindfulness-based stress reduction as a treatment for vestibular migraine and it actually worked pretty well, and a lot of people seemed to convert the moderate severity vertigo into a mild severity vertigo. So I think stress management is important with with vestibular disease.

- Okay. Patient two, this is a 54-year-old male attorney. He has fluctuating ear fullness on both ears and hearing loss for about five years. He sometimes now gets episodes of severe vertigo.

It used to be worse, it's not as bad now, but he's dizzy most of the time. And maybe we'll go in reverse order. Bill, do you want to kick off, interpret the audiogram and give your initial impressions?

- Sure. So this audiogram demonstrates a low frequency sensorineural hearing loss in the right ear that comes up into the normal mid-frequency range and then drops off in the high frequencies in the left ear. We also have a low frequency loss, not quite as bad, that peaks at 2000 hertz and then drops off in the high frequencies. Your classic Ménière's disease is low frequency that kind of peaks at 2000 and then drops off. So both of these would be considered kind of classic audiograms with the low frequency loss. The second part that's important is to look at the discrimination. So the discrimination in the right ear is 76%, which means when we ask them to repeat the words back, they only got 76% of the words correctly. The way I like to describe this to patients is talking about the old analog radio where you have a volume knob and you have a tuning knob. And the problem that you have in Ménière's disease is that you don't need just volume but you also need tuning that has. Because many times, there was a question earlier about hearing aids in Ménière's disease patients and one of the things that I find that many of these, and I think we kind of alluded to it, but Ménière's disease patients many times will have poor discrimination, which means you put more sound into their ear, they still don't understand more, it just gets more sound. It's just like the old radio when it's not tuned properly, turn the volume up as much as you want but it's still not clear. And I use that analogy because it tends to, people kind of resonate with it if they're over, you know, 30 years old and know what an old two-tone, you know, knob radio is. But it's also helpful for the patients to describe to their friends and family members of why sometimes a hearing aid will not work in that Ménière's disease ear because no matter what you turn up it's just so difficult for them to understand.

- Okay. Habib, what's your workup for this?

- I also, it's in a very classical case, I usually shy away from an MRI unless they're not responding to treatment, which, you know, there's no urgency in getting it in this case, in my opinion. The fact that they're dizzy most of the time I want to do a vestibular workup clinical exam, make sure that they don't have any vestibular hypofunction. I also would like to know if they have non-classical Ménière's disease presentation that for example, migraine features that would explain a chronic rocking dizziness is often seen in my migraine patients. And those are the patients who have a vertigo attack but they don't recover. They have this lingering hangover rocking dizziness as well. So I would screen them for migraine features. I would make sure they don't have any vestibular hypofunction. That would be my next.

- So you would do a VNG?

- No, depending on my clinical exam, I rarely do a VNG in those patients. If I have a bedside head impulse test that is positive, I send them to PT. If I want to get a little bit more clarity, I do a video head impulse test, same day add on, like an audiogram basically and double-check my suspicion.

- Okay. And Jeff, what kind of workup would you do for this?

- It's affecting both ears. I usually do get an MRI just to check and make sure there's no intracranial pathology. I will do a quick screening clinic.

- Sorry, do you do the special hydrops protocol or just the regular one?

- We are in the process of getting some scans that are the new protocol. They're not yet at the quality they need to be. So I'd say it's a work in effort. So it's something I disclose to patients that if they're okay getting a scan that may not have good diagnostic yield, but it would be helpful for our efforts, then we'll do it. If not, and most of them say no when you phrase it like that, then we won't do it. I think there's always a question of can this be driven by an autoimmune mechanism? So I usually will send out a panel of autoimmune labs and maybe Dr. Vambutas will inform us more what the right ones to send are. I do a quick screen for like syphilis and Lyme just because I am curious if I could pick up a case of otosyphilis once in my career. And then I think there is a question of genetics here that I don't know the answer to. So I usually don't do genetic testing, but maybe that's not the right thing. And then the the final thing I'll say is when someone's dizzy most of the time I think the most important thing to figure out is, is why and what's driving the patient's most bothersome symptom. Meaning clearly there's something going on peripherally. And I think we do need to understand this patient's vestibular function. So frequently I will get vestibular testing for a patient like this, especially if I see abnormalities on my bedside exam. But I want to know is, is is there dizziness most of the time being driven by ongoing peripheral disease? Is it migraine? Is it 3PD? Is it a bilateral vestibular dysfunction or what's driving their symptomatology? Because that way I can at least try to address that.

- And what do you do if he says, well is it safe for me to drive?

- Who wants to comment on, anybody on the panel?

- Habib's doing some work on this.

- So yeah, that's why I looked at him.

- Oh, okay.

- We don't have any guidelines. We're currently doing a focus group. We are kind of in phase one of preparing a dizziness and driving questionnaire to understand the impact of various vestibular pathologies on dizziness ability or perception of ability. So I mean I tell patients to use their best judgment obviously, and I've haven't had, I don't know if others have, haven't had a patient get a Ménière's attack that leads to a crash, and most of the time you have a little bit of a warning sign, you can pull over. It's about the anxiety of having an attack when they're stranded

on the highway, which they will decide if they are able to do it or not. But most of the time I leave it up to the patient right now until we get more evidence or data.

- No, I was just going to say most Ménière's patients have a prodrome though that they know to pull over. I mean, I've had patients that have pulled over, I let them drive because they usually know when the attack's coming. They may be stranded, but they're still safe is my point.

- So it's, it sounds like there's not a consensus that this patient actually has Ménière's disease based on at least what I've given you here. Is there a role for electrocochleography? I'm taking that as a no.

- Okay. You know, there's so many things. I mean electrocochleography, there's some people that do it, but the correlation between symptoms, it's the same thing. Even with just the imaging. You know, most the time when I get the delayed imaging, I find it's the other ear that has the hydrops, not the diseased ear. And so the same thing you find with electrocochleography, I'm just not sure how sensitive it is.

- Right, right. Okay. Very good. Any other comments on this case?

- So I would, I've been getting genetic testing on everybody that has anything that I cannot explain. Now most, and what's amazing is how many times I'm finding genes that are associated with the cochlea, but it's described as undetermined. And what I found, which many of you may know this, but the American Society of Genetics has a five point category of how they classify what is definite correlation. So it's not correlated at all, yes correlated, maybe correlated, probably not correlated, we don't know. And there's this five category, apparently they'll vote on this, is my understanding of how it happens. So my thought is I want to get genetic testing on all these people because now at least we're registering that these patients who have these genetic defects have symptoms. Because if we're not testing them, it's not until you're going to have multiple papers and as you know these cases are so rare. But like I just have a patient just like this, the 32-year-old woman, one ear popped up, four years later the other ear pops up. I do genetic testing. She's got four different genes that are all associated with some type, that have been reported with some type of hearing loss. And yet the same time, you know, the tests come back and say, well, but it's not significant. And I'm like, how can this not be significant that she's got these four genes that are all correlated with the inner ear. It's just we don't know yet. And the society has not stamped the approval yet. So that's why I do genetic testing and I tell them probably there is some genetic relationship here that's causing this type of thing.

- Okay. Let's move on to the last patient. I think we have a few minutes left. Okay. Patient three, 59-year-old female school administrator has had right-sided hearing loss for many years and now has fullness in the left ear. She's kind of dizzy all the time. Habib, you want to start off, interpret the audiogram and what would you do?

- Sure. She has a right severe to profound hearing loss with poor word discrimination almost on all frequencies. And on the left she has a mild low frequency hearing loss rising to normal and

then a high frequency hearing loss in the moderate range with also reduced word discrimination. Does her fullness in the left ear fluctuate? That would be an important point to figure out. At this point, I'm not thinking of a recurrent vestibulopathy along the lines of Ménière's disease. Even just the symptoms we have in front of us, the generalized dizziness all the time, I will want to do a full vestibular evaluation and the clinical exam to make sure there's no vestibular hypofunction and screen for causes of, other causes of constant dizziness and imbalance, whether it's a peripheral vestibular cause or a central vestibular cause.

- Thank you. Okay. So Jeff, let's say you followed her a little bit, you got repeated audiograms and the right ear is pretty stable down there, but the left ear is fluctuating up and down. What would you do?

- Yeah, I think I was taught that that sort of pattern could be seen with delayed endolymphatic hydrops. So this is the idea that one ear has lost hearing years ago. And then you developed a Ménière's-like syndrome in the healthy ear. And I believe the imaging studies in that condition have correlated that, that you do see hydrops in the ear that's fluctuating now. Generally speaking, most people treat that like a Ménière's disease if she's dizzy all the time. I think we have to figure out, you know, what's driving her symptoms. Because if, you know, she clearly has a vestibular problem going on, sometimes that is what's driving the constant symptoms. Sometimes it's more of a 3PD-type mechanism where it's the central maladaptation that's driving the symptoms. Because that could be more responsive to an SSRI or an SNRI versus just the standard Ménière's management.

- Okay, Bill, she's freaking out. She can only hear out of one ear. She's worried about can she even continue in her job? What are we going to do to save her hearing?

- Well, so I think the thing that bothers me the most is that left ear has a 72% discrimination problem, even though the overall pure tones aren't that bad. And as you said, she's fluctuating in this only hearing ear. The right ear if it's been down and been stable, from a hearing perspective I would consider a cochlear implant in that right ear based on, and then what we do with the dizziness, if we need to do more for the dizziness, that's something to consider. So I would consider it a cochlear implant for single-sided deafness. She's not going to do well with a hearing aid in that right ear with that 32% discrim. The other thing that I think is extremely important in these individuals, especially somebody who's 59 years old, anybody who's right around 60, I always tell them Medicare does not pay for cochlear implants for single-sided deafness. So don't decide you want to wait till you're on Medicare to have it done, even though she's 59 years old. Because she's maybe disabled because of this hearing loss and the vertigo. She goes on disability and gets on Medicare. Then again, that's a problem from a, you know, just from a insurance reimbursement perspective. So that's one of the things I talk about.

- Sure. So now I guess we're going to kind of hold off on this case. Are there questions from the audience about any of the cases that we've talked about today or basically any topics? Because we got the panel of experts right here.

- I'm going to make a comment. For all these patients I think that the first question you have to do is to ask for a familial history, if they have symptom in the family. This is more easy to do than many of the sophisticated tests. And imagine that all this other that you have shown here that has no history of vertigo, no history of vestibular symptom. Would you consider doing genetic testing to any of these? I would do to all of cases, particularly the 32-year-old woman. Why are we discriminating patient because they have vestibular symptom? We should have the same criteria because just according to the audiogram, all of them deserve genetic testing. And you will be surprised.

- I love the discussion of barometric pressure. I was at the University of Iowa for 10 years and a majority of my Ménière's patients could predict thunderstorms. I moved to Seattle 20 years ago. Nobody notices any variance of weather with their Ménière's disease. And the difference was always incredibly striking to me and has remained so to this day.

- But they're just dizzy all the time in Seattle?

- No, no. It just rains all the time in Seattle. The barometer doesn't swing like it does in the Midwest.

- Oh, okay.

- We don't get thunderstorms in Seattle. Almost never.

- Got it.

- And so you don't see this pattern that obviously they have in South Carolina.

- It's like the old farmer says, you know, when I get the bursa in my elbow, that's when the thunderstorms are coming, right?

- Yeah. Other questions or comments? This has been a great discussion.

- I would make one comment about this last case. I would definitely get a full vestibular evaluation before doing a cochlear implant on the right side.

- A VNG.

- A VNG, v-head rotary chair, just to get a full workup given that they're, they have generalized dizziness all the time. And if there's a hypofunction, I make sure that they go to rehab before doing the implant.

- Yeah, just one question. I'm a hearing scientist and I work for a hearing aid company, but a couple years back I developed dizziness, kind of ongoing, very, maybe one out of 10. And then a couple months later I started having fluctuating hearing loss. Low frequency, very much what

you showed for one patient just in one ear, peaking or normally 2K. And because I'm a hearing scientist, I would just measure the hearing loss every day because I work for hearing aid company. Sorry, so I could do that in C two role. And I had fullness and low frequency tinnitus. So it was suspected Ménière's, tried a couple things, but in the end, maybe eight months into it, I asked my ENT or my sort of different doctors if they could try statin and two weeks, three weeks into statin, the dizziness and the hearing loss vanished. Have you ever seen anything like that?

- So at Northwestern, this isn't Ménière's disease, but at Northwestern they actually have a statin trial right now for sudden sensorineural hearing loss. So there is some correlation between, and again, I'm blanking on the biological characteristics of it, but there is some potential correlation they found in their basic science labs there. And that's why they went to the clinical trial for it.

- Is that just like a leg of oxygen basically dyslipidemia-related or hypoxia or?

- I don't know.

- There's also all that interesting research from Lisa Cunningham about statins being protective of hearing in vestibular schwannomas.

- Thank you. Thank you.

- Just a comment. I work in Germany and we have a quite different attitudes to what driving for Ménière's patients. There's a very strict rule that Ménière's patients with attacks that are not always accompanied by symptoms that arise before the vertigo, they must not drive. And that's the main problem for our patients because many of them actually lose their job because they cannot treat it.

- Yeah, yeah. The driving's a tough one. I'm always hesitant to put anything like that in the medical record for fear that it follows the patient around. There was one other point somebody made about being able to, oh, you just made it about repeatedly checking your hearing test. What have you guys been noticing with like the iPad, iPhone hearing tests? Are patients doing that? Is that helpful?

- It's actually fairly a good correlation between those smartphone apps and the actual audiogram in the booth. So I tell patients to download the app in clinic and to use it during their episodes. And I kind of tested it kind of in real time. They would tell me they have an episode, they would send me the audiogram, I bring them in and it correlates. And I've been using it to decide whether I give oral steroids or bring them for it steroids.

- So I was thinking I might just ask, oh, sorry Bill.

- Well, I was just going to comment. So, you know, we, I had a sudden hearing loss November 22nd in my right ear, got an audiogram. Because obviously 1:45 in the afternoon I have audiologists, kind of like your hearing scientist, I could do that. The Mimi app I think is the best app. Because I've tried several of them. It's M-I-M-I, it's free. It will test their hearing on a daily basis. It correlates extremely well. It's a Békésy-omic audiometer test and it works with your AirPod Pros. And I've actually had hearing tests in the office with the audiologist hearing tests with my Mimi app and it correlates so well.

- Oh, thank you. It's only on the iPhone.

- Yeah, it's only, it is an Apple product or an Apple phone product

- On Android there's one called Hearing Test. I have less experience with it.

- Oh. And I've also done the Apple test and it's also very good too. And I've used the Apple Air Pros as a hearing aid, it's okay. Not as well as a hearing aid. But anyway.

- It's just a comment. Maybe it's not a big problem if it's correlates to a clinical autogram and just as to have a baseline that you can relate to so you can see how your hearing will fluctuate if it has a decent test, retest reproducibility with the hearing test that you're using. So I think it's a very good idea that the patients actually can use these apps. And I agree the Mimi is probably one of the good ones that's out there. But I think there could also be some for other people not using iPhones, using other mobile phones or maybe even with other types of headsets. Because this also will have an impact on where your threshold will will be.

- Thank you. So we just have about two minutes left and one of the points of this seminar was to stimulate research in Ménière's disease. And so I thought I might ask each of the panelists, if there was one area of Ménière's disease that you think is the most important to study with research? You know, maybe you could just say what you think it is and if you can why? Bill, do you want to, do you want to start?

- I always start with diagnosis and etiology because the problem is we can have all these different clinical trials and I think what you've shown, what several people have shown, Ménière's disease is a very difficult disease to treat. And the problem is you probably have just a category of multiple different etiologies in there. And I think we have to figure out what are those subtypes so we can figure out this subtype gets this treatment, this subtype gets this. So I would go to diagnosis and etiology as the biggest issue.

- Thank you. I agree with that. I think as long as we don't know if we're treating the same disorder or a thousand different disorders, we're not going to make headway in the clinical trials. But I also think we need also a consensus on the outcome measures we're going to use and these should be set in stone and used in every trial.

- Very good, Jeff?

- Yeah, I find that I'm just a very concrete thinker, meaning I'm going to leave it to the smarter folks to figure out the pathology and what's actually going on with Ménière's disease in the current landscape of just having all these treatments that we don't know if they work or not. I feel that it's very important to do well-run clinical trials to figure out if we have a theory, like I presented a theory that migraines related to Ménière's disease. But it's just a theory, like at the end of the day we have to test that with a rigorous clinical trial and figure out if that's true or not and if it can benefit patients.

- Very good. Well I thank the panelists. It was a great discussion. Thank you.

- All right, thank you. And I just want to thank everyone who was our speakers and our panelists for our first half of the symposium focusing on the clinical side of things. We're going to take a 10 minute break right now and when we come back we will be focused on lab science and knowledge gaps. So please do come back and don't forget that after the the seminar, we are going to have a networking session reception in the back. Also, we have our QR code with the survey. Don't forget to take that. So we will see you back here in 10 minutes. Everybody. Thank you.
[indistinct chatter]

- Hi everybody. We're going to get started in just a couple minutes, so if you want to grab some water from the back, grab a seat. We're going to get started. I'm going to invite the speakers to the second half to come up and join me on the podium. Thank you. Hello everyone. Welcome back. We're really excited to continue on with our symposium and go into the second half, the lab science and knowledge gap side. It's going to be the same format. We're going to have some speakers, they're going to do their presentation followed by little Q and A and then another moderated panel discussion. So we're going to jump right in and Dr. Andreas Eckhart is going to talk to us about the molecular basis.

- Thank you so much. Thanks for the organizing committee for inviting me to speak here. It's a pleasure. And I want to start out by introducing our fantastic team at Mass Eye and Ear as well as the otopathology lab at Mass Eye and Ear where most of our wet lab research happens. So we kind of talked about the prevailing dogma of Ménière's disease already, we heard about different etiologies that we suspect play a role. We heard about endolymphatic hydrops being in the centerpiece as a fluid overpressure, over-fluid, over-accumulation phenomenon that we think causes these symptoms. Well there is evidence out there in the literature that this might not be true. We see endolymphatic hydrops being associated with a range of other conditions. We can even see it in asymptomatic ears. But still it is the prevailing dogma that informs our research as well as how we interpret the clinical course of Ménière's disease. Shown here on the right side in that diagram with a time on the X axis and inner ear function on the Y axis, we usually start out with a normal inner ear. And due to endolymphatic hydrops and overpressure phenomenon that we think stretches these membranes, leads to repeated microtrauma, the inner ear degenerates progressively over time. And there is that phase early on where also according to the dogma, pressure-induced episodic symptoms occur the time when we

diagnose this disease based on that characteristic pattern. Well this dogma is derived from analogies to glaucoma, another fluid overpressure disease drawn more than a hundred years ago. Ménière's disease back then was even described as glaucoma of the inner ear. But it is important to note that we heard about this in the first session. The therapies that this concept yielded are questionable in their efficacy and it certainly does not have yielded any cures or causative therapies. But still we're living with this hydro-centric paradigm. This paradigm is also the basis for most of the animal models that have been developed for Ménière's disease or endolymphatic hydrops with the idea to induce over-accumulation of endolymph fluid or overpressure in animals with various methods. We don't know if that really reflects the pathophysiology of Ménière's disease. And even more complicating, we now are becoming more and more aware that this is not a homogenous disease. We see different subtypes and that poses the challenge that we also have to figure out which animal model actually recapitulates the pathophysiology of which subgroup. Another approach in research is to look at human ear tissues from patients with Ménière's disease. There should be some ground truth buried in that because this is the tissue that actually carried the disease. And this is something we do a lot in our lab, in the otopathology lab at Mass Eye and Ear. But also this approach comes with challenges. We know that Ménière's disease usually takes place between 30 and 60 years of age, and by the time these organ donor or tissue donor's disease and the inner ears become available for study, the disease is usually in their burnt out disease stage. It has ravaged through the inner ear, degeneration has progressed to a level that hearing thresholds have leveled on a permanent, moderate to severe level. And when we look in these inner ears at the cellular elements like hair cells, the stria, or neurons in something we call the cyto-cochleogram, we see that a lot of these cells have degenerated, here indicated by the white spaces in these bars. So we get a very murky picture out of these tissue specimens. And on top of that, these patients might have had a history of occupational noise exposure in their lifetime. They might have ototoxic drugs that cause additional damage and teasing this apart retrospectively needs an approach, larger studies where we look at a large number of temporal bone specimens at a time. So I want to talk about our approach, our research approach towards the underlying etiology and pathophysiology of Ménière's disease that we have pursued over the last five to six years and present some of the findings that have led us to think in a radically new way about the nature of endolymphatic hydrops and how it actually ties in into Ménière's disease. So we leveraged our human temporal bone collection at Mass Eye and Ear and we focused our studies on the endolymphatic sac indicated here in purple. What we found is that the endolymphatic sac epithelium expresses a set of ion transport proteins that are regulated by systemic hormones like aldosterone in order to transport ions and fluid across the epithelium. This is consistent with many previous studies that have been done on the endolymphatic sac epithelium on the molecular level, but it really emphasizes that this structure in the inner ear seems to be an interface with our body in terms of sensing physiological needs and probably adjusting inner ear fluids according to these needs. When we looked at the endolymphatic sac in many patients, we saw consistent pathology in that organ. We saw in some of the specimens we had available that the endolymphatic sac degenerated. And this includes also specimens from rare specimens from patients who passed away during the early course of the disease, not in the late burnt out stage. We saw other many specimens in which the endolymphatic sac had never fully developed. My colleague Amy Juliano already talked about this. We call this a

hypoplastic endolymphatic sac. And we have then developed CT MRI diagnostic criteria to visualize these different endolymphatic sac pathologies in live patients clinically to tease apart these patient subgroups. And we have used these diagnostic methods in retrospective and prospective studies to show that these subgroups truly have distinct features. And these diagnostic criteria even allow us to predict what's going on. For example, in the second year of a Ménière's patient to predict the risk of developing Ménière's disease based on finding of a abnormal endolymphatic sac. So with these findings, we then pose the question, well, when the endolymphatic sac is consistently affected by pathology and Ménière's disease, how big of a damage is that? Actually because looking at an endolymphatic sac, a human endolymphatic sac histology, it becomes pretty quickly apparent that this is a large epithelial organ. So we went out and using serial sections, hundreds of serial sections from normal and Ménière's affected inner ears, we measured the endolymphatic, the epithelial surface area that is in contact with the endolymph in the endolymphatic sac as well as in the other parts of the inner ear, the cochlear and the vestibular system. And what we found to our surprise is that in a human inner ear, the endolymphatic sac is truly a large organ, which makes up a third to almost a half of the epithelial surface or cell mass. And when we do the same quantitative analysis in inner ears from Ménière's patients, for example, those with a hypoplastic endolymphatic sac, we saw a massive reduction of endolymphatic epithelial surface in the endolymphatic sac. So the question, the answer to the question is yes, the endolymphatic sac is a site of major injury in Ménière's disease. An inner ear affected by Ménière's disease sustains a massive pathology in terms of a massive loss of epithelial cells. So with that in mind, we turned away from the endolymphatic sac and towards the cochlear and the vestibular system where we know hydrops forms where these membranes expand. And we wanted to revisit the nature of endolymphatic hydrops, focusing specifically on the cells in these membranes. Here, the Reissner’s membranes, the epithelial cells, and the mesenchymal cells. And we tested a basic prediction of the prevailing fluid pressure paradigm, which says when the endolymph volume increases and these epithelia gets stretched, what is supposed to happen is that the number of cells should stay the same, the cell count, but because they're getting stretched, they come further apart. The cell spacing or the distance between neighboring cell nuclei should increase. And our fellows, Deanna and Cory, were are also here in the audience, they trained a deep learning segmentation model that recognizes these cells and measures the cell spacing between neighboring cells and applied it to a large number of specimens in our collection. And what they found is indicated here as heat map patterns. The cell count in a hydropic Ménière's ear is substantially higher in these Reissner's membranes compared to a normal control ear. The cell spacing in contrast stays the same. So what we observe, and this is the aggregate data from a large number of specimens on the X axis, you see all different degrees of hydrops, basically from no hydrops on the left side to very severe hydrops on the right side, and on the Y axis, again cell count and cell spacing. And we find an almost perfect correlation of cell count with expanding membranes where a cell spacing stays the same. So this is literally the opposite of what the fluid pressure paradigm predicts. What we see, what we think, what we see, the most likely explanation is that these epithelia proliferate, they increase their cell numbers by up to four or seven times. And I urge you to check out a poster that Deanna and Corey are presenting on Tuesday with a lot more data on these findings. So how do we reconcile that? We think the inner ear in Ménière's disease sustains a major injury and we have identified the endolymphatic sac as the site of

major injury where cell loss happens in the cochlea and the vestibule. It seems like the epithelia are proliferating, expanding by proliferation. And to understand what's going on here, we turned to other organs. And you can literally look at every other organ in the human body. When here, for example, the kidney sustains injury, the remaining cells leverage two mechanisms to compensate for that functional loss. The first mechanism is called hypertrophy, which means the remaining cells upregulate the gene expression, they put more ion transporters, more enzymes, whatever in their cytoplasm or their membranes to work harder and they grow their cell surface area. The second mechanism these remaining cells leverage is called hypoplasia, which means the remaining cells undergo mitosis and replace the lost cells. This is different from regeneration. Hypertrophy and hyperplasia replace lost tissue in a patchy way. This is qualitatively minor tissue and that is a problem. When the initial injury is too big and hypertrophy and hyperplasia have to replace too much tissue with qualitatively minor tissue, this can cause further damage and end up in a vicious cycle, which is called maladaptation. And maladaptation in the example of the kidney can then lead from an acute kidney injury to chronic kidney disease. And the clinical course of chronic kidney disease is shown here in that diagram on the right side with GFR, the glomerular filtration rate, being a measure of kidney health. And you see it progressively degenerates. Maladaptation drives it down to the point where the kidney is basically dead. And phosphate and calcium levels in the blood are a measure, a functional measure of kidney output. And you can see they are stable for a long time. And then when kidney degeneration and maladaptation have progressed to a certain level, we end up in the early phase of chronic kidney disease where function starts to fluctuate. The kidney cannot keep up with physiological demand all the time anymore. So these levels start to drop and recover. And when degeneration further progresses into endstage chronic kidney disease, the function completely ceases. And now you might remember the clinical course of Ménière's disease I showed you on the first slide, and we can literally overlay this ear, starting from a normal ear and ending up in a dead ear with a course of fluctuating function in the middle. So what we think based on our data, what happens in Ménière's disease is that injury affects the inner ear in Ménière's disease and the remaining cells in the cochlear and the vestibular system try to compensate for that initial damage. So endolymphatic hydrops we think is an active compensatory process that reacts to an initial damage. And the etiology of that injury, like in any other organ can be, range from genetic infectious of avascular and other causes. Clinically what we see is basically maladaptive progression, right? The losing a third or almost a half of all cells in the inner ear is a massive injury and the proliferation that happens in these hydropic membranes is probably maladaptive in the way that it drives degeneration of the organ over time. So we go through all these stages including an early fluctuating phase and finally ending up in the burnout disease stage. So with that I want to refer to a podium discussion and a poster that my colleagues, Divya Chari, Paula Roberts Bolivar, and Arpen Bose are presenting regarding a group of Ménière's patients with a hypoplastic endolymphatic sac where we looked further upstream in this pathophysiology and we think we identified for the first time a gene that is clearly associated with hypoplasia of the endolymphatic sac in a definable patient subgroup. And this translates very nicely into a mouse model that Arpen Bose and Divya Chari are presenting on that poster. I'd like also to refer again to Deanna's and Cory's poster who are showing more data supporting this maladaptive progression mechanism between hydropic membranes and the endolymphatic sac that I was pointing out. And finally, I also want to refer to

the poster of our colleague David Bächinger from Zurich, who is exploring the clinical outcomes between different groups of Ménière's patients in with regard to CI eligibility or CI indication. Thank you so much.

- Thank you Dr. Eckhard. I believe we have time for maybe one quick question if anybody in the audience has a a question?

- Yes, yes, you can hear me? Yeah. So very interesting. First of all, congratulations on the changing paradigm and suggesting new ideas. I felt I missed something in the Reissner's membrane argument, that you had two type of cells, mesenchymal cell and an epithelial cell. You showed them on different layers, but then you went to the hydrops condition and it was only one cell.

- Yep.

- In your cartoon.

- Yep.

- So what, what did I miss? Did the mesenchymal cell become an epithelial cell?

- Yeah, that's a very good question. I want to say in the cartoon, I just omitted the mesenchymal cells. In our analysis we analyze both the epithelial cells and the mesenchymal cells. So the mesenchymal cells on the perilymphatic side, if your question is, are the mesenchymal cells transitioning into epithelial cells, we don't think that's the case because the initial number of mesenchymal cells in a normal Reissner's membrane or normal saccular membrane, where we did the same analysis is by far not sufficient to explain the increase in epithelial cells.

- Okay.

- So we think it's the epithelial cells that are actually proliferating.

- Okay yeah, but are you still counting the two layers, or are you just counting one effective layer when you do the quantitative analysis?

- We counted both layers. Yeah yeah.

- All right, thank you very much. So now I'd like to bring up Dr. Antonio Lopez-Escamez. He's going to talk about genetics which we kind of talked a little bit about in the first section, but now we're going to hear a little bit more.

- Thank you so much for inviting me to be part of this wonderful symposium. This is my disclosure. I have no potential conflict of interest with this presentation and this is my current grant support. The first thing I want to start with is that we all probably agree right now that

Ménière's disease is not a single disease. So this is the first thing that we have to have very clear. We published these studies a few years ago and using cluster analysis we were able to identify that there are five subgroups of patients. And this is not just an academic classification, this patient has different clinical feature in terms of age of onset or associated comorbidities. But that was a few years ago. What we all agree also is that endolymphatic hydrops is observed in most of patients with Ménière's disease and has been clearly explained before is mostly associated with a degree of hearing loss. So it's reflecting the degree of in ear damage. But other conditions can also show endolymphatic hydrops. This is something that we cannot jump into conclusion. So Ménière's disease and and endolymphatic hydrops are completely different things but they are associated. What is the situation with what we think we have right now? So we have identified molecular subtype of Ménière's disease. I will skip most of these because there will be a field presentation later. But we already have been able to identify three subgroup of patients with Ménière's disease according to the immune response. We have a subgroup of patients with autoimmune, what that means is that they have high level of TNF alpha and low level of IL-1 beta. This patient can be distinguished from the autoinflammatory subgroup that are patients that are defined for high level of cytokines. They have multiple cytokines including TNF alpha and IL-1 beta, but also IL-6 and other cytokines. And this autoinflammatory we have also shown that are mediated by changes in the gene expression in monocytes. So this is something that are already, we have already consistent data to identify these patients and this can be distinguished measuring cytokines. And we have a three, a third subgroup of patients that are defined by high level of immunoglobulin E and these are associated with type two cytokines. So there is a set of cytokines that include IL-4 IL-5, IL-9, IL-10, and IL-13 that have a special chronic inflammation. All these patients have a systemic inflammation. I'm not talking about finding in the ear, it's something that we can test making a blood test. It's something that we know. But then there's also a subgroup of patients that their immune response is normal. We think that the majority of these patients that we are estimating that could be up to 40% of the patients may have a genetic origin. And I will dedicate the rest of my presentation to talk about that. So we know that familial Ménière's disease in European population is 9%. So the only thing you have to do is to ask your patient, do you have any relative with symptoms like that? If we do this to patient with hearing loss why not are we doing the same question to the patient with recurrent vertigo? It's very easy. We are missing the familial history of many of them. We know that this familial history, as I mentioned, is also observed in East Asian population, but they are, the prevalence is lower. And we already know that the most common gene in familial Ménière's disease is OTOG which encode for otogelin and I will talk about that later. And then what happens is this have in the majority of the cases are recessive inheritance and we have found multiple families exactly with the same mutation. This is called compound recessive inheritance. And the prevalence is highest in European as I will show later. So there are many genes that has been reported for Ménière's disease already in families. We are estimating about 20 genes, 20 genes for familial Ménière's disease. These are the first gene in the world that were reported 10 years ago, DTNA of FAM136A. That was part of the work of Teresa Requena who was one of my former PhD students. And I'm not going into the detail, but this is the summary of what we know already about genetic of familial Ménière's disease. There's around 20 genes as I mentioned. The three more common are otogelin, MYO7A, I think for a hearing loss gene already well known is myocin. TECTA is another gene that is associated with alpha-tectorin, a

protein, the tectorin membrane, and the recently discovered gene, GJD3, which encode for a Connexin that you will show that is a very, very special location. Most of the genes in familial Ménière's disease are still, not now, but some of them have seen already reported in a single family. So there's no reason to continue ignoring that genetic testing can be probably a very good choice to underlying the molecular mechanism of Ménière's disease. And this is actually the approach that we are following from animal, from human study to animal studies. So I'm going to be very fast on this. This is how we identify familial Ménière's disease, recessive familial Ménière's disease with OTOG gene. For this we use something that is a technique to identify burden of rare variation in familial and sporadic cases. And we found over-representation of rare variation, rare missense variation in familial Ménière's disease. But as you can see here in the upper and lower part of this panel, we found that some of the variants were shared also between the familial cases and the sporadic cases. And that was the work of my former also PhD student Pablo Roman-Naranjo. So what we have found is that four unrelated families with Ménière's disease have exactly the same two mutations that I'm putting here, and these patients were not aware of that. And the thing is that they even don't think that could be a recessive condition because the parent of course, as you know, they have no symptoms. This is how the audiogram of this different families. And what we found in this patient that were carriers of the mutation in otogelin is that the hearing loss was developed in the first two years of the disease. So they usually reach like a flat hearing loss involving of all the frequencies in the first two years. Most of the patients in our familial patients were also female. So these are just one of the pedigrees that we have. One thing I would like to say is that we continue extending our study in the core and we found more missense variant and we found that this enrichment was confirmed in more familial cases. And when we compare with the different population, this is a image of of otogelin protein, we have found that most of the mutation allocated in the head and in the tip of the tail of the protein. Otogelin makes dimers, makes homodimers that have anti-parallel distribution. And we have found a five missense variant could alter the otogelin stability according to different predictions. And eight of this variant were enrich in non-female European population. The relevant thing here is that we think that one of the potential explanation that familial Ménière's disease is more common in European is because one of these variation may have a founder effect in these families. And one of the interesting thing that we were also doing, and this is part of a poster that we will be presenting also, is a sixth variant were found in constrained region. That means that this region in the sequence of the otogelin gene cannot tolerate mutation. And this is not observed. This is also that is observed in many of the populations but not in other populations. Probably this low tolerant that the European has may explain this accumulation and this potential founder effect. Another of the gene that we have also found is MYO7A. We have found nine families, two of them have autosomal dominant inheritance. That's a start-loss and a stop-gain mutations. These families have a second variation that can explain biallelic inheritance. And we have found an association between one mutation in MYO7A and another protein that are in the stereocilia link that have a direct interaction with MYO7A. And this is how we think that probably this explain, something that was mentioned before, how variant of a non-significant can explain the association with the disease because probably the sowers were only looking for a single variant. We are not looking in this report that you can find for genetic diagnosis service for multiple variant interacting in the same individual. That this gigantic polygenic combination is something

that we have to consider. So this is what we found in this family. Just for example, family do have a variant in cadherin 23 and also a second variant in MYO7A. And this is something that we are observe for different family. So each family has a different pair of combination and this is how we explain the association within MYO7A and a second gene. The third gene I want to mention is TECTA gene that then encodes for alpha-tectorin, which is a protein of the tectorial membrane. We observe the identical missense mutation in two families and also we found for the first time some insertion, sorry, some deletion in two of these families. So this is the finding that for the alpha-tectorin and this is the, the highlighted variant that we have found in family one and family two. So what happens in this mutation is well known for knockout mice. We know that that the deletion at the end of this protein has an effect and that leads to a limbal detachment of the tectorial membrane or a tectorial membrane is lingering. And probably we think is that makes a tectorial membrane very fragile and is really a structural changing. So this TECTA deletion has been observed as I mentioned in the the mouise model. What happened is that tectorial membrane deattached from the stereocilia and that can explain the hearing loss that they develop. And this is all these finding as you have seen leads to an accumulation of mutations that are located in tectorial membrane stereocilia, tip links and other links between the different stereocilia, about the idea that probably we need some kind of environmental factor that may trigger the disease. And we think that probably noise could be one of the trigger of the disease because noise has been already associated with the development of endolymphatic hydrops in a very short period and we think that the association, the carrier of this rare mutation have a high risk to develop the Ménière's phenotype if they have exposure to noise. Finally, the last gene I would like to mention is GJD3 that encodes for the Connexin 31.9 that we have found in familial and sporadic Ménière's disease. We have found this mutation in a total of 18 individuals, three unrelated families segregating the variant. And the variant is a complex sequence that include an haplotype including two variant, a synonymous variant and a downstream variant. So this was found in familial and sporadic cases. This I would like to remind if you see the allele frequency of single variation is very high. However the combination of all of them is what we have found that is associated and that was not found in the reference population. What is the effect of this? We think that the protein becomes unstable. You know the Connexin may make extra dimers and you need two Connexins to play between two cells. And what happens is probably the interaction between the two Connexin is involved and we think that probably that creates an unstable connection. This is what the protein is predicting and that was published in last month. The most surprising finding for us is that this Connexin is located in the tectorial membrane and this is something really unexpected. But we think that this Connexin is probably related with the interaction between the tip of a stereocilia, that this is making some kind of channel that has been already reported relating to the calcium microenvironment across the mechanical transaction channels. We have seen also other labelings in the stria vascularis in other areas. And finally I would like to finish with some comments about the genetic structure of sporadic and familial Ménière's disease. We have extended our exome sequencing study to sporadic cases already and we have found that there is a burden of missense variant in all the genes in that this is also observed in all genes that are associated with the audio vestibular phenotype, but particularly in genes that are associated with stereocilia and tectorial membrane. So within that really it's not a single gene. We already know that there are more than 20 genes, but for sporadic cases probably there are more genes involved, but most of them are located in

the stria and that's what we lead to the hypothesis that probably this fragile ear is able to develop the disease. So we have a burden of missense variant. There are about 71 genes that are shared in sporadic and familial Ménière's disease and that is an estimation about 28% of sporadic cases. So this is how we think that 10% of familial cases, but about 28% leads to close to 40% of cases that may be a genetic etiology. So I will not go in much more detail with this just to say how are we working with this high inheritance in familial Ménière's disease? We are developing a machine learning model and just using genomic data without any type of clinical data, we are able to classify about between 17 and 28 patients with sporadic Ménière's disease as familial Ménière's disease. So this is what, what is the model doing? And we think that we have really a heightened hearing loss. We are here excluding the familial case. We know that the familial are very easy. All we have to do is a good clinical history to identify the families. But some of the sporadic probably are according to this model. And in this particular model we are only using coding regions. We are only using exon sequencing data and that's probably something that we can improve with the addition of other omics including transcriptomics and epigenomics as we are currently working. So the genetic structure of Ménière's disease is complex. We may have different structure in familial in sporadic cases, but we are start to decipher in this complex structure. And just to summarize the last thing, I would like to think that we are trying to build with all this information human atlas for Ménière's disease gene and cells. And this is one of the main goal. We would like to provide a tool that can be used for the future use, for researcher and for the diagnosis of Ménière's disease. I would like to thank all the funding that we have been supporting previously funding with my research group in Spain and now in University of Sydney Australia and all my current research lab that is growing very fast. Thank you so much.

- Are there questions? Sure I have one.

- Thanks for an amazing talk. How do the genetics influence the odds of bilaterality?

- Yeah, so we have found that within the families, which is a very precise phenotype in the same family we have patients with bilateral and unilateral sensorineural and they share the mutations. So we think that the development of the disease in one on the second ear is something that is mediated by some environmental factor according to that hypothesis. It's very easy to expect that the disease can be developed in the second ear when we look for endolymphatic hydrops using MRI, we don't know.

- So Antonio, there was a beautiful talk, you started out by talking about different endotypes for Ménière's disease. How does the genetics correlate for cytokine expression? Have you started to look at that?

- Yes. One small work that we are doing. So this is one of the thing that I'm very interested because we think that some of this autoimmune phenotype, particularly the autoinflammatory phenotype associated with high levels of IL-1 beta, within that could be related to very rare mutation in some specific genes. So we have one thing but is still not published. But this is of

course an area that we are exploring. Try to explain if rare mutation can drive this autoinflammatory or maybe this allergic type of response. Yeah.

- And then we have time for one more question.

- Oh yeah, two, two quick questions on the, on the TECTA mutant, you seem to have only have characterized that in the cochlea in terms of, you know, changes in the membrane and then changes of the hair cell stereocilia insertion. But that that doesn't explain the vestibular system symptoms.

- No, no I disagree because let me explain. Otogelin is highly expressed in the vestibular system compared to the organ of Corti. The thing is that honestly nobody is doing too much histology in this and, and we don't know that this is something that we really need to do. But we are expecting that the change that we have present for the tectorial membrane can occur in the otolithic membrane. And there are study that demonstrating that this, the focal deattachment of the tectorial membrane can trigger changes in the depolarization of rehearsal.

- Okay, and then quickly this is just a change in the kind of mechanical properties of that membrane or attachment as opposed to an ion transport problem. So would you expect this patient not to show hydrops?

- I think that we cannot explain the development of hydrops with this. The only thing that we can explain with this structural changes is that probably the mechanical transition will be impaired somehow. And we think that maybe the gating, sorry, the gating of the mechanical transition could be altered from my point of view then that could explain acute tinnitus. That there is something because that changed and that, but that could also explain acute episodes of vertigo. But we cannot explain how this structural change leads to the final hydrops. For my view, hydrops is something that you need a damage in the ear to develop that some kind of damage.

- Thank you very much. That was really, really interesting. Before we move on to our next speaker, just a little housekeeping announcement, we did have coffee now in the back. So if anybody wants to quietly get a cup of coffee while the presentations are going on, please, please do so. So now we're going to hear from Dr. Andrea Vambutas who's going to talk to us about immunology and Ménière's disease.

- Thank you so much for the invitation to be here. And here we go. So I'm going to talk about the immunologic aspects of Ménière's disease. However inherent to this is we really need to talk about autoimmune inner ear disease as well. So for people like me who went to medical school quite a long time ago, immunology has changed pretty dramatically in the sense that we used to think of autoimmune diseases, but there's a whole new class of diseases called autoinflammatory diseases and these are really diseases of monocytes, macrophages, microglia where they make IL-1, they make TNF, but they really don't make any autoantibodies. There's no TH-17 cells or other cells. And so many of the talks that you've already heard talked about cytokines being produced, are being produced by these monocytes and macrophages

together. We also know is that several common diseases that we used to think of as autoimmune have actually now been reclassified, most commonly gout and Behcet's disease, are really now considered to be autoinflammatory where they used to be autoimmune. And so that really calls into question diseases like autoimmune inner ear disease and Ménière's disease, what are they really? Because honestly we don't have autoantibodies in many cases and so do they represent an autoinflammatory disease? Are they a multitude of diseases? And that's been a theme today and it's absolutely, absolutely correct because there doesn't seem to be any one common disease phenotype. The other thing that I want to point out to you is that symptoms of classic autoimmune diseases and classic autoinflammatory diseases are very, very similar. So for instance, if you take the example of Cogan's disease, which we know responds to TNF and really is considered to be an autoimmune disease, these patients have hearing loss, they have vertigo, they have interstitial keratitis. However, patients with autoinflammatory disease also have hearing loss. They have uveitis, they have headaches and they have vertigo. So you can't distinguish them based on their clinical phenotype alone. So what I'm hoping to suggest to you is that in some instances, Ménière's disease as we know classically has hearing loss together with vertigo at every single episode. However, in patients with autoimmune inner ear disease, they have fluctuating hearing loss and at 50% of their presentations have vertigo. The case Dr. Oghalai showed you earlier of the patient with a fluctuating hearing loss who didn't always have the vertigo, is that Ménière's disease? Is it an atypical Ménière's disease? Is it autoimmune inner ear disease? And I would've charged to you maybe these are a continuum of the same disease. So we know, and classically the history of Ménière's disease is that it's really regulated by sodium potassium ATPase in the stria vascularis. However, glucocorticoid receptors stimulate the absorption of sodium. So maybe that's how we can explain some patients respond to corticosteroids or not. But we also know from the early work of people like Jeff Harris and others, the endolymphatic sac is really thought to be the antigen processing center of the inner ear. So we really can't discount the potential role of the immune system. Additionally, and this was a lovely picture and a paper that I really would charge everyone should take a look at in eLife showing the regulation of volume of the endolymphatic sac was controlled by a transcription factor of the LMX1bb mutant. And notably that family of mutants actually can be controlled by TNF and interleukin-1. And so there still may be a role for regulation of endolymphatic sac volume associated with inflammatory response. So I look at things from a slightly different lens. I look at it from the ability to respond to corticosteroids or not. And so we know in patients with Ménière's disease, and this is work that's been published quite a while ago, we know that the corticosteroid response rate is much lower in Ménière's disease than it is in autoimmune inner ear disease or sudden hearing loss and it hovers in the mid 40% range. And so one of the things that my lab has been doing is looking at in patients that are corticosteroid-resistant, do they have a different clinical phenotype? Do they have a different set of cytokine expression and can we really capitalize on that? And so what we found initially is that in patients that it were corticosteroid-resistant, they expressed high levels of interleukin-1. We repurposed anakinra, which is an IL-1 receptor antagonist, to treat patients with a steroid-resistant autoimmune inner ear disease. And then recently we discovered that these patients process interleukin-1 differently and the point of how we're going to get back to Ménière's disease, I'm hoping I'll make evident. So this was a work by Antonio Lopez-Escamez that very beautifully pointed out that we have multiple phenotypes in Ménière's and he already

covered this. So I'm going to skip over this for now, but it, the data clearly points out that as we study these patients in clinical trials, that we really need to have very rigorous inclusion criteria as Dr. Rizk pointed out. Otherwise we're going to really be comparing disparate patients and really not seeing the signal we need to see. And so this is work by multiple different labs. Dr. Rizk told you earlier that in patients with Ménière's disease, they have high levels of TNF alpha that's shown in the top left from Dr. Lopez-Escamez's Lab. They've shown that exposure to mold results in high release of tumor necrosis factor alpha. And in my lab what we actually found is in patients exposed to environmental molds that the mold protein and the inner ear protein cochlin are highly homologous and we get cross-reactive TH-17 cells, which suggests that for some patients this does have autoimmune phenotype as well. And then finally we characterize them looking at a whole group of immune-mediated hearing loss and found that in these patients, that patients that are corticosteroid responders start out with very high levels of TNF and then post-treatment, those levels drop following corticosteroid use. Whereas in patients that don't respond to corticosteroids, the TNF levels were low. So again, this is work from Antonio's lab and it points out several things that I'd like to show you. One is that early stage Ménière's disease and late stage Ménière's disease are very, very different in terms of cytokine expression profiles. And it begs the question whether these are two different diseases or whether the disease changes over time because in autoimmune inner ear disease, we know that patients in the beginning of their disease process, 70% respond to corticosteroids. But if you follow them out, and this was done by Broden and Meyerhoff many years ago, by three years, only 14% of patients stay responsive to steroids, which suggests the immune system is changing in how it's reacting to these antigens. Additionally, we've spent a lot of time today talking about migraine and a lot of the data now emerging in migraine is it can be a result of inflammasome activation and interleukin-1 again, not all patients with migraine may have interleukin-1 associated with it, but we do know now from the neurology literature that there is a very clear role for interleukin-1. So I started out by talking about autoinflammatory diseases and the quintessential autoinflammatory disease is something called Muckle-Wells. It's a gain of function mutation in a gene called NLRP3, and it results in excessive interleukin-1 beta release. These patients interestingly have sensorineural hearing loss in the high frequencies. You can stabilize them by treating them, but for most patients their hearing does not improve. So the entire family of autoinflammatory diseases have a fair number of neurologic manifestations and many of these patients, greater than 70% in one study, greater than 90% in another, their symptoms are manifest by headache or migraine. And so the inflammatory connection is very alive and real in these patients. And I completely agree with Dr. Lopez-Escamez that we really need to genetically sequence a lot of these patients. One of the things emerging in the autoimmune literature is that believe it or not, sodium salt actually exacerbates autoimmune disease. This is shown most commonly in patients with multiple sclerosis and in a cohort of relapsing remitting MS, there was a very positive correlation between disease exacerbation and sodium intake. This is clearly a very nice correlate to Ménière's disease. And so we identified that patients with autoimmune inter ear disease process interleukin-1 differently, usually pro interleukin-1 beta should be cleaved by caspase-1 to 17 kilodalton product. We identify that almost uniformly caspase-7 cleaves interleukin-1 to a 28 kilodalton product. And notably in a cohort that we looked at with Ménière's disease, we took their peripheral blood immune cells and stimulated with increasing amounts of sodium salt and saw an increase in interleukin-1 beta transcription

as well as release of interleukin-1 beta. And interestingly in the lower right panel, when you treat the cells with dioxide, you actually could reduce that interleukin-1 processing. And then in panel C, just like autoimmune inner ear disease patients, what we saw is that these patients in exposure to sodium salt made that 28 kilodalton product, to me representing that autoimmune inner ear disease patients and Ménière's disease patients are very similar in how they're processing interleukin-1. Now granted clearly not all of them because we saw that not all of them did the same, but a subset clearly do. So recently one of the residents in my lab also decided to take a look at betahistine because a number of patients clinically say they respond to betahistine very nicely. And whereas we found that betahistine had no effect on these peripheral blood immune cells stimulated with salt at the transcriptional level, we saw that it very nicely blocked interleukin-1 beta release when you co- cultured, the sodium salt stimulated peripheral blood immune cells from these Ménière's patients together with betahistine. And so the other thing that we had looked at was that interleukin-6 is downstream of interleukin-1. And we saw that if patients expressed interleukin-1, that their IL-6 expression followed suit and we found higher IL-6 expression response to salt, again blunted with betahistine. But in the patients that really expressed no interleukin-1 to begin with, they really did not have the effect with IL-6, which fits back to the original discussion that we have patients with multiple phenotypes. And so it really behooves us to characterize those patients and figure out those patients that really express cytokines and would benefit from things like betahistine or anakinra or other things. So we are currently engaged in a phase two clinical trial of anakinra for corticosteroid- resistant autoimmune inner ear disease at corticosteroid- resistant Ménière's disease. This follows the same clinical trial design as our earlier published study, but however in this instance they receive anakinra at a two to one ratio and it's a crossover. So 84 days of treatments, so equivalent to three months inclusion criteria that they have Ménière's disease, they have to have a normal MRI and they have to have failed corticosteroid therapy and exclusion. We do sequence all of them to look for Muckle-Wells syndrome and genetic mutations in NLRP3 and obviously if they've received any other immunosuppressant agents. So this is actually what the trial design looks like. I'm happy to report that we're about more than two-thirds and almost three-quarters recruited. We've passed the futility mark, meaning we've looked at the blinded data and clearly see a signal between the arms indicating that we seem to see responses. Now whether this correlates indeed to drug therapy or not, we don't know at this point. But what you see on the right side are patients from our early stage clinical trial where the number one is the time of treatment. Start number four is where they came off of drug and then we follow them for the remainder of the year. And then take a look in blue, what you see is their pure tone average. The numerical value is their speech discrimination score. And in green is their interleukin-1 plasma levels at the time they of each study treatment. This was a trial that was prematurely halted by our data safety monitoring board because we reached the endpoint for earlier than we ever anticipated. We anticipated a 30% response rate and we saw a 70% response rate. And then if you take a look at the magnitude of the response on the far right, and this was we published in 2014, in anakinra responders the pure tone average improvement was significantly better than the serial audiometry trial where they looked at the effect of steroids in autoimmune inner ear disease. And similarly, the word recognition score also improved pretty dramatically. And so I'm hoping we will be unblinding this trial within the next year and we'll be able to look at autoimmune inner ear disease, Ménière's disease, and hopefully have some better answers for

all of you. So in summary, the way that we hypothesize autoimmune inner ear disease and subsequently also Ménière's disease in that in patients that corticosteroid responses, they have high levels of TNF to begin with and it drops in response to that TNF, but they're corticosteroid-responsive to begin with. Whereas patients that are steroid-resistant, they have very low TNF levels, they have high IL-1 levels and they respond very nicely to anakinra. And just as a side note, there are other IL-1 inhibitors out there, we have tried a number of them and really have not seen the same responses that we have seen with anakinra. And at this time we don't understand that. But anyway, I want to acknowledge everyone in the lab who's worked so hard at this and it's been a long work in progress. So thank you.

- Are there questions for Dr. Vambutas?

- Yeah, you mentioned sodium chloride cleaving IL there's 10 was it?

- 1.

- 1, IL-1, yeah. Do you understand the mechanism for that?

- So we actually really do not understand the mechanism. What we think is happening is sodium salt, just like any other factor that stresses the cells in autoinflammatory diseases such as in gout, it's uric acid crystals or other things. We think that that is a single stimulus that is causing the cleavage of interleukin-1 to create a pro-inflammatory environment.

- Where is the cleavage occurring?

- So the cleavage is occurring upstream at it's, I can go back to the slide, but it's amino acid 28, between 27 and 28.

- Oh. I was meaning in the inside the cells or an extracellular fluid.

- So as we believe this is occurring in monocytes.

- Okay.

- Hi, that was great. Thank you. I was curious if, you know, what are the cellular players responding to IL-1? Do you know where the receptor's located?

- So that's a really, really good question because part of this is we're looking at peripheral blood immune cells. We're not looking at the inner ear. We're actually looking at two potential models right now to try to answer that exact question.

- Great. Thanks so much. Sure.

- Any

- Other questions?

- So I have a question regarding the mechanism of of betahistine to reduce. Do you have any idea, have you done any gene?

- No, we looked, we actually looked at histamine receptors. We looked at a number of things and we can so far cannot figure out how that works. And it's interesting because it wasn't all patients. There's some patients that do not respond to betahistine at all and others that do.

- But this is something that is only observed in the patients that have high level of IL-1B.

- Yes.

- And not in the other one.

- Yeah.

- That's amazing.

- Okay, thank you

- So, so far today we've heard about, you know, drug responses, clinical responses, imaging, molecular, but now we're going to hear about another important topic, the psychological and social triggers with Ménière's disease from Dr. Joanna Wolfson.

- Okay. All right. Everyone can hear me okay? Yeah, we have a lot. Okay. So first thank you so much for inviting me. I'm shifting gears a bit and first thing is I'm not a physician, I'm a psychologist. I work at NYU Rusk and I work in one of my roles as part of a vestibular disorders clinic. So it's been a privilege to be here. I love interdisciplinary care. So for me it's nice to not be at just a psychology conference but really learning from physicians. And I hope you know vice versa with this talk. Okay. So first I have no disclosures and the learning objectives today are to identify the psychological and social stressors of living with Ménière's to really recognize the interplay between the stress response and Ménière's symptoms. So really the way that Ménière's can cause understandable stress and that stress has its own symptoms that can really loop back into the way that Ménière's can exacerbate or kind of be cyclical. And then to understand how psychological interventions may help people to improve symptom management in particular. And just a point that this doesn't have to mean that people need to be referring all the time to psychology, but really just thinking about what can people do in even a given bedside interaction or just a routine appointment, with language that they might be able to say to help someone with some of these interventions. So first I just want to acknowledge a lot of the different stressors that people who deal with Ménière's disease face. And some of these are really based off of the patients that we see in our clinic. So whether it's an individual therapy or we run a vestibular stress management group. So these are the things that themes that come

up a lot. The first of course is just the traumatic nature of symptoms. So people say just not knowing when I may have another vertigo attack, a drop attack, just walking around with this experience of one eye sort of open a lot of the time to my safety, which is very tiring. And then some have had this traumatic medical experience in the pursuit of getting a diagnosis. So I think Heather mentioned it earlier, just kind of getting worked up for all sorts of different scary sounding diagnoses, whether that be a stroke or a brain tumor or other of course scary sounding neurological or immune conditions. And so sometimes people may have a PTSD-like response to just where this all started and thinking that they were dealing with something Ménière's but maybe even, you know, more life threatening. Uncertainty about the future is something that comes up a lot. So of course worry about the progression of all this. And at one point I was able to speak just for one session at a support group for people with actually any vestibular condition but were out of work as a result of their condition. And they sent in questions ahead of time. I just wanted to read a couple that people sent in. So saying that they worry that it will affect their ability to play with or help their future grandchildren. So these may have been people in their forties thinking about when I'm a grandparent, you know, what will my life be like? And then, you know, worry about can I drive, what is that safe? And people wondering how to live a full life even if these vestibular symptoms never fully go away. So people can have all sorts of images of becoming, you know, completely dependent on a spouse or just how this all transpires. Loss of the life that used to be. Many have had very active and vibrant lives before this and so they know what it was like to feel better than this. And the hidden disability quality is pretty big. So not being able to have someone else just take their body for a week and really get what this is all like, some say that they may have a good day, they go out to dinner with a friend and the friend may say, oh you're okay now. And so just this idea that no one really fully understands exactly what this has been like. And lastly, sometimes if symptoms are dismissed by providers along the way or friends as just anxiety. So just a note, vestibular dysfunction and mental health in general. So there's really a high degree of distress associated with dysfunction. So 30 to 50% of people with any vestibular dysfunction do end up having a diagnosable mental health condition often as a result of the stress of the condition. 80% or more report worse in quality of life. And then specific to Ménière's disease, anxiety and depression are very highly prevalent. Studies show that like usually between 50 to 60% of people with Ménière's do experience some level of anxiety and depression. And when we think about rates, if we are able to kind of parse apart what's a pure Ménière's versus migraine versus BPPV or other conditions, rates are higher with Ménière's disease. And I'm thinking about, you know, two patients in particular, one who said that she had Ménière's and she had at one point like a sudden drop attack at a Trader Joe's, many people in the U.S. may know what that is. And so you know, kind of being shopping and then being on the floor the next minute. And then someone with BPPV who said she kind of figured out that she's triggered in the mornings after sleeping. And so all she would have to do was just, you know, prop a lot of pillows up and then she'd be okay. So just the level of control of varying diagnoses can feel very different. And over 50% of people with Ménière's do report on self-report measures severe levels of anxiety versus only 3% in BPPV and 20% will report moderate to severe depression. So in terms of correlates, you know, I think it's really tough because as other people were talking about just difficulty with classifying how do we run a study or how do we even place people into a Ménière's group? So a lot of these are just kind of studies that exist where data is still out a little bit, but patients report

vertigo to be the most intrusive symptom causing the most distress on the whole. Tinnitus and anxiety are highly correlated. So about 90% of people with tinnitus will report some level of anxiety. Anxiety is usually higher than depression in the Ménière's population. And there was one study I want to highlight again, it was just one study, but they did use a statistical analysis to help understand causation. It was large, based in Europe, as we heard maybe highest incidence rate, you know, in Europe of Ménière's. So it was 350,000 people of European descent and looked at the relationship between anxiety, depression, and Ménière's. And so the first thing is they found that purely having preexisting anxiety and depression does not seem causative. Many people may have had it but it's not causing this to happen when they looked at something that was called neuroticism, which kind of gets a bad rep, but it really just means being kind of reactive to stress. So they used it to mean, you know, reactive to stressors that may come up. They saw that it did present as a potential risk factor. And so that was in particular things like being sensitive to environmental and interpersonal stress and people might even report having always felt lonely, experiencing mood is fluctuating, maybe having their feelings easily hurt and then being sensitive again to kind of like interpersonal interactions. We do actually show patients this in our support group, just how a vicious cycle can emerge. And this is talked about in some articles where people may have these symptoms on the top, it could really say anything, but let's take vertigo, dizziness, tinnitus, and then you know, that causes the brain to have this detection of danger, of threat wondering am I okay? It's a stressor on the body and then that leads to a state of hyper vigilance, more anxiety, sometimes panic, and then all of that can really just play back into the dizziness and make people feel even, you know, more symptomatic. I like this as well. It breaks it down a little bit more. I'm sorry, it's little busy. But the things that we really try and highlight for people are that whenever someone's in a state of stress of any kind, the first thing that we all do is hold our breath. And often that's a way to kind of prepare ourselves to fight or flee. And so many people with Ménière's and other vestibular conditions are not running away or fighting when they have this. So they then have extra oxygen in the brain which can lead to feeling dizzy and lightheaded. And so we just kind of talk about the science behind it and how does this present and how can it exacerbate symptoms, you know, similarly muscle tension if people are especially tensing their shoulders and their neck muscles, it can be a tinnitus trigger of vertigo trigger and that when we're under a state of fight or flight, we are really, our pupils will dilate to let more light in. However, if we're in a busy environment it might feel very overwhelming and then we're overstimulated and everything feels harder to manage. And racing thoughts is common. So if there's like an emergency situation, we want to know where the exits are and think our way out of it. But it can present as just being overly anxious and an overly anxious thought spiral. I want to do this very quickly, but you know, a patient I'm currently working with, an example, he's a white male in his late sixties, he was a reporter in New York and he worked a lot like 60-plus hours, 60-plus hour work weeks. He has a 20-plus history of Ménière's, the symptoms are listed and he's, you know, been to many what he would describe as like many top doctors at many top institutions where he's just really feels like he's gone through it all. And I know, you know the, the quote earlier I think from Dr. Bigelow was that, you know, it's not that the more treatments the more success. So he's been through a lot and he identifies, you know, his symptom triggers are what people were saying earlier, sharp weather changes, noisy environments, but periods of stress. And so before kind of a recent exacerbation which brought him to psychology, he had this experience of having a long-term job

that was highly focused on Covid reporting and he was responsible for reporting on Covid-related deaths at the start of the pandemic. So a very upsetting position to be in. He ended up because of his condition retiring earlier than planned and while he identified his job as very stressful politically, he liked it. And so this wasn't how he imagined sort of going on with his life. And his wife's father had been ill, actually recently passed, but it had meant she was traveling a lot away to be with him. And so she was really his safety net and so he had a lot of just stress that he viewed as possibly, you know, involved in some of the symptoms that he was experiencing. And so his quality of life feeling depressed, anxious and having panic attacks started to avoid a lot of things and partly because of his symptoms and partly because of that reduced confidence whether he felt he could do it or not. Interestingly, he found this interesting, which he shared with me. He found that in his yard, if his neighbor happened to be there, you know, in in between houses, he could talk to that neighbor spontaneously for hours and be okay. But if he knew there was a plan get together, even if it was in a very controlled not noisy environment, he would feel very anxious in advance, vigilant to his symptoms, and experience symptom exacerbation even before he got there in terms of psychological intervention. So it's not, again, there's not studies that say here's what you should do with someone with Ménière's. But there is really good research on tinnitus in particular, and I'll show in a minute a slide on that. And then even with the PPPD, so a lot of these concepts do relate to the Ménière's population as well. Just how do we sort of prevent that superimposed stress response on these symptoms? First, again, just sometimes explaining that vicious cycle and the fight or flight response. I've never had patients say they don't believe in it or that they respond poorly to it. They seem to really appreciate the science of it. Relaxation and mindfulness, you know, we heard today a little bit about that mindfulness-based stress reduction, but it could be anything, deep breathing, people like relaxing their muscles. I really highly recommend, you know, just language of the CBT nature. So just really developing alternative ways of responding to symptoms. So an example is, you know, this is from a patient had an idea that if I leave home, I will have a vertigo attack, fall down in the middle of the street and be in severe danger. And so just to be able to get it kind of into check a little bit that that's a really scary thought and we can't say that that won't happen, but just a different thought would be my symptoms can feel very scary but I've never been in a life-threatening situation. Similarly, you know, for tinnitus there's a lot of examples and one from the manual for tinnitus is if my tinnitus is loud when I wake up in the morning, I know I will have a bad day. Versus saying something like, I'm learning ways to have a good day even when my tinnitus is loud. And then, you know, helping people find ways of getting back to things that they enjoy safely that feels doable. So not having this idea that I have to have no symptoms to engage in an activity, but that I might have symptoms and it doesn't mean that I will be in danger, but the goal is to do it even though I have some level. So acceptance and commitment approaches, I think this is the hardest part is like accepting a new normal and accepting that like there this, this isn't necessarily something where there's an off switch. So accepting that there's a level of symptoms as part of one's life usually goes better than trying to keep fighting against it and kind of spinning the wheels with seeking care over and over. So this I just want to show everyone, this is publicly available through the Veterans Affairs Department website. They obviously, you know, have a lot of ways of getting, had been getting funding for care. So I direct patients sometimes to this workbook and it has a lot of good interventions specific to that for psychology. I just lastly want to talk about barriers and

considerations. So these are things that you know could potentially kind of get in the way of people getting better. By the way, did the volume change or it's still okay? It changed. I think the echo is back.

- We're looking into that.

- Okay. Is it okay to keep going or I can stand a little farther away maybe. Okay, so some of the things that really are, can get in the way of, of care for people in a mental health capacity and I think I'm not even speaking to an audience I need to be because everyone's here because they believe in the condition. But sometimes if people experience that others don't know what it is or they, you know, don't really buy into the whole inner ear disorder just feeling invalidated. I think I really can't kind of overstate the importance of the patient-provider relationship and that a lot of research on a lot of different conditions shows that when people have a good experience with their medical provider, meaning they believe that the person wants them to get better, is kind of caring to figure it out with them, you know, speaks to them as a partner and is there for them, they do better. And that's shown like in a lot of studies when we think about the placebo effect, a provider has to be involved in the placebo effect and again kind of pursuit of a cure where they're just sort of going for more and more and more opinions and treatments. So considerations for all of us might be things like, you know, messages about the condition, how are we phrasing it to patients? Are we off the bat saying there's no cure for this, calling it progressive or might we say something like, you know, hearing loss is something you might deal with but there are ways to manage the symptoms associated with it. Thinking about if you're going to involve psychotherapy, you know, how are you making a pitch for it and at what point does it enter the picture? So I was talking to Dr. Rizk earlier and we were talking about how if a patient hears at the end of like a two-year search or nothing's working, if someone's then kind of saying maybe psychology would be helpful, that seems to be a little more, you know, of a hard sell than if it's sort of woven into the team or as something that could be helpful for symptom management from the start. I'm just going to move on for the sake of time. And so options for, you know, again some of these things can just be done in a routine interaction but sometimes people may want a little more psychological intervention and so I always think first about if people are in a larger medical system, are there options there? Whether it's social work, psychology, et cetera, referring to a clinic, that's a hard thing to do sometimes, but if someone practices health psychology, rehab medicine psychology, or a geriatric provider, there's a lot of like telehealth options now too. And lastly, a lot of community or online support groups I think kind of interpret it with a grain of salt depending on what they are. But you know the, the VeDA website has one specific to Ménière's disease. So summary, you know, that's very stressful situation obviously to deal with. People do become prone to anxiety and depression but it's not the cause. And then these symptoms and psychological distress can enter into the vicious cycle which complicates the symptom picture at times or figuring out what's causing what. And then we know that relaxation, CBT, reducing avoidance, and acceptance are good intervention points and again, just the positive patient-provider relationship really helps patients feel hope and support. And that's all. So thank you.

- Are there questions for Dr. Wolfson?

- Sure. Thank you for a great talk. I found it really exciting. One of the things I found in my practice I, and it may just be the patients that I see, but the patients with Ménière's disease tend to be more, I don't know, I hate to use the phrase but white collar versus blue collar. Do you think that fits with the stress anxiety thing?

- Actually when I was seeing the previous panel and all the patient examples of like the store owner, the lawyer, I think the administrator, my first thought was like, do they have help or is there, you know, what's the stress level involved was my first thought about all those patients. But I do think there is something about, you know, similarly we'll see a lot of people who I wish I could do research on this, but will say that they've had really, really kind of high level jobs and they, it's kind of an off comment they're making, but come to find out, you know, they've really been involved in a succession level in their life where they've sort of made it in the job world but it comes with a tremendous amount of being overworked, pressure expectations set upon them, especially women in like maybe a male-dominated job, minorities and people of color who say that like they have to almost get like 110% to prove themselves. So yeah, I would say I don't know the research on that but I do agree with you in that way.

- So that was great. Do you do a formal depression screening at intake on all patients?

- Yes. So we usually give the PHQ-9 and the GAD-7 and then sometimes our vestibular physical therapists sometimes do it first, which helps them understand who should come to psychology. They also give, you know, the DHI and then sometimes I'm trying to think like other kind of quality of life measures. But yes.

- My headache neurologist has gotten really interested in these adverse childhood experiences or ACEs and they're screening in their headache clinic for those ACEs and finding correlations and there's published research with that and disease severity. Do you screen for that and do you see any connection between ACEs and vestibular disease?

- Yeah, so we don't give a formal screening measure, but I do ask about it and I don't always ask about it in the first meeting. So you know, I find the good thing about therapy is you can see people weekly and they'll eventually tell you, you know, a lot of things going on, but sometimes it's not, it's really not uncommon that people with Ménière's and other vestibular conditions have reported a level of some type of chronic stress. Sometimes it is more childhood adversity, but commonly it's also something like, I was on a job for this many years and had a boss who was, you know, I don't know what word they would use, but not a very nice person to work for, I'll say. So usually some level of chronic stress is seen and not uncommon to see childhood adverse experiences.

- All right, well thank you very much. Yes. All right, so now we're going to transition to our final panel of this session. And I really think this is gets to the heart of why we're all here today. The topic is going to be barriers to Ménière's disease research and Dr. Divya Chari is going to be our moderator.

- Perfect. All right. Hi everyone, this is our last panel for today. I'm very excited to be here just a little bit longer and then we can all go and have a drink and enjoy ourselves. So my name is Divya Chari, I'm an otologist in Massachusetts and the topic of today's panel discussion is barriers to Ménière's disease research. So we are very fortunate today to have three really expert panelists with us. We have, we have Professor Lopez-Escamez, Dr. Vanbutas and Dr. Eckhard, and we've heard all of them speak today. So just to begin with, I'd like to ask each of you just to share a few words about your journey to Ménière's disease research. What I'm really interested in is, you know, if you can tell us a little bit about what you originally studied before you got into Ménière's disease research and then really what helped you kind of focus your research into Ménière's disease. So maybe we'll just start right at the end. So Dr. Eckhard, if you can start.

- Sure. Well I guess I started out my research on Ménière's disease or during my doctoral thesis in Germany, I worked on aquaporins in the inner ear. So that was from the get-go a relation to water regulation and ion homeostasis in the inner ear. And that expanded then later to cell pathology mechanisms on the ear using human temporal bone resources.

- So I started my Ménière's disease research about 2002. I think the reason for starting that is because I was setting in a primary hospital starting to run a neurotology clinic by that time and might see that this patient has no specific treatment, no specific diagnosis. That was a kind of patients that nobody really wants to manage because it was a difficult, difficult test. That was the origin of the research for me.

- So actually I started by doing HPV research for my K08 and I had an aha moment at one point. Jeff Harris had come to be one of our speakers at our institution for an annual otology endowed lectureship. And he said to me, you know, it's really schizophrenic if you're, if you're clinically an otologist, what are you doing doing HPV research? And I was like, you know what, you're really right. And so that really launched my decision to change what I did in the research realm and started out by looking actually at cochlear implant patients with endstage immune-mediated hearing loss and asking why are they different from people with stable hearing loss, and harvesting perilymph and stimulating their immune cells to get to where we are today.

- That's great to hear. It's always nice to hear about people who have started in one area of research and then been able to transition and you know, people who have been able to kind of pick one and then move forward because it's sort of, you know, as you're starting to think, especially for early career researchers is you're starting to think about what area you want to focus your efforts on. It's nice to know that, you know, you're not necessarily locked into one going forward. So perfect and I should have mentioned this at the beginning, but the structure of this panel is that we'll spend about another, you know, 10 minutes or so going through a series of questions that I've designed specifically for our panelists and then there'll be time at the end for questions. So please save your questions for that as well. All right, so I just want to spend a few minutes discussing the evolution of our understanding of Ménière's disease. We've had a lot of really great talks over the course of this afternoon. You know, really seeing that there have

been just, there's been just a really incredible transformation over our understanding of Ménière's disease, but there's still a lot that we don't really understand. And so, you know, if we start from 1861 when Prosper Ménière first described the condition and then 77 years later when two researchers, Yamakawa and Hallpike, independently identified endolymphatic hydrops as the histopathologic correlate of Ménière's disease. And then, you know, it was another 30, 35 years later that the American Academy of Otolaryngology defined the diagnostic criteria of Ménière's disease and that was later refined a number of different times. And then there have been a number of different advances maybe since then and maybe during that time period. So Dr. Eckhard maybe we'll just start with you. What I'm really interested in hearing is maybe you can tell me a little bit about what you see as the major advancements in Ménière's disease over the past 150 years or so and how would you describe the state of our current, you know, current state of our research in Ménière's disease?

- Well, I would say the, the biggest leap came with evolution of time. The first concepts about what happens in Ménière's disease starting from Ménière and then later going into the 20th century, were pretty much, I would say formed by a mechanical understanding of how fluids move in the inner ear, how pressure evolves and the therapies were then also designed to either release pressure build in valves in the inner ear or tackle a basically a mechanical problem. And then with the advent of the molecular age, so to speak, we're now trying to understand that disease on a cellular and molecular level. Yeah, and I think that was, I would say the biggest leap.

- Yeah. Fantastic. Professor Lopez-Escamez. Do you've any?

- So I think that probably one of the biggest changes has been the identification in my view of familial cluster in Ménière's disease that does something that was studied in I think 1945 or something like that. So that was the first description of the families and grew the history that has been reported in the sixties and in the eighties. And, and then we started to, to to see that, so the familial clustering is something that is known for a long time, but the advance of exome sequencing and the application of that has made a change, a big change, because now we can study this family that has been also a big change in the identification of genes. And from that we I think that we have made a great progress.

- So I think one of the other things that, and this is not just for Ménière's disease, but this is really in any pathology of the eye, brain, or inner ear, we used to historically think that there was a very tight either blood-labyrinthine barrier, blood-brain barrier, and things in the peripheral circulation didn't get in and things in there didn't get out. And we now know there's very routine immunologic trafficking of peripheral blood immune cells into the inner ear, into the brain, into the eye. And there are multiple evolved mechanisms to protect those critical organs. For instance, decoy receptors, which we really didn't talk about today, but there are basically immunologic sponges that prevent further downstream signaling and that is one of the major ways of protecting those organs while still allowing that immunologic traffic.

- Okay. So for the next question, you know, one of the major challenges that we have in clinical research, and this has come up a few times today, is that Ménière's disease really has a natural tendency to regress and then improve over time. I'd like to know, maybe we'll start with you Dr. Vambutas at the end. How do you think that this will impact our clinical trials, particularly in being able to, you know, address the efficacy of the treatments and are there ways that you can think of that we can try and design the trials in the future, really to try and distinguish between whether or not they're effective treatments from placebos?

- Yeah, so it's an excellent question specifically for Ménière's disease with a placebo rate that in some studies have been as high as 80%. And so especially for if you're studying the vertigo component of Ménière's, it's incredibly challenging. For that reason, most of our clinical trials have really looked at the hearing response because the audiogram is definable and measurable from time, you know, from point A to point B to point C. The vertigo aspect is a lot harder to design a trial. But then also from a recruitment standpoint, it's really important that you design a trial that you're not in competition with your other local otolaryngologists. And the most common example of that is a sudden hearing loss trial when people were getting reimbursed a huge amount of money to do intratympanic steroid injections. No one wanted to refer in for the sudden sensorineural hearing loss trial. So, and trying to create a trial, you want to do one that is really not in competition with the people that need to refer the patients to you.

- So I think that this is really the most important question. If we want to advance in the treatment of Ménière's disease, the design of the clinical trial has to change internally. I think that I would say most of the current clinical trial has very low value and the reason is the selection bias. We have to define a biomarker when we are selecting patients for a clinical trial and measure the biomarker, and I'm talking something that we can measure before and after the intervention because this is the only way that we can really assess the effect of any kind of intervention. Most of the clinical trial cannot rely only on reporting symptom, even from a point of view. We cannot understand what is going on in a, a specific subgroup of patients because I want to insist this Ménière's disease is not a single disease anymore. We have to measure cytokines before and we have, if we think that this is possible, we have to design the clinical trial according to a specific subgroup of patients. And that's probably a big change because all the current clinical trials are not selecting patients according to that.

- Yeah, I agree with everything my colleague said. It comes down to a signal to noise problem and reducing noise or noise is introduced by the fluctuating unpredictable course of that disease and reducing the noise would mean longer follow up times and so on. We heard about this. And on the other side, increasing the signal means, I agree with Antonio selecting subgroups of patients being more aware who receives what treatment and testing more effective treatments cures, I think would also boost the signal.

- Yeah, that's great. All great points. You know, one of the things that occurs to me is, it's been brought up a couple times, I think Dr. Rizk brought it up earlier, this idea that if we could do multi-center trials, right, that would be better. Ménière's disease is an overall rare disease. We want to increase our overall in especially if we're going to then start subdividing patients into

different groups. You know, one of the challenges that I foresee is that Ménière's disease has this very broad diagnosis. I get tons of referrals for Ménière's disease and when I see the patient I say, there's no way this is Ménière's disease. Agree. And the patient says, no, no, no, I've had Ménière's disease for the last 15 years, you don't know. And I'm like, no, no, this isn't Ménière's disease, this is migraine or whatever else. So are there ways that we can standardize that diagnosis? I mean I'll pose it to any of you, whoever wants to take the question.

- So yes, that's why I want to remark that we need to use a biomarker. For example, we can distinguish very easily patient with vestibular migraine from patients with Ménière's disease using biomarkers, measuring cytokines. And that will be a very important criteria. Patients with vestibular migraine never have high level of IL-1 beta. We know that this is very rare. So if we can select a group of patients with high level of IL-1 beta, we were selecting probably active patients and we know that this is specific, let's say immuno-phenotype can be, can be specifically treated. This is one example. Yes.

- Yeah. All right, I'll move on just for the sake of time. Okay. Moving on to basic science research, you know, there I've just posed a few different potential challenges for basic science research. So of course there are many others, but you know, for me at least, I think about this ideal reality as being one in which we can obtain predictable results, have high reproducibility and something that can really reflect the human pathophysiology of Ménière's disease, this fluctuating progressive hearing loss, you know, decline of the vestibular function, things like that. My question for anyone who wants to take this is, you know, what are potential ways that we can overcome some of these barriers? I mean, are we just sort of doomed to never have a reliable animal model? Are there other things that we can learn from animals outside of this, even if they're not a perfect match for what we see in the human version of Ménière's disease and what do we do about the fact that we have sort of a lack of standardized biomarkers?

- I think I alluded to that in my talk and I think in much of the research we're doing at Mass Eye and Ear, we're dealing with that problem on a regular basis. Ménière's disease affects the entire inner ear and just from a structural basis it is apparent that the inner ear looks and probably works different than in the inner ear of rats, mice, and even lower species. So reproducing Ménière's disease as we see it in patients in an animal is one question, is that possible at all? And if not, are we satisfied with animal models that reproduce only parts of the pathophysiology and how do we make sure that this is truly part of the pathophysiology and not a pure correlation that we see in these models? Yeah, I think that's a challenge.

- Yeah, go ahead.

- I think that we have a solution for that and the idea is going from human data to animal data. So what we have to generate a transgenic, humanized transgenics model, that had exactly the same mutation that we have found in the humans. We are already developing a double mutant autogenic mouse model that contained exactly the same point mutation that we have found in human. And we are inserting exactly the human exome try to resemble the same pathology. And this is probably is going to represent a model that reflect the pathology that we have found

exactly in for families. And this is something that if we are able to demonstrate the phenotype in this mouse, that will be really reliable, and we can use also of course that model for clinical trial for gene therapy.

- So I just have really two more kind of groups of questions. We're kind of nearing the end here, but just one quick question. Maybe I'll pose this to Dr. Vambutas. You know, you mentioned a little bit about how your K08 was in a different topic. I wonder if you could just speak very briefly about, you know, securing funding for Ménière's disease. Did you find that to be a challenge? Was the rarity of the disease an obstacle for you? How have you overcome that or circumvented that?

- So I mean it, it's an ongoing problem because quite frankly today you cannot define Ménière's as a rare disease. It doesn't meet the criteria for rare disease in getting additional funding because part of the problem is defining the duration of disease, right? If you have a self-limited disease that ends, let's say six months from now, it's fairly easy to very discreetly define the rare disease population. But for a disease that goes on and on for years and years and may wax and wane, it actually doesn't meet the criteria for rare disease. And so you don't get the additional pharma benefits of developing drugs for Ménière's because it doesn't fit the criteria.

- Yeah. Even though it has relatively low.

- Absolutely correct.

- Okay. Very last question for the panelists. If there was one major barrier to Ménière's disease research that you would like to see removed in the next five years, what would it be?

- So I would say the recurrent theme that we've had all day today is one that we very tightly define these patients and as we enroll them into trials, we really discretely define who they are, what their cytokine profiles may be, what their responses to drugs are in other fields. Response or failure to respond to a drug is an entrance criteria for many trials and it actually increases the homogeneity of the patients you're studying.

- Fully agree.

- Perfect. All right, done there. So we can, if there's any questions, we can open it up to the audience for Q and A.

- I think we learned a lot today about how we commonly think about Ménière's disease as having several different causes, but interestingly it leads to the same common clinical phenotype. And so I'm curious if you know some of the basic research that you all have done has helped you understand why the disease causes vertigo and why it is episodic in nature.

- You want to do this?

- Yeah. Okay.

- Well I'm, I'm going to refer to what I talked about today and I think in short we don't have that answer yet. I think what, what I presented today is one part of the pathophysiology and I think that's also one challenge in our field that we at least have to be aware of. It's a complex disease. The pathophysiology are most likely a sequence of events with side arms merging into each other. And when we're tackling, it's most likely difficult to tackle the entirety of that pathophysiological process at a time. So breaking it apart is a necessity. And I think we don't have that answer yet.

- So the symptomatology may be identical and similar, but the underlying cause of how you got to that symptomatology may be totally different. And if you look at the example of Cogan's syndrome versus Muckle-Wells syndrome, Cogan's syndrome responds to TNF antagonist very nicely clinically. It looks almost identical to Muckle-Wells syndrome. And yet in those patients, the treatment is used for an IL-1 antagonist. So your clinical symptomatology is where we get completely hung up. They clinically look the same, but the treatment is different. And if we have tried to apply the same treatment to all of these patients, we're going to fail miserably. So we really need to identify more clearly identifying the underlying molecular mechanism that's causing the symptoms we're seeing.

- So we have time for just one more question. Two more questions. Okay. Two more questions. Come on up. Come on up. We can take your question as well.

- Great presentations and session. I'm a engineer, I'm not a clinician, so pardon if my questions sound like silly. So what I got is that it's affecting the hearing thresholds. Is there, can you comment on some physiological biomarkers, electrophysiological biomarkers which comes into picture before it affects thresholds, either like peripheral or central processing?

- That's a great question. Unfortunately I don't have an answer for that one.

- Me neither.

- I'm not sure I understand the question.

- Hi, this is not as much of of a question as an announcement. Just to say when we were talking about funding, HHF, we are going to have Ménière's funding. The deadline for submitting a proposal is the letter of inquiry is going to be next Thursday, March 3rd, is the deadline. We started in October. What we will have Ménière's funding this year, so if the grants are going to be 50,000 a year for two years, so it's a hundred thousand dollars, a hundred thousand dollars grant. So if that's something that you're interested in pursuing, please go to our website that funding is available and we are looking to increase the amount of funding that we're doing in Ménière's disease. So please follow us at hhf.org.

- Thanks. Great. Everyone should get their applications in. All right, a huge thank you to our sponsors, the American Hearing Research Foundation, Cures Within Reach, and Hearing Health Foundation. This has been a really great session. Thanks.

- Alright everyone, what a day. I've learned so much. I've taken a bunch of notes. I'm really excited to hit the networking session. Before we do that, just a few words closing from the American Hearing Research Foundation.

- Thanks, mark. Good evening. I'm not sure this is working, but I will try. My name's Mark Muench. I have the, oops, sorry. I'm sorry. I just want to sneak in here. Put that up. Thank you. I have the pleasure to serve as chairman of the American Hearing Research Foundation. I'm also the last thing standing between you and free drinks and hor d'oeuvres. So I will be brief. I'd like to conclude our symposium today by thanking all of the speakers, panelists, the researchers who presented today. I have neither a clinical background nor a research capability or background as well. But I found all the talks fascinating and I really appreciated learning more about Ménière's disease and the impacts it has on people and all the good work that everyone is is doing here. I'd also like to thank our sponsors and co-sponsors Hearing Health Foundation, Cures Within Reach, VeDA, Spiral Therapeutics, and Scott Dorsey from central Indiana. So thank you all for helping us put this event on tonight. The last thing I wanted to say is any type of event like this, and I'm sure most of us have been involved in these types of things before. There is a small, but usually a very dedicated working group, steering committee, call it what you will, individuals who really work very hard behind the scenes to make all of this kind of happen. So I just wanted to thank them, Dr. John Oghalai, Dr. Anna Lysakowski from American Hearing who serves on our board, Dr. Bryan Ward, Dr. Divya Chari, who was just up here. Dr. Michael Hoa, Clare Thibodeaux, Dr. Thibodeaux, who works at Cures Within Reach, Chris Geissler from Hearing Health Foundation. And a special thanks to my colleague and good friend Joan Wincentsen, who up until two months ago served as our executive director at American Hearing Research. She has decided to have the audacity to retire on us. I will miss her both in a professional capacity as well as a personal friend. But I thank all of you for all the hard work that was done. I would get periodic updates from Joan and know how much work went into this. So thank you for all the work that all of you have done. Again, I'll ask and remind that if you can get a chance to snap our QR code and take our survey, we'd really appreciate that. Trish has tickets for people who need drink tickets still. So she's in the back, you'll find her. Enjoy the rest of our symposium and our networking time tonight and have a great ARO. Thanks again.