Hi, everyone. I'm Krista Vasi, and I'm the executive director of the Usher Syndrome Coalition. Welcome to our "Ask the Researchers" panel-- our final live session of USH2020 Connections Week.

Dr. Marly Kenna of Boston Children's Hospital will be moderating this research Q&A panel. So, thank you, Marly. We have monitored questions submitted in the event app, as well as through registration, and panelists will do their best to answer all questions that remain unanswered.

You're able to ask additional questions by typing them in the Q&A area at the bottom of your screen. It's typically at the bottom center to the right hand side. If you need help with anything related to Zoom or logistics, things like that, please try to ask those questions in the chat function. Just-- we'll keep them separate to try to keep things organized. So research questions in Q&A, logistical questions, Zoom questions in the chat.

And there will be an interpreter signing throughout. The interpreter will be spotlighted so they will be-- they'll remain visible for you. And you should be able to also click the closed caption button at the top of your screen if it's not yet visible.

Now, I'd like to pass it on to Marly to welcome all of our panelists.

Thank you very much, Krista. Thank you, everybody, for hanging out. I know this is the last day of the conference, and we appreciate your attendance. As Krista mentioned, I'm Marly Kenna. I'm a pediatric ear, nose and throat physician at Boston Children's Hospital. I direct our hearing loss program, and I have the good fortune to work, also, closely with the Usher Syndrome Coalition.

I'm going to introduce each panelist by name, and then they will give a little description of who they are and what they do. And I'm going to start with Dr. Alaa Koleilat.

Hi. My name is Alaa Koleilat. I completed my PhD at Mayo Clinic, in which I studied the zebrafish model of Usher syndrome due to variance in the gene, myosin 7A, and I am currently a fellow in laboratory genetics and genomics at Mayo.

Thank you. Dr. Ben Shaberman.

Thanks, Marly. I'm not a doctor, so I'll just get that out of the way right away. But I am senior director of scientific outreach and community engagement at the Foundation Fighting Blindness. I've been with the foundation for more than 15 years now. And my primary role is to communicate science and

research to our constituents and donors. I do that verbally, I do that in writing, I do that one-on-one.

And I also have a small team that does outreach to eye care professionals so they're aware of the resources available to patients with inherited retinal diseases, like no cost genetic testing, as an example.

Thank you very much. Dr. Mansfield.

Hi, Marly. Thank you, and welcome, everyone. I'm Brian Mansfield. I'm the executive vice president for research and the chief scientific officer for the Foundation Fighting Blindness, and I've now been with the foundation for nine years. And my role is to oversee the science strategic plan and the programs that we support in the foundation to accelerate treatments and cures for the clinic.

And one of my passions, as you may have seen from the presentation I did earlier in the conference, is genetic testing. And my passion is to see everyone who has an inherited retinal disease get access to the genetic testing to understand the cause of their disease. And it's a pleasure to be here with you today. Thank you.

Thank you so much. Dr. Corey.

I'm David Corey. I'm professor of neurobiology at Harvard Medical School. My laboratory has worked on basic mechanisms of hearing for more than 30 years, and we've started to elucidate the function of proteins that are responsible for this process. Of course, defects in many of them cause Usher syndrome. So we started to think, in recent years, about how we might use gene therapy to correct some of the defects and, eventually, find a treatment for Usher syndrome. Especially Usher 1F.

Thank you. Dr. Asmus.

Thanks. My name is Fritz Asmus. I'm vice president of clinical development at ProQR Therapeutics based in Leiden in the Netherlands. I'm a board certified neurologist and pharmacist since 2013. I'm leading programs, global programs of drug development in retinal diseases.

Since last year, I'm with ProQR working on our inherited disease platform, that is, RNA therapies for different genetic forms of IRDs and high unmet need. It's a pleasure to be on that panel and try to address questions of the audience.

Thank you so much. And Dr. Lentz. Can't hear you.

Thanks, Marly. Hi. I'm Jennifer Lentz, and I'm a basic science and medical researcher at LSU Health in

New Orleans, Louisiana. The focus of the research in my lab is Usher syndrome type 1C. But we also work with a number of clinicians who see Usher patients in our area and in clinics around the world. And we currently conduct several natural history studies with patients that have Usher syndrome.

Thank you very much. So we're going to-- we've been lucky to have several questions submitted to the panel. And so I'm going to run through those questions. And some of them have an obvious person who may answer them, but believe me, anybody who can answer them, that would be great.

So we're going to start with an Usher 1B question. The question is, how is one able to determine if they are candidates for treatment to restore hair cells in the ears? Dr. Koleilat, this has your name next to it, but anybody is welcome to answer.

Great. So, I'll go ahead and answer in a little bit. And I would love input from my fellow panelists. So, humans currently don't have the ability to regenerate hair cells. And so many scientists have explored the possibility of stem cell therapy. And stem cells are cells that have the ability to differentiate into multiple cell types. So they haven't really been designated as certain type of cell. And so researchers are exploring how we can make these stem cells into hair cells.

At this point in new therapeutic approaches in the hearing loss world, there's really no FDA approved stem cell therapy. However, there are recent advances and preclinical models, such as animal models.

And I would like to mention that there was actually a study out of MIT, Brigham and Women's Hospital, and Mass Eye and Ear that showed using a small molecule along with stem cells, they were able to, pretty much, cause supporting cells in the cochlea to proliferate. This is now being used this method is now in a phase two clinical trial with Frequency Therapeutics, I believe.

So this is the most recent information I have, if anybody else on the panel has anything else to add. Yeah, that's-- we're not at the point where we're recruiting patients for restoring hair cells, but this is where the field is at.

Thank you. There was a corollary question to this, which is, is there anyone working to develop a type 1B zebrafish model, or, perhaps, any model on a wider--

Yes. So this is a wonderful question. There's actually currently a zebrafish model of Usher syndrome, or Ush 1B. It's termed the mariner mutant. And it's actually the work I did my PhD on. And in 2001, an investigator named Teresa Nicolson did some work on this, where she showed certain aspects of the hair cell and some of the functions of this model.

But my PhD work took a deeper step and looked at elements of the hair cell found at the synax. And we took it a step further and identified that this zebrafish model is actually responsive to pharmacological therapy. And I believe that the talk is still available, if whoever asks this question is interested in listening to that. And the research paper is currently under review, and should be available to you all soon.

Thank you. Does anyone else on the panel have anything to add to these two questions?

Yes, Marly, maybe I could add a little bit of flavor from the Foundation Fighting Blindness, where, of course, our focus is very much on the retinal disease component of Usher syndrome. And, a few years ago, in fact, we funded Dr. Jackie Duncan at UCSF and Dr. Joe Carroll, who's at medical college of Wisconsin, to generate a number of different Usher fish models-- Usher zebrafish models, I should say. And these included models of USH1B, USH2A and USH3A so that we could examine the retinal phenotype and characterize the degeneration caused by different types of mutations in these genes.

So that work is ongoing. I know they have created the models and they're currently characterizing the progression of the disease and the characteristics of the disease in zebrafish. I think what is exciting about Usher 1B, though, is if you think about drug development and therapeutic development, then it's very important to have larger eyes to be able to experiment on.

And so while the mouse and zebrafish are great models, we're always looking for an animal with a larger eye that's more like the human eye, which has that central cone rich region that brings color vision and visual acuity.

And so, to that extent, the foundation is also supporting some researchers who are developing other models. So the same model researchers that I mentioned before, Jackie Duncan and Joe Carroll, are also working on a 13 line squirrel model.

Now, the squirrel has a larger eye, which has more characteristics in common with the human eye than the rodents do. And they are also making these three different Usher type models of USH1B, USH2A and USH3A.

And then, finally, Dr. Martha Neuringer who is at the Oregon Health and Science University has created an USH1B non-human primate model. And, now, non-human primates, unfortunately, they take a long time to create. They take a long time to mature and to develop disease. They're not like mice, who can do this over a matter of months. The non-human primates, of course, they're more like

humans, and these diseases take years to start developing properly. But they're currently examining that model, and they're creating a few additional non-human primate models of USH1B to characterize.

So there's a lot of work at the moment, actually, in different models going right from the small eye, like the zebrafish and the mouse, right through to the eye that's almost the size of a human in the non-human primate.

So, I just have a question for you. For the squirrel model, do you know anything about the hearing in those models?

Unfortunately, I don't. But we could ask the researchers what they have characterized in those. We could certainly report that back.

All right. Thank you. Anybody else? All right. So we'll move on to--

[INTERPOSING VOICES]

Marly, I thought it might be useful--

I'm sorry.

- --for someone to explain why the zebrafish is a good model.

[INTERPOSING VOICES]

Ah, excellent.

Alaa may be the perfect person to- why would we go to this strange little animal when we have mice?

Yeah, I think this is a great question. And, in general, scientists always think about what we're trying to-- what question are we trying to ask? And then we look at what model best suits to answer that question.

So mice have a lot of advantages, and one of them is that they have a cochlea, similar to humans. But zebrafish, although a fish, and very small, does have some advantages, particularly for drug development.

So there's a complete zebrafish genome available. That means all of the genes that have been identified in the zebrafish are available for us to look at. And there's actually a high conservation

between humans and zebrafish. In, particularly, myosin 7A, there's over 70% conservation between the human gene and the zebrafish gene.

Another advantage is that they have hair cells in their ear. So yes, zebrafish have ears, as well, on the outside of their body. And this is called a lateral line. And this is really important for scientists, because we're able to easily access the hair cells for some of our experiments.

And, lastly, for drug development, It's quite easy for us to add drugs to the fish. We just add it in their water and are able to observe the effects that way. And they also produce hundreds of embryos during one meeting session. And so we're able to conduct our experiments having a very large sample size.

So for different types of potential molecular genetic therapies, do you think one model will be better suited than other models?

I think it depends what you're doing. Again, I think for things like gene therapies or even stem cell therapies, starting in a mouse might be more advantageous because you're able to see how you're going to overcome the main challenges in those things. Like, with stem cell therapy, how are you going to deliver the cells? How are you going to inject it into the cochlea? And that's going to be better suited in a mouse model.

But, for instance, like pharmacotherapies, which was what I was doing, it's easy to go through a lot of drugs with an animal model such as a zebrafish.

Thank you. That's great. We just got a, we got a question through the Q&A that Krista sent to me. And someone said they noticed a substantial amount of research in Usher type 1, which is what we're talking about right now, compared to type 2, although type 2 is more is really more common. And so the question is, why isn't the research targeting Usher 2 and why more on USH1?

Does anybody have-- I think, for me, just as a clinician, I think USH1 is probably the most clinically apparent, at least in very young children disease. And, perhaps, that's why the research started there. But I'd be interested in what other people might think.

So I can start to answer that. This is Brian again. Actually, there is a lot of research in both USH1B and USH2A. So USH2A, of course, the gene that causes it is also called USH2A. And that not only is involved in Usher syndrome, but it's also one of the most common genes that causes retinitis pigmentosa in a non-syndromic form. But you just have the retinal degeneration.

So, actually, there's a lot of work going on in both. And if you look at USH2A, for instance, there are two clinical trials already in progress. One is a gene editing clinical trial. The other, by ProQR, is using a oligonucleotide approach. So both genetic approaches. But there is that in clinical trials, and there's a lot of similar types of research coming along, which haven't quite reached the clinic yet.

So I think that both of those forms of Usher are actually very well represented by the research at the moment.

Brian, just to add one more research effort is the Foundation's RUSH2A study, which is a natural history study for USH2A. 100 people are being evaluated. And that really helps with clinical trial design for USH2A therapies, as well as finding potential participants.

Yeah. I can only echo that. There is a high interest, and all that Brian and Ben said is correct, that, of course, we are very interested also in the FFB's RUSH2A study to better learn the USH2 natural disease progression. Specifically, if it comes to define genetic causes, because that will further enable drug development.

And I think we went quite a long way already with our drug development. And ProQR is set up as a platform to also then potentially add other mutations in the USH2A gene. We're currently focusing on a specific and frequent subgroup of the mutations in the so-called exon 13 that we set out to extend that further. And all the activities that are ongoing within ProQR and outside are regarded extremely helpful to that objective.

Thank you. The next set of questions that have come in are actually about USH3. But before we went onto that, I know there's several people on the panel actually studying other forms of USH1. So Jen or David, if you had things you'd like to add to this discussion, or Alaa, that would be great. Nothing? All right.

I could add just a little bit.

OK.

I mean, the real-- especially from someone like me that comes from an auditory background, the real challenge is that the cure, I think, is going to be addressing the loss of vision. We think that, for the most part, we're not going to have a lot of success in restoring hair cell function, at least in the near term.

And the big problem, then, is that we have a nice mouse model. We can treat the hearing loss in

mice. But for many of the Usher 1 mouse models, they really don't develop very much retinal deficiency, and it may take six months or a year to see any kind of a deficit. And so that makes testing a restorative therapy very difficult in a mouse model.

And, as Alaa mentioned, the zebrafish is much better than that, because everything seems to grow much faster. And they do show more of a retinal phenotype when the gene, whether it's MYO7A or in my case protocadherin 15. When the gene is deleted, then you actually do get a good retinal phenotype. And that's a better model for testing restorative therapy.

Now, on the flip side, the therapy in human is going to use something like an adeno-associated virus. But zebrafish isn't very good for trying AAV vectors that there, the therapeutic gene has to be delivered in a different way.

So we're really going to need a variety of animal models. Fish, because they have the retinal phenotype. Mice, because we can test the AAVs, primates, because we need to test the toxicity before anything gets to the clinic.

Yeah, I'd like to build off of that. Just, generally, when we're talking about therapies and developing therapies, I think it's important to keep in mind that because hearing loss is so vast and diverse, there are different causes of hearing loss and how it manifests. I know we'll be talking about genetic testing soon and why it's so important to know the genetic cause for the hearing loss.

And that kind of will spill into the therapies-- that it's not going to be a one size fits all, that it might be one therapy for this genetic cause or a combination. So, again, I think we should keep our minds open to this idea that it's going to be a spectrum and a little bit fluid in how we're going to be addressing this, and that's not going to be so bend and clear cut.

And actually, that leads right into one of the questions we got from the audience, which was, will research on USH1F-- this is, I think, for Dr. Corey-- help those with USH1D, and, if so, why or why not?

Well, I think, in general, the kinds of strategies that we're developing for one will at least be applicable to some of the others. For instance, you said USH1B?

I'm sorry. 1D. Sorry.

1D. Actually, 1D is a little bit more challenging. That is a result of mutations in the cadherin23 gene. So the big challenge with many of the Usher genes is that they have very large coding sequences. You have to put a lot of DNA into an AAV vector in order to get the full coding sequence into a cell,

and the AAV vectors just won't hold that much.

In the case of the protocadherin 15, we're trying a couple of ways of trying to squeeze the DNA into an AAV. With the cadherin23 gene, it's really quite large. And that's actually going to be much more challenging than the Usher 1F protocadherin 15. So in principle, we can use some of the same ideas, but it's going to be harder.

Thanks.

And maybe I could just make a comment about the gene therapy with these very large genes. Because it is challenging, especially for Usher syndrome. So at the moment, as David said, most of the work that we see going on is with viral-mediated delivery. But there is a growing interest in people using methods which don't depend on a virus. So you can start to consider that you can use larger and larger constructs.

Because the problem with the virus is, the virus has a size limit. And once you go beyond that, you can't get a larger gene in it. So if you can find a different way of delivering the gene that you want to without using a virus, it releases you from those strain constraints and the need, as you would have heard during the week, to split genes up and hope that they recombine accurately in cells.

And so there's a lot of work going on around the formation of nanoparticles. And the foundation funds a number of programs on this where we try and encourage those large bits of DNA to wrap themselves around molecules that help them fold up into a shape that will allow the cell to, basically, eat that complex. And, in doing that, hopefully, the DNA will go into the cell, into the nucleus, and be expressed.

And so there's been some work done on a larger gene codes that causes Stargardt disease, which is the ABCA4 gene. And the hope is we've seen some success in that in the research environment. And the hope is that if that works for a gene like that, then maybe the larger and larger genes will also be able to use these alternative methods of delivery.

But they're still in a very early stage of development. So, really, we depend, at the moment, on our clinical trials and the leading candidates with using the viral vectors. But there is hope coming in the future that there will be other ways of delivering these large genes into cells successfully.

Thank you. There actually is a question for Alaa. So I think we'll ask it now. The work you're doing now, as it relates to correcting hair cell structure for hearing auditory loss, would this also treat vestibular problems, or do vestibular issues need to be addressed separately?

Yeah. This is a great question. And it was something that we briefly looked at, but wasn't really a central component of the research study I conducted. What you'll notice with zebrafish circling mutants, is what we call them, those that have this abnormal swimming due to variance in genes that affect hearing, they swim in these tight circles. And maybe you saw the videos in the presentation. They are also, kind of, laying down on their sides due to the balance defects that we're seeing.

Now, one thing I noticed-- again, this is observational. I didn't quantify this and do replications on it. So this is just an observational. What I did notice is, upon incubation with the drugs that are used in the study, I did see that the fish were more upright compared to laying on their sides. Again, it wasn't something I quantified, but is a really great question moving forward and I think will be something that-- Lisa Schimmenti is the advisor I was working with. I think she'll be exploring that in the mouse model as they move forward.

Thank you.

Maybe I can add from a clinical development perspective. I see within our company, we have autosomal dominant our retinitis pigmentosa program. And I think there's a similarity. If you learn how to really assess several Usher syndrome or retinitis pigmentosa forms clinically and optimize your tool box for that. And that, of course, will make it much easier, also, to run the clinical development trials for other Usher forms and forms of retinitis pigmentosa.

So I think for those who suffer from an Usher form that is currently not worked on, there is, of course, then, the benefit that the armamentarium, the toolbox of really setting up a clinical trial and making that informative is worked on continuously. And then, other assets will, hopefully, come into the clinic over the next years.

Thank you. So there are a few USH3 questions that are on our document. So what is the most promising treatment in the pipeline for USH3A, and will this therapy work for USH3A with advanced vision loss? And there are two corollary questions. What is the current research on USH3 and how relevant is USH3 for USH2? So nice, easy, short answer, right?

So Marly, I'm going to start off. And I am, by no means, the USH3A expert. But I did come across a couple of projects, which I think are very interesting. A researcher, Astra Dinculescu at University of Florida, has been looking at gene therapy for USH3A. And, I might add that the University of Florida is where a lot of gene therapy development has come out of. So if you can pick a lab to develop your gene therapy, that's the place to be.

But a recent paper that she had published February 2020 showed that the USH3A protein, CLRN1, is expressed in Muller glial cells. And that's a very new finding. And that's where it's predominantly expressed. And that new finding gives the research community and her, as a gene therapy developer, a nice target for gene therapy development.

And backing up, there are genes that, obviously, we're interested in, like CLRN1. And one and one of the goals researchers have is to understand where the gene is important in the retina, where it's expressing proteins. Is it in the photoreceptors that make vision possible? Is it in the RPE cells, which support photoreceptors?

And you really have to figure that out if you're going to target replacement or augmentation of that gene with the gene therapy. So I think her finding is really important to gene therapy development.

And then, earlier today, Brian and I were talking about an USH3A hearing therapy that's being tested at a fairly early stage. It's a small molecule that helps get the CLRN1 protein into the right place in hair cells of the inner ear. And that project is ongoing at Case Western Reserve University in Cleveland.

So I think those are two of the most current developments for USH3A. But I will take any other thoughts or help from others out there.

Marly, as you know we've also worked on USH3A and few years ago, found that if we put the CLRN1 gene into a new type of adeno-associated virus-- one called exoAAV1, then we were able to restore some, but not all of the hearing in a mouse model for USH3A. And that was-- the incomplete restoration was partly because of gene regulatory elements, and partly because of the adeno-- the AAV vector not being quite perfect.

So since then, Kumar Alagramam has shown that if you add some of an additional bit of DNA, the three prime UTR, then that helps a lot. And we've tried a very new AAV that we and collaborators have developed, and found that we were able to get much better rescue of the auditory phenotype if we combine these two things. Adding a bit of the extra DNA and trying new AAV vector.

So there's really a lot happening in this, and we hope that what we find in the ear is going to be translatable to the retina.

One of the corollary questions for USH3 was whether any of the techniques or findings that you folks just discussed is applicable to USH2. I don't know the answer to that, but maybe?

Well, I think gene therapy would definitely be applicable to USH2A. The challenge there, as Brian was mentioning, is that the USH2A gene is large, so it's hard to get it in the current vectors. But the dual vector work going on for USH1B might someday apply to USH2A.

And there's also-- I haven't heard it being targeted for USH2A, but there's also the mini gene approach where you're cutting and pasting a gene together to take out the parts that aren't as critical as other parts so that you can make a smaller gene and fit it into the current viral vectors. And I know that work is going on in collaboration with IVERIC bio for Stargardt disease and LCA CEP290. And I don't see why that might not apply to USH2A.

[INTERPOSING VOICES]

Perhaps, I could add too, that, in reverse, the work that's going on in USH2A can help the other types of USH, such as USH3. So there is a big effort at the moment in the gene editing field, and USH2A is certainly one of the targets that everyone's looking at.

And so what you learn about gene editing, a lot of the information that you really need to understand is how to make the editing really specific and how to stop it changing other parts of the cell-- only changing the bit of the DNA that you really want it to do. So the lessons that you learn in getting a target for USH2A, for instance, will be useful information that will guide you on how to do it with the other types of genes involved in hearing and retinal loss, too.

So I think there's a lot of crossover whenever you're using a technology. The lessons you learn about the delivery and the specificity and the toxicity carry over, to a large extent, into other related programs. And that's one of the benefits, of course, of the pan disease type work that Ben gave a presentation on earlier in this meeting.

Thank you. I was actually just about to ask about gene editing. I think when I sit-in the clinic, people say, can't you just do CRISPR? Sort of like, can't you just take Tylenol? And I know that because it's on the cover of all magazines. And I think it's a fabulous potential tool. But we try to explain that it's-- as you said, it's great, but it's tricky.

And there's lots of different type of gene editing. And when I tell people we want their liver to continue to work, they go, oh! So but it is a very exciting tool.

The next set of--

[INTERPOSING VOICES]

I'm sorry, go ahead.

Well, I think for the future, I think we have to consider different therapeutic modalities. And as you all rightly said, we are obsessed about learning about the benefits and also potential challenges with them. And I just want to, not because it's in my company, because I really think it's a useful addition, the RNA therapy, because the administration is straightforward.

Diabetic eye disease or age-related macular degeneration-- we have hundreds and hundreds of thousands of patients receiving drugs by the same route of administration that we use for RNA therapy. It's adaptable, and not the least of those can be individualized. Patient can be dosed at six months or even yearly intervals to really-- and based on their need and their outcome.

So I think there are a lot of factors to be considered in the future when we compare these modalities and individualization of therapy and potential for retreating are, to me, important factors. And maybe also, then, later on combining. There may be a scenario where with gene editing or with a gene therapy, gene augmentations therapy, there may be a partial benefit. And then there's still the question, what would we have to add, or would there be in another modality improving patients further? These are, of course, important questions for the future.

Marly?

Yes?

I just might add to the current research for Usher 3, that there is significant research going on in detecting the different types of mutations in CLRN1. And these kinds of studies really improve our ability to diagnose Usher syndrome type 3 as well as to give researchers targets to use in the development of new therapies. And these are kinds of studies that patients themselves can get involved in.

And so it's a good time to get genetic testing done if you haven't done it before. But there's a fair amount of new literature on Usher 3A genetics and the mutation spectrum and how these mutations work on a molecular level.

Thank you. Actually, then that feeds right nicely into the next question, which is, there seems to be a

lot of potential therapeutics occurring in laboratories or on the research side. But how realistically is this for me as the patient either from hearing loss or from a retinal degeneration side? Anybody.

I know what we tell our patients. We try to stay in touch with all the researchers as much as we can. We always tell them to check in with the Coalition, because a lot of the most recent research is there. And I know it's very frustrating for them to hear that we're not ready yet.

I don't know which therapies are more likely to be ready sooner. And I think that's a very hard question to answer. I don't know if anybody has anything they'd like to add to that.

Marly, I just want to chime in on some things that are in clinical trials right now that might apply to people with Usher syndrome. And I'm shamelessly hearkening back to my talk which is a recorded talk. And before I do that, I think an important thing for people to keep in mind is that if you have Usher syndrome, you really have RP, which is causing the vision loss with hearing loss and, of course, potentially, vestibular problems.

And a lot of the cross cutting therapies for RP that are in or moving toward clinical trials may apply to Usher syndrome. And some of those trials are enrolling people with Usher syndrome. We're collaborating we're funding a company called Nacuity in Dallas that has an oral antioxidant that is designed to slow vision loss to mitigate oxidative stress.

And they've looked at it in different animal models including RP. But they've, in fact, launched a clinical trial for people with Usher syndrome in Australia. So that's one case where the Usher folks are getting it before the RP folks. We're hoping that that trial will move to the US in 2021 for RP patients. But that's an example where Usher syndrome patients are the first to get that treatment.

And then, on the stem cell front, both ReNeuron and jCyte have had clinical trials under way now for a few years. Both have shown some encouraging results. Publicly, they target RP, but I know for a fact there are Usher people enrolled in the ReNeuron trial and I'm pretty confident Usher folks are in the jCyte trial as well.

And then there are other therapies like SparingVision out of France. It's a cone-targeting gene therapy that is cross-cutting that I'm sure would potentially help Usher patients, as well. That should move into a clinical trial next year.

That's perfect. You might have what the next question was. The next question was, there are, obviously, currently multiple clinical trials gearing up for progress for RP. Do any of these include USH1B individuals?

And as you mentioned, I think it sounds like they cut across different types of Usher, is that correct?

I believe so. I don't want to speak for the clinical trial investigators or the sponsors. But out on the street, I hear, oh, there was an Usher patient enrolled in this trial. I was actually at Mass Eye and Ear, and met an Usher patient who was enrolled in the ReNeuron trials. So that was a firsthand observation. So yes.

Thank you.

Because these approaches are, if you talk about jCyte and their mutation agnostics, the therapy should work. In principle, if it works without having specific mutation constellation, which is, of course, potentially very, very good to broaden the spectrum of the population that would be eligible for such treatments.

And it's possible that you might only have to do it once. I know some of the therapies in development are every few months. Obviously, it would be nice if something lasted a little longer than that.

We're going to switch gears a little bit. There are a lot of questions, inevitably, about COVID-19 and Usher syndrome. And I think, Jen, you might be able to answer some of these questions. But the first question is whether underlying health conditions associated with COVID-19 put people who have Usher syndrome at a higher risk. Either the COVID came first and then you have Usher, or vice versa, and higher risk compared to the general population.

So I'd just like to reiterate that I'm not a clinician. And so when I read this question, what I did was to go and look at the CDC website. And so that would be the first thing that I would encourage anyone to do.

They have some of the most up to date information on COVID-19. And so with respect to risk factors, what you can read on the website is that they state that disability alone may not be related to a higher risk for getting COVID-19 or having a severe illness. Most people with disabilities are not inherently at higher risk for becoming infected with or having severe illness from COVID-19.

However, some people with disabilities might be at higher risk of infection or severe illness because of their underlying medical conditions. And they do state that all people seem to be at higher risk of severe illness from COVID-19 if they have serious underlying chronic medical conditions like chronic lung disease, a serious heart condition, or weakened immune system.

And adults with disabilities often are more likely-- in fact, three times more likely than adults without disabilities, to have some of these underlying conditions. And so they also specify disability groups that may be at risk would include people who have limited mobility or who cannot avoid coming into close contact with others who may be infected, such as direct support providers and family members.

And this is the category that made me think about individuals with Usher that have decreased mobility because of their vision loss. But I would say to anyone with Usher to get the most up to date information, to visit the CDC website, and to stay informed that way.

Thank you. There is another question that came in through the website, but also, actually, we've been addressing whether it affects hearing. There have been some adults associated who have had documented COVID-19 who have had some degree of hearing loss. There's been a handful at the Mass Eye and Ear. We've had two at Children's. There have been several reported in New York. And we're trying to, basically, get them all together to see if there's a relationship or whether it's coincidental, or whether they just had disfunction of a eustachien tube or ear infections related to the COVID.

So I don't know. There is a-- as we know, an alteration of taste and smell is now one of the well recognized symptoms of COVID-19. And, ironically, one of the areas that the Usher genes can affect are the olfactory nerves, which have to do with smell. And so what I don't know is whether people who have Usher syndrome genes who, perhaps, theoretically, would be more likely to be susceptible, actually are susceptible. I don't know, but I have wondered that. So it's certainly an area of reasonable investigation, I think.

I think what Jen said about being in close quarters out of necessity is certainly at a risk. And the other thing that we have noticed in our patient population in our hospital is that information about COVID, which is often auditory or visual, may be-- and not necessarily presented in either a very readable fashion or in ASL, is definitely lacking.

And our governor in Massachusetts actually has an ASL interpreter with him for every briefing that he does, which I think has been very well received. And it makes it a lot more available to other people. But I worry there is a lack of information or lack of accurate information just because of a communication problem. So just something to be aware of from a patient's standpoint.

Another COVID question, which is a very good one that came in is, do you have concerns that the COVID-19 will have a significant impact on the advancement of research in Usher syndrome because all the resources have now been diverted? Or in our hospital, all the labs were closed for months and

months. And do the teams and laboratories have contingency plans to not lose traction?

A really good question. Although those of you who are in labs, do you have what's happened in your place and what have you been able to do?

I guess I could start to say that, here in Louisiana, we have well-oiled protocols for disasters because we are in hurricane zones. We were able to enact these protocols very quickly, which allowed the research in our area to continue on rotating schedules of individuals coming into the facilities.

And so we were lucky to have some preparedness there. But I do think that, for myself and many of my colleagues that I speak with, we are concerned about whether or not there will be difficulties or delays because of an entirely new focus for the world and that research dollars will be funneled into those areas.

For us, we're able to continue our research right now. But it would be great to hear from others of my colleagues around the world to see how they're doing. David, did you notice any effect on your work which, is down the street from where I am, but different--

[INTERPOSING VOICES]

Well, yes, certainly. So we were shut down for about three months. Almost everything ground to a halt during that time. But people are back in the lab. They're not letting me back, because I'm not considered important enough to take the risk.

It might be safer than what I'm doing. (LAUGHING)

I'm sure it's safer. And we worry a little bit about diversion of resources. But otherwise, we're back to business.

Alaa, what about you?

Yeah, so here at Mayo Clinic, anybody that wasn't seeing patients, and even those that were seeing patients, if it wasn't an emergency, you were pretty much at home for those three months. But I do want people to know that are in this session that we weren't just sitting at home for three months. People were continuing to do data analysis or write up papers, too. That's also a part of science, not just the actual experimentation.

But now, slowly-- and people were just doing the bare minimum, like keeping the fish alive. Keeping the mice alive. But now, slowly, people again, like Dr. Lentz said, are on a rotation going into lab. And

hopefully we'll pick up soon again. But, yeah, it was a challenging time.

Now one of the-- yes. One of the questions that came in was-- and I don't know if we know the answer to this, but-- are we learning anything about the speed at which COVID-19 trials are being approved by the FDA and will this be applicable to future Usher trials?

All I can say is, I hope so. But I think we don't know. Some of the-- I think some of the information that came out on the clinical side initially, it came out so fast that it, perhaps, was less accurate than it could've been, and made it difficult to interpret it. So I think on the research side, things could be a tiny bit slower and maybe just get it right the first time.

But it's a really good question. There may be development of speedier pipelines. I know that our IRB, our institutional review board that approves all clinical research in our institution, for a month or so, only looked at COVID trials just to get things up and running and make patients eligible for therapeutic trials. But they actually relatively quickly went back to doing additional work. And I think that was also true in most other institutions.

Yeah, I would like to add that typically, things that, for instance, a pandemic will get a little bit more priority, especially in FDA approval and things like that. So you might see research in that realm develop a lot quickly. This was also seen during Zika virus. So a lot of things were happening really quickly for that because it was a life or death scenario.

So there are mechanisms in place with the FDA and other approval boards like Marly mentioned, that do expedite the process for things like COVID. Yeah, so it kind of puts other things on the side.

One of the questions that came in is, do we think that there'll be some sort of crossover research between patients who have Usher syndrome who did contract COVID-19? And we know the virus attacks the lungs and certainly other organs-- the heart, the kidneys, the liver. And are people going to start looking at, for example, the eyes or the ear? And Jen, I know you had and had an answer, at least a preliminary answer to this.

So as of today, this morning I looked. There are 429 clinical studies related to COVID-19 listed on clinicaltrials.gov. Those are the clinical trials that get registered with NIH. Of these, there are 252 conditions that are being studied with relation to COVID-19. So things like lung disease, asthma, and so on.

None of them list Usher syndrome or deaf-blindness. Interestingly, there is one study in the category

or the condition of hearing loss. I'm sorry, not hearing loss-- vision loss. But this study is studying the validity of doing a visual acuity test via telemedicine.

So not all of the studies are even involving COVID-19 patients, but they're related to if you were to have COVID-19 and seeing a physician via telemedicine in this case. So to my knowledge, none of the studies that I know of are including patients with Usher syndrome and COVID-19. And I've not seen any reports or data to suggest that COVID-19 infection or disease affects hearing or vision.

I think there may be more research that's needed to know the full spectrum of cells in our body that express the receptor that the virus uses to get into the cell. Right now we know those cells include the cells in the lung and the lining of the nose that makes its way towards the lungs. So that's a primary target for this virus.

So in terms of, can the virus get into hair cells or photoreceptors or other cells in the ear and the eye that affect hearing and vision and would it make the disease course for an individual with Usher is not known at this time. And, to my knowledge, I don't know of studies that are ongoing with respect to this. I don't know if anyone else in the panel would like to chime in.

I'm assuming that-- because I think there are a lot of-- just as in our institution, I'm sure there is some at Mayo and elsewhere, where they are looking hard at groups of patients who have recovered. And I'm assuming for this meeting next year, there will probably be a lot more information along those lines.

As much as I hate to leave--

[INTERPOSING VOICES]

Oh, I'm sorry.

[INTERPOSING VOICES]

No, I was just about to say that maybe also, methodologically, quite difficult to assess. It may also be an option when patients that have the suspicion that they have COVID or know, and they realize the change, that they really get active and contact organizations or their physicians to report that. Because, otherwise, like you rightly mentioned, the ongoing studies may not have that focus. And it may make difficult in a relatively rare disease to really capture the full extent.

Although, I agree that a priori and biologically, I would regard the likelihood there is a major impact

of these genetic mutations on the course of COVID-19 is unlikely.

Thank you. Well, we'll stay tuned. We have several genetic testing questions, which I think would be to get to. The first one is, is the Foundation Fighting Blindness going to open access to free genetic testing to countries outside the US, for example, India? What are the supporting infrastructure needed to make this happen, and what may be possible challenges to implement it?

Dr. Mansfield, that sounds like this is for you.

OK, Marly. Yes. So I hope everyone had a chance to look at our presentation on genetic testing. But just to summarize it very briefly, the open access genetic testing program that the Foundation Fighting Blindness is currently offering is the opportunity for anyone who's had a clinical diagnosis of an inherited retinal disease-- now that means, of course, those with Usher syndrome.

But it's important to understand this needs to be done by a clinician who believes you have that disease. They're not just taking a guess and hoping that the screening test is going to answer it for them. So if you have a clear clinical diagnosis of an inherited retinal disease, then that clinician may order a comprehensive genetic test, and also, genetic counseling to support that. And there will be no cost to the clinician or the participant, and there'll be no billing to the insurance company.

The foundation, through some very, very generous sponsorships that have come from other foundations and also industry, has been funded to initiate this program of offering this testing. So the testing is very comprehensive. It covers 322 genes, which are nearly all of the genes that we know are involved in inherited retinal diseases. Certainly covers the Usher genes, and it even looks to see whether genes are completely missing or whether genes may have increased in the number of genes in the cells called copy number variations.

So it's a very comprehensive test. And the challenge of offering this is one of regulation. So there are regulations that control the way personal health data can be transferred across international boundaries. And that is something that we are looking at and we need to understand better. But clearly, before we go international in a program like this, we have to make sure that we're doing it in an appropriate manner.

Secondly, a key part of this genetic testing program is genetic counseling. And we think this is as important as being tested. And the reason is that when you get a genetic test, you don't come out with a result like you do with a blood test. Your sugar is high, your sugar is low, you sugar is normal. What you come out with is, to those who don't really understand it, it's hieroglyphics. It's a genetic

readout of all the things they've observed across those 322 genes. And you have to understand what do they mean? Are they actually things that cause disease, or are they just things that are, genetically, the difference between me and you? We're all different. We will have different hair color, size, and growth and all of these characteristics are all genetically driven. So all of these things can show up in genetic testing.

So we have to understand, is it causing disease or is it not? And we also have to understand the clinical context of the patient's presentation. Because genetic testing itself is not the diagnosis of the disease. It is a supplement to good, strong, clinical diagnosis. The two go hand in hand. The same way as a blood test is not going to tell you necessarily you've got diabetes or not. They're going to be coupled with other clinical characteristics to come up with a definitive conclusion.

So that genetic tests, that genetic counseling component is where the patient is spoken to by someone who understands the clinical characteristics of diseases, the genetic characteristics of the diseases, can assimilate them and put them into lay language to tell you, this report you've got really means the following. And these are the opportunities that you might like to follow or that may even be in clinical trials that you would like to get in contact with and ask about. So genetic counseling is really important to couple with testing.

Now we run into some regulatory issues with genetic counseling also. You have to be approved by the federal government to be able to carry out genetic counseling. And genetic counseling is also regulated at the state level. So different states have different requirements about how you can be counseled.

So the group that we use to provide genetic counseling are qualified to provide genetic counseling in all states in the US and US territories. But currently, they are not allowed to provide counseling again across an international border. So we have the genetic testing as a problem with handing information across international borders. Genetic counseling is creating a problem for us also.

And so we really have to be thoughtful about how we can get around these problems and do things in an appropriate and regulated way. So we are trying to come around solutions to this problem, and we're working on different models and discussing how they may or may not work.

Another problem I have to be very honest about this program is, it's really expensive. We've been running it for about two years now, and we've been through $7.5 million dollars. More than that. And obviously, as a foundation, we've raised money to support research, and people want treatments and cures. And so, in raising money to support genetic testing, we have to be very careful that we do not

impinge on the money that we're raising to support treatments and cures.

So we have to go out and we have to get industry and other elements which are not part of our normal funding stream to support us. And honestly, that is very challenging. And so before we really can expand even with outside the US, we need to be able to create a model which makes this genetic testing option sustainable. We believe everyone has the right to a genetic analysis done to understand the genetics of their disease. But when we're having to find the funding for it, this creates challenges for us.

So at the moment, no, we cannot offer the free genetic testing overseas. But there are, maybe, some workarounds and ways that we can help reduce costs for people who are overseas at the moment. And I'd be happy to talk to that in a moment, if that's appropriate.

Brian, could you comment quickly about whether patients need to travel to participate other than to their clinician?

Right. That's a great question. So the clinician is the person who orders the tests, just to make that clear. Patients can't do it themselves. So you may need to travel to your clinician's office to have a clinical consult. By the way, the clinician may charge you for that consult. We don't actually cover that. We cover the cost of the testing, which is several thousand dollars, and we cover the test with the counseling. But if the clinician decides they need to do additional testing on you, we can't actually cover that part. But it's normally a fairly small part of the total cost.

Some clinicians who know you well may be willing to order a test for you over the phone and have a sample kit sent to your home. Typically, they collect now, saliva. So they give you a tube that you basically dribble into. And you have to really dribble well, because there's a mark you have to reach before you can send it back. And then it comes with some packing materials which allow-- and some instructions on how you send it back to be tested.

For the other part of it, the genetic counseling, the service that we have used, which is a company called InformedDNA, do genetic counseling over the phone. So you do not need to travel for that. They will call you. They will arrange a time that works for you. It may be during business hours, it may be in the evenings, it may be in the mornings. It may be even in the weekends. And when you've found a mutually appropriate time, then it's just a phone call for you to sit there and discuss the outcomes of genetic testing and what it means for you. So there should not be much travel involved in this.

I just-- for those who are listening online, I think I'd just like to reiterate what Brian said. We do a lot of testing within our program, but I think the counseling is, at least, as important. And for people to understand really what they might be getting themselves into or not. And so we usually will only test people that we have met, or we partner, as you just mentioned, with their local physician to order the tests. But we also work very closely with a counselor. And all of our patients, even if they live elsewhere, get counseling before we do the testing.

We're doing-- since the hospital, right now-- our current hospital is not sending out elective genetic tests because of the pandemic, we've gone completely to saliva and cheek swabs and buccal collection. Actually, it works great. And the patients love it, because they don't have to have their blood drawn. And they just think that's fabulous. So that's very successful. It's not 100%, but it's certainly-- and, as you said, you don't have to travel. You put it in a FedEx box and ship it to the lab.

But it is expensive. You're completely right. We're running a research study now, where we're getting the exome for free from some philanthropic support. But we're doing the counseling, also, for free to the patient. But the philanthropic efforts aren't covering that. But it's another way to get it done.

I do have a question for Brian. For the information that you have, if a company comes to you and says, we think we have a new treatment or intervention for one of the Usher genes, what kind of access do they have to your data and what are the HIPAA rules around that?

Yes, Marly. Actually, we do a lot of interactions with industry, and also with academic researchers, actually. So it all hinges around the My Retina Tracker registry, which is the foundation's registry, which is in a way a companion to USH Trust registry. Ush Trust is really a registry that's looked to capture everything about Usher syndrome, both the hearing and the retinal defects, whereas My Retina Tracker is very much focused just on the retinal issues.

So people should be encouraged to join both registers. But within our registry, we have an institutional review board protocol, which means they have looked to make sure that we are handling patient information appropriately and protecting the privacy of it. And we have a mechanism by which we will share de-identified data about the genetic testing or any other information in our registry with researchers and industry partners who we believe are respectable.

And I have to say that nearly every one of those partners that we deal with or who've approached us are, there are a couple of companies who do stem cell therapies, which we do not think of being done in an ethical manner, and we will not work with them. But nearly everyone else we will. And we share de-identified data, which means that we will tell them all the information that is known about

the genetics and any of the information in our surveys that we have about how the person is affected by the disease, how they're coping with the disease, the impacts of it on their life.

But we never, ever share their name or their contact information, where they live, how to get in touch with them in any way at all. And we have a protocol in the registry where, if industry look at these de-identified data and say, there are ten profiles here, that we'd really like to talk to that person, we actually pass that information on to the person and tell them-- because we know who they are-- that, here's a company that's interested in you. This is what they'd like to know about you. If you're interested, here's the contact information, the company have given to us. Follow it up. If you're not sure, talk with a clinician. Find out what your clinician recommends for you. But it's in the hands of the person who's affected at that stage. They have the contact information. They can reach out and connect with the researcher or company asking about them.

But, on the other hand, if they're really not interested in that opportunity or don't want to be bothered, they don't need to do anything, and no one knows how to get them. Only the registry staff do, and we're not telling anyone.

So we do share a lot of that data. The sorts of questions we get are, can we get people for a focus study where we'd like to understand the patient journey? Can we get people to enroll in the clinical trial, in a natural history study?

And companies also just want to know about the prevalence. How many people in the US have this gene which is affected? Or how many people in the US have this gene with this very specific mutation affected? All of that information, we share with industry and academia. That's a key part of our mission in accelerating these treatments and cures that we're all focused on.

Thank you. And a corollary question to that from the participants is, natural history studies-- are of the panelists involved in natural history studies, and if so, which gene? They're obviously very important, because you don't know if it improved somebody's health if you don't know what they looked like before.

So the foundation, the My Retina Tracker registry does support a number of companies who are doing natural history studies. For reasons of confidentiality, I can't name those companies. But we've certainly been approached. We've helped them to enroll people with a variety of different genes affected.

The foundation also has its own clinical consortium, which is a consortium-- an international

consortium of clinicians around the world who use common protocols and share data amongst each other to carry out natural history studies. And we have ongoing natural history studies in the USH2A gene. And we also have one that's just started up in a gene called EYS, which causes retinitis pigmentosa.

And again, the registry has been used in helping to identify people who qualify for that. I think one of the important things for people to realize, though, is that if you're in the registry and you have a particular gene, you may not be contacted. The industry and academic partners often come with other criteria. So they want someone, say, with an USH2A gene, but they'd like people with only a visual acuity between a given range. They would like only people who have a particular age range. And they may even want them in a particular geographic region, because the clinics that they're working with are in a particular region and it cuts down on travel and other consequences.

So rest assured, if you meet the criteria that we are provided by the industry, we will certainly connect you and tell you of the opportunity. But also, understand if you haven't been connected, it may simply be because you don't quite fit these criteria that our partners are asking us to match at the time.

Thanks. So the next question--

[INTERPOSING VOICES]

I'm sorry, go ahead.

No, I just realized that there was a question from the audience on that aspect. If we have certain eligibility criteria for a trial, then there was the concern that they would be too narrow and only finally allowing approval for a certain subset of patients. So I think, first of all, most of the trials or all of them are in early stages. And at these stages of development, you want to just have first, prove that your drug really does something. That, in most cases, doesn't allow to include too early or too advanced patients, just for technical reasons.

Then, as you advance the program, you try to make the eligibility criteria as broad as possible to really have a sizable population that can benefit from your treatment. That can be done until registration or even after the first subset of the entire population is registered and the drug is approved for them.

So it's not the intent to go super narrow. Intent, if you develop a drug, is always to get it to benefit as many patients as possible.

Thank you.

Marly, I'd just like to add that my laboratory also conducts three national history studies for patients. One of them is for all types of Usher syndrome for residents in Louisiana. And it's a retrospective study, so there's no travel that's required for participants. And for that, we review medical records in all, in hearing and balance and in vision. And we also provide genetic testing for those participants.

And the other two studies are prospective studies. And they are for patients with USH1C and patients from around the world with USH1C can participate. And we have clinicians in Louisiana, as well as in Montreal, Canada with Dr. Robert Koenekoop and at the National Eye Institute that participants would need to travel to see our retinal experts or our balance experts for those studies.

Thank you. One of the other questions is, if your particular type of Usher syndrome doesn't seem to be represented in one of these natural history studies, how would you-- this is a big question. How would you go about starting your own sub-type so that you make sure that you get represented? I think there are a lot of different ways to approach that.

[INTERPOSING VOICES]

Yes?

Is this asking-- is it how to go about doing a natural history study on a sub-type that's not currently represented?

Yeah. The exact question-- sorry-- is, what can patients do is support more natural history studies if their sub-type isn't yet being studied?

Right. So one thing to appreciate is that natural history studies, when they're done in a clinically controlled manner, are very expensive studies. We're talking multi-million dollar studies, here. There's a lot of expense in setting these up and getting everything calibrated, certified, and then all of the clinical exams that are required to make these useful. You really want to be looking at a wide variety of clinical endpoints. You don't just want to watch what happens to visual acuity or what happens to a specific aspect of hearing. You really want to take every technique out there that may be useful and examine how the characteristics on those tests change over time.

Because in natural history study, you're not only trying to find out how the disease changes over time across a population of people with that disease, you're also trying to understand, at the end of it,

which of the measures that you used are going to be the most useful and most significant to use in a clinical trial? You want to know that when you do a clinical trial, the measurement or the end point that you're using is going to show a significant difference during the length of the clinical trial.

So picking the right measurement to use in a clinical trial is critical, and that comes out of natural history studies. So it is challenging. The foundation's clinical consortium has discussed trying to design studies where we use multiple different sub-types of the disease such as Usher into a single study. And those discussions are ongoing.

The foundation also works with Usher groups who might have some funding to try and find a way where we can co-fund, together, a natural history study. And, in fact, there is the one Usher group at the moment who are in discussions with us about the way that they together with us may be able to fund a study of their particular sub-type. So one way to do it is to talk with our vice president of outcomes research, Todd Durham, and talk to him about natural history studies, talk to him about the cost and the design of them, and also, explore ways that we may be able to do that in partnership with his clinical consortium.

Thank you. I think we have time for one more question. We're almost at the end of the time limit. Wow. So this question came from a participant. Many community organizations are raising funds to support the efforts of the researchers. In addition to these funds, are there other ways to find additional funding? How to advanced efforts specific to Usher syndrome from larger entities, or government support? Always a good question.

I know that-- I can speak, and maybe Krista can speak to this, actually. There has been an effort, certainly from the Coalition, to work with the federal government to carve out money for Usher syndrome research, both on the hearing loss side and the vision impairment side, which has been, to some degree, successful-- at least get on the radar screen. But I'm sure there are other ways people have approached outside funding agencies. They don't have to be the government.

Any other comments about that? Finding money is always tricky.

I will just make a comment. One thing that we do at the foundation, obviously, we fund a lot of research, is we work with corporations and foundations, especially in the United States, and try to identify those that have programs that will support eye research or some other aspect of our mission. And sometimes, you'd be surprised. Your own employer-- especially if you work for a big corporation-- may have a separate foundation that funds research or public awareness or something that might connect to the mission.

So that that's how we-- we obviously, at the foundation, raise a majority of our funds from the families and patients. But we do work with corporations and foundations. And if you happen to be connected to those or you want to reach out to those, some are very interested in vision and hearing research.

Thank you.

Marly, I just might add, to piggyback off of the last question, as well. If you are a patient or a family with Usher syndrome, one of the ways to help support natural history studies is to continue to see your clinicians annually, having detailed clinical records of your specific course of Usher syndrome, will be helpful someday. And natural history studies have become a very important aspect of therapeutic development.

In my research, colleagues and the environment at the National Institutes of Health, the current movement is such that participating in a natural history study won't guarantee that you would be able to participate in a clinical trial. But having that kind of detailed clinical history will become more and more required. So even just seeing your clinicians every year will be very important, in addition to receiving care for your symptoms.

And then, lastly, from the perspective of a patient or a family, how can you help support research? In addition to-- there are a number of foundations. So reaching out to them and getting to know them and working with Usher syndrome foundations or foundations specifically for your type of Usher is a great thing to do.

Also, as you mentioned, reaching out to your representatives in the states to put pressure on Congress to divert dollars towards Usher syndrome has put Usher research on the map for the Eye Institute and the Hearing and Balance Institute. So the more pressure that way, the more money will get funded or funneled towards research. Those are also good things to do.

I do want to piggyback, on that note, from Dr. Lentz about the importance of contacting representatives. I've lobbied on Capitol Hill twice for biomedical research. And really, how it goes is, you will talk to someone-- an aide that works for a representative, and that aide will pass on the information. So if it's one person calling about general biomedical research from the state, it might not have as big of an effect. But as Dr. Lentz said, if 100 people are calling and the aide goes to the representative and saying, this is a huge issue in our state, 100 people called in the last two months, then they're more likely to listen.

And I don't think we take that as seriously as we should. And we need to remember that our representatives work for us. So thank you, Dr. Lentz, for bringing that up.

Thank you. That's exactly how we got the hearing aid bill in Massachusetts. We had everybody in Massachusetts who had hearing aids that hadn't been funded call the government. And then they showed up at all the hearings, and that's exactly how it worked.

There was one last question on Usher syndrome 2C, which we haven't really touched on yet. I know Jen, you maybe answered that at some point in one of the asks. But we just got the last question about that.

Oh, we can't hear you, I'm sorry.

Remind me of what the specific question is?

No, it just was a question about whether there's any information on Usher syndrome type 2C, as it hasn't been touched on yet. But I know there's nobody in particular on this group that is a Usher 2C person. But anybody has any information, that would be great. Otherwise, we'll just respond to these questions online.

There is one last question that came in before we started, which was about whether there's any research showing the lack of tooth enamel related to Usher syndrome. And Jen, I know you answered that question. So we can maybe almost close with that.

Yes. So, in the past, there have been reports of clinical overlap with Usher syndrome and the symptoms of tooth or enamel defects. So there is overlap with Heimler syndrome as well as Zellweger syndrome, spectrum disorders, and Usher syndrome. All of these syndromes have components that include hearing loss and visual loss. And the Heimler syndrome also has the enamel defects in teeth, and Zellweger also has neurologic dysfunction and craniofacial abnormalities.

And there actually has been specific reports on Usher syndrome with these other syndromes, as well. So these patients appear to be carrying mutations in both Usher syndrome, as well as other genes that cause these syndromes. So De La Pena and Galea reported on an Usher patient with Heimler syndrome in 2011. Balmer and Fayle also reported on a patient with Zellweger and Usher in 2007.

So you can reach out to me, and I'd be happy to forward some of those reports. But there is some

clinical overlap with other syndromes that contain hearing loss and vision loss.

Thank you. I mean, we actually see patients who think they have Usher syndrome, and then when they're carrying one mutation or they have a variant unclear significance, and it turns out they actually may have something else. So it really speaks to the necessity to have, not just genetic testing, but updating interpretation of the tests that you might already have had.

I think we're at the end of our time, so unless anybody has anything else they would like to offer, I'd like to thank everybody for lasting for an hour and a half. I think this is just the tip of the iceberg questions. And I'm sure there will be updates to some of these things at next year's meeting, whether it's virtual or it's in Texas.

Marly, I just-- if I could just mention one last thing. We just updated the Usher syndrome type 1 gene reviews, which is published on NCBI. And so, as of last month, we have a whole new updated Usher syndrome type 1 that has a lot of the updated information on genetics, genetic testing, other disorders that look like Usher syndrome, all of the new therapies that are in clinical trials now that involve Usher patients, and a whole variety of resources for patients and clinicians.

And we are about to have the Usher 2 gene reviews published, as well. So stay tuned to the next month or so. This one will be updated. So there's a lot of great information for everyone on those.

Oh, thank you so much. Because that's one of the places we send our patients, certainly, or they get there ahead of us.

Well, thank you very much. I know this is in the middle of your afternoon, at least here on the east coast. People who were maybe in other places. But thank you so much, again. This was a lot of great information. I certainly learned new stuff, and hopefully we'll see you all at next year's meeting. Thank you very much.

Thank you.

Thank you.

Thank you. This has all been recorded, so we can always rehash it or think about it. If not, everybody could hear everybody. Also, thank you very much to the interpreters, who have been working very hard and switching over every 20 minutes. I'm sorry if we talked too fast. I know Dr. Lentz knows better. All right. Thank you very much.

Thank you.

Thank you.

Bye bye.

Take care. Bye bye.