

July 13, 2013  
Usher Syndrome Family Conference

Mark Dunning: Okay everybody. Sorry for the delay. We're just trying to get everybody situated here. Thank you for coming. I'm Mark Dunning, chairman of the Coalition for Usher Syndrome Research, and I'm also known as Bella's dad.

She's on her way to the museum with the other kids. I'm going to introduce Krista Scheall in a minute, But she deserves a big round of applause. She is the Executive Director of The Usher Syndrome Foundation, and I want to thank Todd and Lane McKittrick who helped, did a lot of the arrangements for today but also have helped to fund this event here today.

And Todd is also doing the duty of taking the kids to the science museum today, which is really hazardous duty especially since he's with his mother-in-law for the day.

I want to thank them both for their efforts, and I want to thank CM Hall who helped organize all of the interpreters and SSP's I see here today, and there are a lot of them, so thank you for that.

And Elizabeth Archer over here with Archer Captioning is doing all of the captioning today, and we will be getting a transcript of this at the end, so we'll have the transcript available too, so thank you for that.

I also wanted to thank Duane Davis who brought the FM system. If you are in need of an FM and you haven't picked one up, we have them in the foyer out there. Please make sure you return those at the end. They are loaners.

And I want to thank Mitch Turbine who helped get us get in touch with the key people I just mentioned, so thank you, Mitch, for that.

And I can't tell you how excited I am to be back in the Northwest. There is a vibrant group out here, and it is great to have people like CM to help with the interpreters and SSP's because in the rest of the country it is just not available at all, so it is great to be back up here, and we hope to be back up

here soon.

So Krista will talk to you about the housekeeping stuff and then we'll get started.

Krista Scheall: Thank you everyone and good morning. Thank you all for coming. Thank you for your patience. If you haven't seen, the restrooms are located outside in the hallway to the right. And as Mark mentioned, if you are in need of an FM system, they are in the foyer with the breakfast and coffee.

If you have trouble getting set up with the real-time captioning on your personal device, if you brought your iPad or tablets, we can help you with that. Find me in the back and I'm happy to get you taken care of.

We're going to be taking 15 minute breaks during the presentations, so there will be a pause and the interpreters will switch. So break every 15 minutes to allow for that transition.

On the note of breaks, we do take fairly long breaks. We have a break from 10 to 10:30 and one in the afternoon and an hour-and-a half long lunch. We allow longer breaks to network and meet with the folks here, so I hope you can take advantage of that.

And we have a coupling of fliers on the tables where you are sitting. They are a Save the Date for next year's conference on Usher Syndrome.

This is going to be in Boston in July of next year, and we hope many of you can attend and be part of both the science research side and family conference that we hold each year.

And the other flier is for the Usher Syndrome registry. We are hoping to voluntarily register everyone with Usher Syndrome on this registry for the purpose of clinical trials, and if you haven't signed up, you are more than welcome to do so.

We'll have the registry set up in the foyer as well, and you can find me and we can help you with that.

And I think that covers everything for housekeeping. And if anyone needs anything, has any questions, feel free to find me. Thank you very much.

Mark: Okay. Thank you. This mic is not at the right height for me. Dangers of being tall.

I wanted to talk to everybody a little bit about the Usher Syndrome Coalition and specifically around our goal of trying to build an Usher Syndrome community and providing more hope to people with Usher Syndrome.

And I apologize. I had a request to change the background of this to be a little bit more visually friendly, but I didn't have enough time to make it successful, so we're going to have to deal with the black on the white.

I'm the chairman of the Coalition for Usher Syndrome Research. I'm really Bella's dad. She is now 14 years old. She was born deaf, profoundly deaf. She has two cochlear implants. She was diagnosed with Usher Syndrome at the age of eight, and as you can see from the picture, she loves horses.

That's her main thing, and she grudgingly loves her little brother Jack.

But my story's a lot like a lot of people in this room. I think it is important that as we hear about all the science today we remember it all comes back to the families that are here. That's one of the reasons I'm excited to hold this symposium next year to have the scientist and families get together. I think it is great for both sides when we're able to do these kind of things.

So, if you are here you know what Usher Syndrome is. But I know we also get a lot of young families at these conferences who are just learning about Usher Syndrome, so I'm going to take a couple minutes to talk about it.

And my whole talk is about hope, but as I go through this there is scary stuff about Usher Syndrome and some of the relations of Usher Syndrome, but I'm also going to be able to break down some of the myths around Usher Syndrome and some of the things people assume are the case that are not necessarily true.

It is the second leading cause of deaf-blindness in the United States and

Europe. Does anyone know the leading cause? Malnutrition.

We have a number of people here from the Helen Keller Center, which was dedicated to solving deaf-blindness, and if you go to the website, it is almost solely about malnutrition.

So Usher Syndrome is the second leading cause of deaf-blindness in the United States and Europe. It is congenital hearing loss and progressive vision loss from retinitis pigmentosa.

We diagnosed about three percent of patients with congenital bilateral hearing loss that have Usher Syndrome, but the percentage of people who have the Usher Syndrome mutation among that population of congenital bilateral sensorineural is probably closer to eight to ten percent, and I will talk about why that is in just a minute.

We're talking 30 to 50 thousand people in the United States having Usher Syndrome, and since it is an orphan disease, does everyone understand that with 200 thousand, Usher Syndrome is still an orphan disease? And

that includes all the different types.

There are twelve different genes now Jennifer? Eleven? Eleven different genes, so we're lumping together eleven different diseases under the term Usher Syndrome, so it is quite a rare disease.

I'm going to talk about the clinical impact, so for our parents this is sort of the scary stuff.

When we say congenital hearing loss, we mean hearing loss at birth, and I put a question mark in there about at birth.

There is a question about whether or not the hearing loss is similarly progressive as the vision loss, so there is a chance kids are born with more hearing than we realize before we test them.

And this is important because we have Jennifer Phillips here and we'll get more into the science of this, but she's been working on a treatment to rescue the hearing and vestibular function in mice, so the question is is



there enough hearing in the kids to benefit from that and rescue the hearing?

So that's what we mean by at birth. But essentially for kids with Usher Syndrome it is at birth. When we say bilateral, that is both ears. One ear, it is unlikely it is Usher Syndrome and sensorineural, which means the hair cells in the ear. It is not the structure of the ear; It is the hair cells that are the problem.

And it is usually moderate to profound hearing loss that we're talking about. But there are cases of mild hearing loss. We know a woman who claims she has Usher Syndrome genetically but claims she has no hearing loss. Most likely it is mild.

We're fortunate today and we're going to have a speaker soon, Dr. James Philips, who is going to talk about vestibular function, and he will do a better job of explaining vestibular function and Usher than I do.

There are balance issues associated with that. So people tend to appear

clumsy when they are younger. They have low tone, although if you see the picture of my daughter in the bikini on the horse, she doesn't have that.

But Type I, they are late walkers with poor balance. IT is a little harder to identify, so they tend to get caught at the younger age than people with usher Type II or III.

There are three componentS that go into balance. I learned all this from Dr. Philips, but they are vestibular function. That's the inner ear, your vision and muscle. You can see the problem here if you have vestibular problems to start with, and then you start to lose your vision. you become almost completely reliant on your musculature, so as people get older balance, is a bigger issue for them.

The part that is probably the most scary is the retinitis pigmentosa and mostly because we don't have any real treatment for this at this point in time.

Retinitis pigmentosa is a degenerative condition of the retina cells

impacting rods and cones, but you see in the rods initially and the initial part people notice they start to suffer from night blindness, and that was the first thing we noticed with my daughter.

We took her camping and my son could run straight to the bathroom in the middle of the night, and my daughter was clinging to me like Saran Wrap. So the night blindness is noticeable and then the slow deterioration, so the narrowing down to tunnel vision.

It doesn't work specifically like that. You are getting spots in your vision, but you might not notice that because the brain fills those in. It takes the surrounding areas and fills in the spots.

So as my daughter gets closer to driving age and wants to drive, she doesn't know what she doesn't see half the time.

So, retinitis pigmentosa, I stole these next slides from Bill Klingerling who couldn't be here today. But that's where you can only see the brightest of the lights.

This is normal peripheral vision. And you start to get the holes in the vision that the brain tends to fill in. As you get farther along, you end up with the tunnel vision.

Now traditional diagnoses of this, and when I say traditional diagnoses, this is the way it has been delivered to families. They heard that they have Usher Syndrome, and I can tell you that people in this room, the doctors here today don't deliver this, but there are people here who have heard this. People with Usher Syndrome are deaf and they go blind. There is no treatments for Usher Syndrome, that there is nothing you can do to slow the progression of it, and it is so rare you probably won't meet anyone else with Usher Syndrome. You can guess I'm going to dispel these.

Anyone in this room met anyone with Usher Syndrome? So that is not true. The Internet helps us with being able to connect with other families. One of the many things I love about this conference is getting to meet people who I talked to on the Internet for a long time, and I can see you smiling here. You were one of the people I talked to for a long time and

today we have a family from Alaska and a family from England that are going to be here and have talked to each other for a long time that are getting to meet finally through this stuff.

So we're, the whole idea you won't meet anyone else with Usher Syndrome is not the case, and I will talk about these other things in just a second as well.

But this diagnoses has a big impact on the individual when they get it and families when they get it. And this is the scary stuff I'm going to talk about in a second here. It is not really the disease that frightens families and not the future, the future with hearing loss and blindness, it is the idea of social isolation.

That's what scares people is the idea because I'm deaf and blind what can I do? I can't be with my family and friends and have the career that I want. That is what frightens people.

And I stole the next four slides from a social worker who has done a

number of studies on the social impact of Usher Syndrome. I think she will allow me to steal them when I tell her I stole them

When you talk about the diagnosis of retinitis pigmentosa, people are having problems. In the case of people with Usher Syndrome, they are already dealing with hearing loss.

With my daughter, we thought we had the hearing loss under control. She was heading into mainstream schools and doing great with the hearing loss aspect, and we addressed most of her vestibular issues. She was taking horseback riding and then comes the retinitis pigmentosa, and the future changed completely.

So that brings on all the fears and anxieties about the future. You have this progressive disease, and you don't know what the future holds for you, and that leads to fears, anxieties and suicide.

People with Usher Syndrome are two-and-a-half more times to commit suicide than the general population. What we want to try to solve here

with the Usher Syndrome Coalition is to address these psychosocial issues, and my goal and the goal of the coalition is make it so the last number is the same as the general population, if not better, and if we build a stronger community, it can be better.

Deaf-blind people generally don't fit anywhere. By that I mean you are not hearing loss; you are deaf-blind, so you are not just in the deaf community and not just in the blind community. You don't necessarily fit in the normal hearing seeing communities.

And what happens to people when they have Usher Syndrome, they find their friends tend to withdraw, and it is not because friends are put off by Usher Syndrome, but they can't figure out how to deal with people who are having problems with vision, and it is difficult for the person with Usher Syndrome to constantly advocate for themselves.

You are going to a party? Can you pick me up? They don't want to have to do that, so they slowly lose touch with their friends.

And here in the Northwest, Seattle in particular, there is a strong community, and that helps a lot, but that's another thing we're trying to address to ensure people don't have to deal with that social isolation.

People lose their jobs when they lose their vision, and that's the reality of it, or the job is too difficult to continue to do. People get a job that is less of a challenge than they really wanted, and people, fewer people work as their vision deteriorates, And 82 percent of people who are deaf-blind are unemployed. 82 percent. That's another issue we need to address.

And Usher Syndrome, being a progressive disorder, it is on-going and a lot of the adults here can testify to this. With Bella we thought we were dealing with hearing loss and then hearing loss and vision loss. First night blindness and then night blindness and loss of peripheral vision. And you think you have that under control and there is another advancement in the disease, so it's a constant on-going feeling of grief always trying to adapted to where your vision loss is at any given time. So that's all the bad news. And at lot of bad news, but hang in there. Let's talk about the good stuff.



First, the world is changing. We talked about the Internet and our ability to communicate now that is there and it is a big thing.

Technology is a big thing. Krista was talking about getting CART on the iPad and iPhone. Five years ago that wasn't there, and now you can do that.

There is a lot of hope for families with Usher Syndrome. And one of the things I want to address is the truth about the diagnoses.

Hearing that you're deaf and you are going to go blind and nothing can be done is not really true. We don't know the normal progression of Usher Syndrome. We have a general sense of what the normal progression is. We don't know enough about it at this point.

I talked earlier about the three percent. We used to diagnose people at three percent and now it is more an eight to twelve percent number. The question is why did we only get three percent before when there is really eight to twelve percent of the people that have it. And there is a chance that's because people, the vision loss don't always deteriorate as we

thought. So being told your future includes blindness is not true, but it could be at a slower rate.

As we talked before, blind is not necessarily blind. If you told people you are going to go blind, the definition, people view blind they can't see anything and they have zero vision; they are in darkness all the time, but people with Usher Syndrome, about 50 percent of them can still read a newspaper at 50. So the deterioration is not to the degree that you might get with the sense of when people say you are going to go blind.

And the big question: What if we can slow the rate of progression? Say my 14 year-old daughter, if you were 50 percent of the people who can read the paper at age 50, what if we can find something in the next five to ten years and turn the 50 into 80? Does that mean people are going to go blind? Why are we telling parents their kids are going to go blind?

And deaf is not deaf. Not everyone is using manual communication for their communication with deafness any longer. A lot of people use hearing aids and cochlear implants, and as a lot of my deaf friends can tell, you

being deaf is not that big a deal.

The definition that you are deaf and you are going to go blind gives you a sense you are destined to social isolation, but from the community here today you can see that's not necessarily the case.

There are treatments available for Usher Syndrome today. When people say there are no treatments, that is not necessarily true. This is not necessarily 100 percent widely accepted treatment, but there's been a long on-going study of vitamin A for people with retinitis pigmentosa and the ability to slow the disease, and it is prescribed to a lot of families.

And if you are interested in that, that's something you should talk to your ophthalmologist about. and there is a strong indication that sunglasses and hats and protection from the bright lights might slow the progression of the disease, and there is a study on Usher Syndrome mice.

We had problems with Usher Syndrome mice and we had trouble getting the vision phenotype, getting the mice to lose the vision at the rate we want

them to, but they found if they exposed them to bright lights, they're able to get that vision phenotype going. That is long way from proving sunglasses are going to slow the progression, but it can do that. If you ran into my daughter, she has those glasses that automatically tint, so if she's coming in from the outside she has sun glasses on.

So this is hope. Okay. If these things slow the progression of the disease and you have vision at 50 and you were able to slow it down 10, 20, 30 years, you may never fully lose your vision.

My concern around the way the diagnoses is presented can be summed up here. This is a quote: The future influences the present just as much as the past. I view that when you tell people you are deaf, you are going to go blind and nothing can be done, people fear what that future means for them, so they disengage.

Why go to the doctor when it is just bad news, and when those people disengage and don't stay involved in the Usher Syndrome community, it slows the research. So the goal is to keep people involved in the research

that's being done. Engaged families are critical to finding the cure. You guys are the source, the natural history.

We don't know the progression of disease, but we can learn from your natural history, how the disease progressed for you. That is critical information. We need that information because, when we do clinical trials, we need to know if the treatments that we're trying are actually helping or not. The only way to know that is to know the normal progression of the disease.

Genetic information. There is eleven different genes that are known to cause Usher Syndrome. When I started doing this, there was nine. Two or three have been identified just in the last five years as causing it, and that comes from families coming in and being tested.

Families, we are going to talk about the clinical trials and how difficult it is to identify candidates, and you need a large pool of people, so the more people we have in our Usher Syndrome registry the more people we can contact to see if they are interested in the trials and the better the chances

we can have enough people for these trials as they come along.

You guys are the sources for funding and lobbying. When we try to get money from the federal government, if we go with 30 thousand we go farther than if we go with 30 voices. Hear See Hope. I mentioned that earlier. They are doing fundraisers and have funded a lot of research.

So the Coalition for Usher Syndrome Research, one of our main goals is to engage families. One of the ways we do this we run these family conferences, which I can't tell you how much I enjoy coming to these things. We run a registry. It is online.

It was mentioned earlier there. fliers on the table here and we want to voluntarily register everyone in the world with Usher Syndrome. We have 23 different countries available in Spanish and English and soon to be available in Hebrew. We have Dutch and French translations in development, and I mentioned earlier we were able to connect a family from Alaska and is that Cloie in the back there from England? So that is a great opportunity to meet other families.

You might not know a family next door that has a kid the same age as your kid with the same type of Usher Syndrome, but I can promise you we can connect you with someone, and we connect lots of young adults and it is a great opportunity.

We do monthly conference calls, And we are well-aware of our constituency here. Conference calls are not the easiest things to do, but we do have the captioned calls and we have the notes online afterwards, so if you can't attend you can read the notes online.

We do daily communications on Usher Syndrome issues and research. And check out our FaceBook page. we're on FaceBook and Twitter. We have the website, and we have been doing advocacy efforts for funding, and we have been successful in the last few months, and hopefully more federal funding is coming down the pike. It is very difficult in Washington D.C., so it is good for us. we have made many efforts on that front.

The real hope about Usher Syndrome and the thing I really wish was what

was communicated first and foremost for families when they're diagnosed are these facts right here.

People with Usher Syndrome can have athletic success. I know a man with Usher Syndrome who climbed Mt. Kilimanjaro and you saw my daughter on the horse. Having Usher Syndrome does not mean you can't have athletic success.

People with Usher Syndrome go to college. They get advanced degrees. A lot of people with Usher Syndrome have graduate degrees and doctorates. People with Usher Syndrome fall in love and get married. I know I'm speaking to the choir here. They have children. And people with Usher Syndrome have successful careers. So that's the reality of Usher Syndrome.

It is not socialized. deaf-blind, and your future is going to be miserable. Your future really is what you make of it, but I think it is important we continue to building these types of support mechanisms. So one of the things I want to make sure you do today is get to engaged, and being here today, you are.



Join the family network and the registry. We can get you registered today if you are not already. Join our monthly conference calls or read the notes. Follow the blog on our website.

Dr. Jennifer Phillips writes the blog with me and one of the comments, IT is one of the most thoughtful explorations they have seen or understood on the Internet. and it is probably one of the only ones, but we'll take it. And you can follow us on FaceBook and Twitter.

I hope next year You can come to the international symposium we are holding in Boston. We're going to have the majority of the scientific experts, And we hope to have a lot of families, too.

Thank you. That's my piece, and I think that's it. You guys want to switch and I will do the next introduction.

Okay. So, our next speaker is Dr. Jennifer Phillips right over here and Jennifer is at the University of Oregon. She is a research associate, and

she has been writing the blog with me three or four years; a long time. And she's a good friend of mine, and we're lucky to have her here. She is going to talk to about the genetics of Usher Syndrome or similar things. Come on up here.

Dr. Jennifer Phillips: Good morning. Thank you Mark and organizers for inviting me. I'm honored to speak with you all today.

This is the first talk I have ever given that I didn't have to explain what Usher Syndrome is. I do have some main goals of the talk and one goal that is not here is I'm going try to set up the rest of the day's speakers to give you an overview of the things researchers talk about. So I hope this will lead to a better understanding of what is to follow.

And mainly I want to talk with you about how changes in genes cause disease, how things happen in our DNA have a manifestation of anything about our physical appearance, behavior, and things related to disease as well.

And following from that to talk about why there are so many different ways to get Usher Syndrome and the link between these two things really has to do with the proteins that are involved in Usher Syndrome. So I will talk a little bit about proteins and what we know about what they do and how changes in DNA lead to changes of proteins and symptoms of the disease.

So, some of you perhaps know that the molecule of life, the code and blue print of everything that we are is in the DNA. DNA exist within most of the cells in our body. If you took it out it would be three meters worth of information. There is a lot of information encoded on that strand and all the cells have the complete volume of you, 30 thousand bits of information, genes that dictate everything about your physical being.

DNA is organized into pairs of chromosomes. You inherit 23 from one parent and 23 from the other parent. Chromosome is Greek for colored body. They look like stripped squiggly things. They are numbered 1-22 referred to as autosomes and X and Y determine genetic, sex.

So altogether the individual or species is referred to as genome. If we got

DNA from everyone in this room it would look similar. You couldn't distinguish one from the other other than looking at the gender based on how the chromosomes look. We look at the information encoded on those physical pieces and we see some differences, differences in the building blocks that make up the DNA that are called nucleotides and those differences create everything that's different from us from our neighbor and the other people in our species: our hair color, our eye color, and a number of other things including the presence or absence of a genetic disease.

When we look at these genes we see them on a number of different of these autosomal chromosomes numbered 1-22. If you look at number one, you can see a little red star that is indicative of the location of the disease that causes Usher II.

In order to have a diagnosis of Usher Syndrome you need to inherit two defective copies of the gene one from each parent. So every chromosome that has an Usher Syndrome gene you would need to inherit two bad copies and that's why when we talk about type of disease we use

the term autosomal recessive.

So when we look at what is a disease causing mutation and what will give you Usher Syndrome versus not, at the DNA level if we look at disease causing gene it looks like a different code.

When we look in the lab at DNA sequence, you see this on the slide the series of peaks and valleys that show which building blocks are in which place along the gene, but when we translate the code and see what it says, we see the difference between a healthy gene that encodes health information and one that causes problems and that's because the DNA is the blueprint for building proteins. Those are the things that do the work of the cell and whatever function, whatever ability the cell has comes from the actions of the proteins within it.

So changes for the instructions on the DNA result in changes to the protein product. By way of example, mutations can cause a lot of different changes. At the top of this slide you see a normal protein. Many different parts and colored boxes indicate different functional areas of the

protein. Sometimes the protein will stop short and will not complete normal length.

Sometimes the mutation can cause information to be substituted so it can have the old information and new things and sometimes information can be added and poked somewhere.

Any of these changes and you can have multiple changes. The protein's work can be compromised within the cell and it can't fit in the right spot and interact with another protein that is important for a multipart job or otherwise function normally.

So, we already been well-introduced to Bella by her father. I think we can say Bella is probably the most famous person we know with Usher Syndrome Type IB, and she is famous because of what she and her family with done with that information. They have given our community, well, our community. They have helped expose to this disease worldwide. They helped build a community and raise money for this disease, and through the actions of her and her family, they have given us, the researchers,

some new information on the types of mutations that cause Usher Syndrome Type B.

She has Usher Syndrome Type 1B. So in that protein shape, that's in the middle of the slide with the different colored box, this is what a normal protein is, how it is constituted. In Bella's genome, she has two different ones. When there's sequenced, they recognized this as something that was previously identified, but on her other chromosome they found a new mutation that stopped short and added something extra to the bottom right-hand side of the slide.

This was not detected prior to Bella having been sequenced, so this is new information that has contributed. And both of these together is what makes Bella part of who she is.

One question Karman Trzupke is going to talk to you about later today is how we can tell which mutations are going to cause the disease. There is a lot of information to go through, and it is not clear which changes are going to cause the disease versus which ones are there and not harmful.

Prior knowledge is helpful. As we saw in Bella's case, correlation can help us understand what things cause Usher. We can use animal models or cells in culture to create those proteins with those changes to see which ones are going to cause problems in the cell.

But as Mark explained to you, information about the changes that cause Usher Syndrome comes from you. You are the source of our information. So everyone's contribution is valuable and people can contribute new information used to help everyone in the world with Usher Syndrome. So I will pause for a change over, now.

Speaker: We have a question over here. I have a question. Should I stand up? my name is John. My parents went to the doctors for blood draw. I'm curious about the match in terms of DNA.

I'm John from Seattle, Washington. And when my parents went to the doctor to get a blood draw for me they said it cost 90 dollars but it was not successful in some terms, so my question is, will every blood draw be



successful or no. like if you are getting your genes, genetically tested?

Dr. Phillips: I don't know the success rate. But things have changed dramatically and you should be able to get some information, so I would encourage you to follow-up with your physician. Thank you for your questions.

Mark: Karmen's going to talk about genetic testing this afternoon, too and we can take questions on that, at that point.

Dr. Phillips: I'm going to transition now to the second part of the talk and talk about why there are many different ways to get Usher Syndrome and that will require diagnosis of the cell types.

We're talking about proteins that exist within cells and we know Usher Syndrome is a disease of the ear and the eye as well as the balance system, so we'll talk about the particular cells involved in causing those disease symptoms to appear.

First within the inner ear, which in mammals inside the cochlear is lined with a large number of what we call hair cells so called just because of the little paint brush like things that protrude from the top. In the retina the light-sensitive tissue in the back of eye are photoreceptor cells. There are similarities between these cells. It is thought they evolve from a similar ancestor that was used to detect things from the environment and translate that information into a language or into a signal the rest of the body could understand.

And that's essentially what these cells do. They are different. there are differences and specific functions unique to one or the other, but in general they take information from the environment, either sound or light, and they convert it into a signal that the rest of the body, and ultimately the brain, is able to interpret as either sound or light.

It makes sense then that because they have similar jobs they might have some structures in common and in fact they do. They have specialized tops. They have cilia. They have a little rod or stiff area in them that is responsible for structure and conveying molecules up and around in the

cell and they have specialized ways of getting the signal out. When they communicate, they do so through synapses, and they're different from the synapses in other nerve cells.

And because you see the similarities of the cellular levels, you can interpret correctly there are similarities in the molecular area. And Usher Syndrome is a disease of the eye and ear because they use the same molecular structure.

So Mark inferred earlier there are a great deal of genes involved in Usher Syndrome. So far we know eleven of them were identified, and Mark pointed out that this list that is growing. We know there are more genes and more people who have Usher Syndrome that don't fit any one of these categories. But if you know a little bit about proteins, it doesn't make sense at first glance.

They are not all the same kind of protein. They don't fit into a category of things that might work together in a nice pathway or a system that is easily understood by looking at the functional parts that they have.

It is very complicated. However, we know already that mutation or changes that affect anyone of those proteins causes roughly the same symptoms with the vision and hearing and sometimes the balance, so we have a common denominator. We just have to figure out what it is.

When we see human patients with Usher Syndrome we can test their hearing and test their vision. When we use animal models we can look more closely at the cellular and molecular changes that go along with the changes in these genes.

When we look at the hair cells from the cochlear of mice who have defects in Usher Type 1 genes, the top of the hair cells are poorly formed. They have a problem in development. They don't get together and form a nice organized structure that is very important for proper function, and we can see through molecular analysis, which I'm not going to show you today, Usher proteins are localized at the developing structures. They are localized in the hair bundles and likely are responsible for the forming of shapes of them, and we find these at the synapses. We're not quite sure

exactly what they are doing there, but that is another common area of localization.

And it is known from work in mice that many of the usher proteins form physical links between the projections from the cells. They form close contacts with each other. One protein touching the other protein and forming together so that makes sense when we think a loss of function of anyone of those will lead to a very similar phenotype because if you take one link out of the chain, you no longer have a chain.

What about the retina? This story is not quite so clear yet and we're working hard to figure it out. Photoreceptor cells, we have the cilia and the main function seems to be carrying molecules from one cell where they are made to another part where they are needed for function. And what we think at least some of the other Usher proteins responsible for loading that conveyer belt from one side to the other.

There are many unanswered questions about this process. We don't know how much is involved in that process and there is much more

variation on the onset of when vision loss starts to happen between one type and another. It is still a murky area.

And there is more to consider and it's been shown by several different research groups that Usher proteins are present in more than photoreceptor cells. Is that meaningful? We hope so, but we're not sure. It is possible that they are present in multiple cell types but only in the one say photoreceptors.

I have two microwaves in my house, one in the kitchen and we use it all the time, and one in the garage. If an alien came to my house they wouldn't know which one was important for what.

So the way they we have seen them interacting with the ear, they might work alone and they might work with other proteins we haven't identified yet.

The difference in the time of onset of the vision symptoms verses the hearing symptoms complicates things, but it maybe gives us more

information about where to start looking for the types of things that are going wrong in retinal cells, and when we can identify that, we can be more efficient in developing treatments.

In addition to everything we know about studying human mutations by getting information from all of you, we can use animals or cell cultures to look at these in the laboratory. In my laboratory, we use small fresh water fish called zebrafish and we cause them to exhibit something that looks a lot like Usher Syndrome. Other researchers do this with mice and others with cell cultures.

And because the analysis of the retina and the retinal defects has been more complex, having all of these resources available to us is very important to understand that challenging aspect of the disease and work on solutions.

So in my lab, we use zebrafish to study how the protein functions in normal vision and hearing. So far we have shown some of the other Usher proteins are found in retinal cells behind the photoreceptors, and we have

shown they actually are doing something in the other cells. Because we can see vision problems in those fish even though the photoreceptor cells don't express this particular protein, we can see problems because it is absent from the other cell type.

We also can see in the ear that some of the Usher proteins have a role where they take cargo and move it to other places, and it requires them to work together and be physically interacting and we can show there is proteins, that form improperly due to mutation, are causing problems in the cell.

They are building up in the cell and causing the cell to experience stress because of too many non-functional proteins, and when that happens, the cell reacts in a certain way. Ultimately it is initiate as a programmed death pathway. So we're testing to see whether we can see signs of cell stress before the cell actually dies, and this potentially could be another way to target disease and get to the cells and figure out what is going to get to them before they are damaged. If the cell is just sick and not dead, there are could opportunities to augment what is going on.



This is just a little bit of what we're doing, and again everything that we know about these genes that are involved in Usher Syndrome are coming from our human patients. I want to encourage you to join the registry and help us understand everything we can to continue with our work. Thank you for your attention. I'm happy to take questions now or at the break.

Mark: Does anybody have any questions? I see a hand. I will bring the mic over.

Speaker: Hello there. I'm curious. I'm surprised that it's been more difficult to find out some of the information you need in the retina as compared to the cochlear since the retina is so much more accessible. It is really not possible to look at a human cochlear in much detail while the person is still alive while you can look at the retina. So why is the retina research lagging a bit behind what you are seeing in the cochlear hair cells?

Dr. Phillips: Largely I think because the first animal models that we had

for all of the Usher types were mice, are still mice, and the mice provided wonderful information what was going on in the cochlear. Unlike the human patient, we can do more than look. We can excise and section and that kind of thing, so we had a wonderful information from the mouse cochlear.

Many of these mice models that provided information from the ear didn't have the retinal problem. Their vision was fine and they didn't show any signs. And as Mark eluded to earlier, part of the reason that might be is because of the light levels. Mice are nocturnal animals. Their retinas are adapted for low light. In research faculties the place the mice are housed is a low light environment because it is a humane consideration, so it is possible their retinas were not stressed out enough. Other animals like the zebra fish are daylight living and the retinas are showing degeneration sometimes not seen in the mouse model, so we're catching up; we're working hard to understand that.

Speaker: Thank you.

Mark: Any other questions?

We're going to pause for an interpreter switch.

Speaker: Hello. You are speak about eleven different genes. What percent follows the geographic area? For example, Ushers 1B or 1C, I can't remember which one is dominant in New Orleans, Louisiana. So I was wondering if you knew something about that.

Dr. Phillips: You are right. Usher 1C globally is not the most common, but people in certain populations settled around the New Orleans area and have some familia relation in the Canadian region. The most common type in that is 1C, so it sometimes depends on geographic areas. And globally I will find different prevalences in different places worldwide --

Speaker: What is the most percent then?

Dr. Phillips: Percentages, I don't know. But I'm sure the other people will know.

Speaker: Do you know if there is a higher percentage?

Dr. Phillips: I'm sorry -- higher percentage of?

Speaker: What genes are more common?

Dr. Phillips: The most common globally I believe is Usher Type 2A. The most common of Type I is 7AB so the most common worldwide and then have you pockets of communities where there could be a more prevalent type based on cultural or geographic isolation and whatever is in that particular genetic makeup.

Speaker: Okay. Thank you.

Mark: I think we have time for one more question. Right here.

Speaker: Given the low number of people who have Ushers here in the United States, what do you find with regard to research funding? Is it

more difficult to get funding for your research and that's where we come into play where we need to sponsor this type of funding.

Dr. Phillips: That's a good question. Research and funding in general is pretty tough right now. And I don't know; I don't have a sense it is more tough because of what we're studying. But certainly more avenues would be open to research dollars the more people who know about Usher Syndrome and the more people who appreciate the complexity and severity of it, so we work very hard when we write our grants to connect it to human disease to make our research on the track of impacting and improving the human condition. And the more that is known about it, the easier time we'll have, but at the end of day it comes down to how many total dollars are allocated, and that's something we don't have control over.

Mark: I want to chime in on that one. Yes. Your involvement is very important to all of this stuff. There are diseases just as common as Usher Syndrome, roughly as common as Usher Syndrome that get much more funding from the federal government than Usher Syndrome does, and they should get that kind of funding. That's not saying the funding should come

to Usher Syndrome, we're more important, but they get that level of funding because we have not had a strong voice as a single community to get that funding, and that's something we're trying to change.

So, thank you Jennifer for your talk.

We're not running too late. We're going to take a 20 minute break right now and get back together at about 10:40. I think it is 10:20 right now. Please take this opportunity to talk to Jennifer and the other doctors and myself. And I will be happy to answer any questions and hopefully you will get a chance to meet each other.

Mark: So if I could ask every to take their seats.

We're going to get started again.

Good to go here? all settled?

Okay. So, by way of introducing our next speaker I'm going to introduce

somebody that's not here at all, Dr. Margaret Kenna, who has worked with us since Bella was first born. And Marley, I know her has Marley because she treats us just like she treats every other human being, has been actively involved with us with all the coalition stuff that's been going on and she is just a fantastic person. Everyone who meets her can't say enough about how good a human being she is in addition to being such a wonderful doctor. I introduce you to Marley because everything I say about Marley is what I hear about Dr. Kathleen Sie. She's the director of the Childhood Communication Center up here at Children's and she's going to talk about hearing loss and Usher Syndrome. Kathy?

Dr. Sie: Thank you, Mark. That is high praise. I know Marley very well and I appreciate that. Thank you for inviting me and it's been a pleasure to work with Mark and the family and with Hear See and Hope. And I think it is wonderful that there is this building of community and this effort to raise the profile of Usher Syndrome because it is a condition that really impacts people in profound ways.

And it is incredibly exciting area. I think the genetic revolution and

medicine is really defining the future for our children and the future patients. I am not, an expert in Usher Syndrome, but I see a lot of kids with hearing loss and I have for years run the Hearing Loss Clinic at Seattle Children's and started the cochlear implant program there.

I will say, through, we tried to be very supportive of any communication choice that a family makes, so I'm not a believer of everybody needs a cochlear implant. Language is the important thing, language and cognition, and so I will just put that out there.

I'm going to talk about childhood hearing loss in general, how we measure hearing, just talk about audiograms and review it, go over the medical evaluation of kids with hearing loss because a lot of times kids diagnosed with Usher Syndrome present with on a hearing loss, so I'm going to discuss the overall approach when we see children who are diagnosed with hearing loss.

And then I will talk about some of the management options for kids with hearing loss, and then the second part I will talking about Usher Syndrome



specifically and the hearing loss and I think we'll do the interpreter switch in between those topics.

So the diagnosis of childhood hearing loss has come a long way in the past 50 years, and so it started with the validation of auditory brainstem testing that allowed us to measure hearing without the cooperation of a patient so we could test physiological how the pathway responds to stimulation. There was developed an automated way to test these responses because initially it was tedious to measure the brain waves, and I will show you examples of that.

With automation it was a test that is more easily done and around that time, the phenomenon of evoked otoacoustic emissions was described and the combination of those two testing mechanisms has allowed us to set the stage for early testing.

And this is, of course, an abbreviated overview, but we were also at the same time really beginning to understand the importance of early intervention so exposing kids to language early, and we had data to show

the earlier they were exposed the better.

But early exposure required early identification. In 1999 the United States government articulated the importance of early identification by creating a federal mandate for newborn screening, but without funding, so it was up to the states, so over the next 10 years states would roll this out and what was initially known as Newborn Hearing Screening evolved into EHDDI. It doesn't help to screen the kids if you don't the follow-up and allow exposure to language.

The goals of EHDDI screening by one month, diagnosed by three months and intervention by six months old. That's a huge change from the old days when I started in ENT where kids would come in with language delay at two-and-a-half years of age.

So in screening the babies, they have a little probe put in their ears and they're presented a tone 30, 35 decibels and they pass or are referred, so yes or no. For diagnoses we test each frequency. And the intervention portion is talking about language exposure.

So, just to review with you guys, the ear. This is, we go over this with the kids and it is really a blast to be a pediatric ear nose and throat because we can watch the kids grow and become adults. This is what I like to go over with the kids so they understand how their body functions, what's going on, so just takes a couple minutes.

This is the outer ear and looking in we see the ear canal and the eardrum, which is connected to the hearing bones and there are three of them. The stapes connects to the inner ear that has three parts, and the semicircular canals help us with our balance. Sound waves come in and when the last hearing bone, the stapes, moves that sends fluid waves in the inner ear and through that the process that we'll talk a little bit more about later activates the endings of the auditory nerve and the signals get carried to the brain, and the brain does the work of making sense of that information. For hearing people our exposure is through speech. So that's why hearing is important to most of us. But language can be attained visually also.

How do we measure hearing? There are two main types of testing.

Physiological tests, which means we're just testing the body's response to a sound and we're not requiring a behavioral response.

Those are the auditory brainstem response testing. These are all letters that refer to the same type of testing. And EOAE is another type of test so we get these types of responses. The beauty is we can test a sleeping baby. But you can see that these are, this is the ABR response and the just wave forms so the sound comes in and then we measure the brain's activity, the response to sound, and it is amazing you can measure these predictable wave forms that basically travel, that follow the signal up to the brain.

This is the response evoked emissions where we actually send a sound into the ear and measure the sound that the ear produces because interestingly the inner ear will produce a sound and if you have sensitive information microphones, we can see the energy coming out. We can test right and left ears and over time we learned these responses correlate very well with behavioral responses for the most part.

The disadvantage is that for kids over six months of age, I would say between six months and about eight years of age requires sedation, so it is not our preferred way. And these are physiological responses, but what is important is how you respond to sound in the environment when you are awake, so we prefer the behavioral responses, the gold standard.

Behavioral testing. There are different ways to do this and it is the type of testing that is offered that is really dependent on the developmental status of the child. And so it goes from visual reinforcement where they're in a booth. There are toys and we condition the child to respond where they hear sounds up to where most of where you adults do where you sit nicely and quietly and you follow the instructions of raising your hand or indicating when you hear something. So this is the gold standard for how we measure hearing.

And so when we graph that out, we generate an audiogram and this is just familiar sounds. As we come across the graph, every center has a different format for their graph, but they are all similar. As we come down, the sound is getting louder. Sound is measured on a decibel measure

scale. Zero is not the absence of sound but a very quiet sound.

For anyone who knows music 250 hertz is middle C on the piano. So every time you double the frequency you are going an octave up. We use that audiogram to help families understand where sounds sit so you can get an idea what your child is hearing and or having more difficulty hearing.

And so this gray area is what we call the speech banana because it is kind of banana shape and it really shows on the audiogram where conversational speech sits and so, and then we break it down into different sounds or either low frequent see or higher frequency sounds, and so can you start to get an idea if a child has a mild to severe hearing loss they might be able to get some of the nasal sounds N and M's and then a baby crying, the vacuum, things something like that. It gives people an idea where sounds sit on an audiogram as far as frequency and loudness.

You hear about moderate to severe hearing loss. It is zero to 20 is normal. And then mild so threshold at these levels are moderate, severe, and profound. If you have thresholds 90 that's a pro found hearing loss.

What is more complicated, people will have sloping hearing losses and so these can be normal sloping to profound.

So, kids whose present with Usher Type I are bilateral profound hearing loss. The right ear are the red O's and X is the left ear. The kids will have responses across all the frequents in this profound range, which means it is difficult to have access to speech information.

These are example audiograms and this is the bilateral profound condition. Here someone has an asymmetric hearing loss. The right ear is different from the left. It would be considered moderate to profound in the right and severe to profound in the left. So these A's are the aided response, so bilateral profound. They may get some benefit in the low and mid frequencies, but it is hard with standard hearing aids to get any benefit in the high frequency so people may miss the important consonant sounds in the English language.

Here the aided response may be better, and you might be able to get some of the speech inflections. they are quieter than conversational speech

represented in this lighter speech banana.

And there are all different types of hearing aids. I won't get into all the different types, but some may take the higher information and transpose to it a lower frequency so you can have access to that information. It is the work with the audiologist to figure out the best for you. And so, you can have any range of hearing loss and the ears may be slightly different from each other.

The challenge for us when we see kids with hearing loss, we don't know what the answer is. Now hearing loss is the symptom. So we diagnose the hearing loss very early when they are babies. And now that's the symptom and we have to find the answers. Is it Usher Syndrome or a virus? So we are drilling deeper and deeper and that's going to allow us to get into different therapies because hearing aids are like a Band-Aid trying to help the kids do as much as they can with the hearing they have, but it's not addressing the underlying issues.

So when we see kids with hearing loss, we take a history, we take a



detailed history, and we have a genetic counselor who takes a really detailed history, and we do a physical exam looking at eye color, ears, rest of the body, palms, hands and soles of the feet, and sometimes CAT scans or MRI scans and that directs us on to what kind of things we should be looking for, and then we start doing testing for the specific causes of hearing loss.

And there are a lot of exciting things going on in the world of hearing loss. There is a viral infection that causes hearing loss and now there are anti-viral treatments they are giving kids to try to prevent progression of hearing loss and then genetic test and the other associated test that we consider of value: EKG, kidney, ultrasound, but these used to be the test we do all the time.

Now we are going to skip to genetic testing. So it is really an exciting new area in how we can treat kids. So, when we see kids with hearing loss the template we have in our minds for hearing loss is that the old number one in a thousand has severe to profound hearing loss, and this is taken out of gene test which is a great source for looking at genetic conditions, but

prelineal or bound with hearing loss it is just etiopathogenic. We don't know the cause, and a lot of these kids are really going to be genetic and we haven't figured out yet. But most of these are non-syndrome. They don't have any other things associated with their hearing loss.

And a third of the kids with non-genetic causes have syndrome hearing loss. And so this hearing loss is where Usher Syndrome fits. So just this gives you an example. People with Usher Syndrome actually usually have normal CAT scans, but this is normal and this is the white is bone and the brain is gray. This is through the cochlear and it should look like a stack of three donuts and there is through the semicircular canal, and those are normal images.

There is, this shows a deformity. Instead of three nice stacks there are just two, here and here. And then the enlarged vestibular aqueduct, which you might have heard about is associated with more progressive types of hearing loss. People with Usher Syndrome typically have normal CAT scans.

Management of kids with hearing loss. It is all about early intervention, exposure to language, amplification for families that choose hearing aids and cochlear implants and FM systems, and accommodations in the school setting and special services. Although we support families in whatever mode of communication, the kids with Usher Syndrome know they have the likelihood of vision loss. Kids, we feel, should have the opportunity for early cochlear implants and early bilateral cochlear implants.

We're now entering the era we're implanting both ears but five, ten years ago Usher Syndrome and kids with meningitis were the ones with bilateral cochlear implants.

Diagnoses of Usher Syndrome in part is family history. Certainly for the kids with Usher I they are born with bilateral profound hearing loss. Mark did a great job of this congenital part of the problem with medicine and hearing loss is the words and the nomenclature. Congenital means you are born, with it but it sounds like there is genetic. But everyone with congenital doesn't necessarily have a genetic form of hearing loss. So these kids ERG has been a test, but I think it is a difficult test, very involved

tested. And I think genetic testing will soon replace ERG.

Clinical presentation is important asking kids are they having problem was night vision. Keeping tracks kids. I think one of the challenges and one of the reasons it is difficult to answer what is the most common cause of ushers probably the type I I and I I I are less frequently diagnosed base the way they present is milder and over longer period of time.

But that will change with the variability of genetic testing, so genetic testing is really looking for in numbers changing, you know, quickly. The different parts of various genes, and we used to have to ask for testing of mutation, so it is one gene we're looking at and the different mutation of that gene, but technology changed so now there are chips which allow us to test for 60 different mutations and 12 or 13 genes, and so we have that capability now.

And I just responded to Well Point, which is a company that sets the standard for insurance authorization of test. They are moving toward no longer approved sing ability mutation analysis but testing and that will

change how we evaluate kids.

Cochlear implantation. I'm not sure how we're doing on time? Am I okay on time?

So, cochlear implants require surgical procedure. There is an electrode that goes into the cochlear and the kids wear an external device that communicates with a magnet. And that allows the signal to come in and we can directly stimulate the auditory nerves so the people with Usher Syndrome can benefit from cochlear implants. And nowadays even though the FDA guideline is twelve months, we implant kids as young as six to seven months of age so they can have access to sounds in both ears by the time they are nine months of age.

I'm going to go through some of these things. We're running short on time. So this, the cochlear implant can bring these kids up so they have access to sound in the normal hearing range. Now the challenge for these kids, they are not normal hearing kids, or kids with normal hearing and now families are finding it is hard because the kids do so well they are having a

harder time getting access to services in schools.

We talked about these numbers and cause of deaf-blindness in the United States. We're learning more and more about how prevalent this condition is in kids. The different types have different levels of involvement. Usher Syndrome types are both. This is Type II and is congenital and this means they're born with it.

So, getting into how Usher Syndrome really affects cells. Dr. Phillips talked about this. In the cochlear you see these little hair cells, which doesn't take up much space, but that's where the business happens. These hair cells are very organized in the outer and inner cells, and it is the physical moment that gets translated to the activation of the nerve. In a cartoon fashion, this is hard to see, but this work is mediated through molecular actions and the proteins.

If you extract the hair cells from this, this is the outer and inner hair cell from. This area we're learning more and more about how the proteins are arranged and work and contribute to the function of the basilar membrane

and these are taken out of a review article that Richard Smith wrote about five years ago and within the hair cells there are molecules Dr. Phillips referred to and this physical movement causes opening and closing of gates and that's how we hear. And so it is amazing how much we've learned in the past 30 years.

So, understanding the molecular mechanisms of hearing loss will pave the way for interventions. The future is bright. We have a lot of people involved. It takes a village to evaluate these kids and provider support for the families, and we do our best to keep abreast of what's going on. Thank you.

Mark: Do you want to take questions now?

Dr. Sie: I will be around.

Mark: Are we good? okay. I think we're good to go. So thank you Kathy that was wonderful. For just so everybody knows this afternoon we asked Dr. Weleber to chair a Q and A, so you can ask anybody that's here

you can ask a question. So if you don't get a chance to ask questions of some of the other speakers, they will be here and you can ask questions then and we have the different breaks and they will be more than happy to be cornered and discuss this stuff.

So thank you Kathy. Also from, we're lucky enough today to have from Seattle Children's Hospital, also, Dr. James Phillips with the Center for Integrative Brain Research. He's an expert on vestibular function around Usher Syndrome. There are not many experts on vestibular function, so we're fortunate to have him talk with us today. I will let you come up for your presentation.

Dr. Phillips: Thank you.

Mark: Shall we use this microphone?

Dr. Phillips: This will be fine. So, I will just handle the discussion a little bit farther, I'm the other Phillips from Seattle. And I am a vestibular guy, which means I study balance, and dizziness, that sort of thing. And I also



run a clinical service: The Dizziness and Balance Center. And I have a diagnostic laboratory at Children's Hospital as well.

So, I will start By telling you a little bit about the vestibular system. What is it? The vestibular system includes the structures of the inner ear that contribute to your balance. It is your orientation in space, balancing your eyes so you can see. It is helping you to feel as though you know where you are.

So it helps with your thinking, it helps with your emotional well-being. There's lot of things of the vestibular system contributes to. It is nerves that relay balance and orientation and helps make sense of all of this stuff and combines information from different sources, but predominately there is a really important input that comes from the inner ear, so you have to combine information from different parts of the inner ear from the visual system and muscles and joints. All of that is used to keep you from falling down.

What part of the inner ear are parts of the vestibular system. You are

seeing all the parts of the inner ear that don't care about hearing. They care about balance. A lot of your inner ear is focused on a different task than hearing.

There are loops here which are really fluid-filled rings, so when you turn your head, these loops tell you that you are doing that. What is telling your brain you are doing that is called the semicircular canals and then there are sacks here and here and they sense lineal motions so front, forward to back, side to side, up and down, and they also sensing it with respect to gravity. These is important for helping you maintain balance, and they communicate through nerve fibers which contribute to the eighth nerve which carries sounds information to the brain.

There is a lot of text, but I will cut to the chase. There are different kinds of hair cells in the vestibular end organs, but they basically work the same way that auditory hair cells do, and if you bend the hairs, which are the surfaces here of these hair cells, if you bend them in a specific way, which is tipping the smaller hairs to the big one, then the hair cell discharges a little bit and releases excitatory neurotransmitter, which increases the

probability of exciting the nerves that is go to the chit-chat with the brain. So these cells, by the bending of the hairs can send more or less information to the brain and the brain interpreters that in the vestibular system.

How do the semicircular canals turn bending of hair cells so when you turn your head the hair cells sends information. They fill with fluid. So when you turn your head, the fluid stays put in space, and your head rotates around that fluid and if you project a sail, that sail has hair cells embedded the apical process embedded so they bend with the bending of the sail.

So that's the neural transduction process that allows you to sense turning with the inner ear. This is the picture of that structure. These are the bodies of the hair cells and the neurofibers that connects to them and that billows away as your head is turning, and this system is capable of very precise information about your movement and orientation.

There are sack organs called otolith. There are heavy crystals and they actually like to stay put, so if you tip or you move forward and back, those

crystals stay put and the jello bends and the hairs bends and that signals the brain you moved in a linear motion. Or if you tip the crystals fall to the side and that bends the hair as well. So this can tell you if you are moving, tilting, or in combination. The sails can tell you if you are bending and the brain makes sense of this, but the hair cells are critical.

What happens when the vestibular system fails? When we see patients at say the University of Washington Medical Center, only one side of the inner ear, only one of the two ears will have failed, and when that happens you get vertigo. You get dizziness. So vertigo is a sense of whirling or spinning and tends to be short-lived. You get that because the brain makes an assumption.

If this ear does more I'm tilting, if this ear does more, I'm moving toward that ear. As long as the ears are doing the same thing the brain says I'm not moving, but as soon as there is a difference you feel as if you are moving to the ear that's saying more. If you have a problem that eliminates function in one ear, people feel like they are spinning when one ear stops working. This is associated with nausea, fatigue, disorientation,

anxiety, cognitive abilities and posture and gait is unstable. You fall over.

And this is a bad problem, but actually in some ways it is not as bad a problem when both ears fail. When both ears fail your brain doesn't know you are moving. It can't contribute. This system can't contribute to help you remaining oriented. In fact, the system does something that doesn't have anything to do balance. It balances your eyes so you can see things clearly. When this system fails the world is blurred even if your eyes are working well, just the absence of input from your ear will make it hard for you to see when you are moving.

This is a failure to stabilize your eyes and this is called oscillopsia. So no vertigo but nausea and fatigue. Other parts of your body are saying I am moving but your inner ear is not. Disorientation, cognitive impairment, and posture and gait are impaired so it is profound when you lose this system.

Is there compensation for the loss of inner ear vestibular function? The answer is yes. Over time we can compensate well even for complete vestibular loss. And that's really reassuring. The brain is set up to make

use of other sensory inputting even when vestibular information is missing. This is true of children. Our brains are designed adjust for loss of input. This adjustment isn't perfect. Your balance isn't going to be perfect, but you can compensate for a loss of vestibular function. You can't eliminate the visual world but you can maintain better balance trying to maintain your posture and walk around.

Compensation is dependent on learning. You have to learn to not misinterpret cues from a non-working vestibular system. You have to learn to use appropriate cues. If you are in a room and there's lots of objects, you can't rely on them to tell you if things are stationery. In a car you can't rely on your visual information. If you are reliant on your information and you get in a car, you will be disoriented, and this happens to people all the time after they had a loss of vestibular function.

You have to learn to develop a strategy that is adaptive over a range of situations. For example, if I'm relying on information from my ankles to tell me if I'm tipping and I'm standing on sand or soft grass, that's not going to be very effective and I will probably be unsteady, so I have to rely on a

system with information from my vision and ankles to tell me if I'm moving in absence of vestibular information.

And mostly importantly we substitute information from other systems when the vestibular system is absent by relying on information from our body to tell us if we're moving, and we rely very heavily on information from vision. We look at objects like corners of rooms and that tells us about orientation in space, so this is important for compensation for a loss of vestibular function. And we all naturally tend to utilize this fairly heavily if we lose function.

Now, what about vestibular loss in Usher Syndrome? Usher Syndrome is characterized by varying degrees of congenital hearing loss, retinitis pigmentosa and there are different genes, at least one modifier gene. I'm not a geneticist. And these guys are working with things I read about. There are three clinical sub types USH 1, 2 and 3 and they have varying degrees associated with them.

Type 1 is 30 to 40 percent of all cases and classic Type 1 has severe vestibular dysfunction. 1B has that classic phenotype. That's about 50

percent of usher type 1

Type 1C. So there are a bunch of others, either have this classic phenotype so a lot of patients have this, or they only have non-syndrome hearing loss. And in fact there are differences if you have missense mutations or truncating mutations in the variety of the loss. Ushers Type II. Those patients have largely normal vestibular function.

And Ushers Type III, that's two to four percent of all the cases. About 45 percent of patients have vestibular hypofunction. In the few studies that have been done, 36 percent of those patients that waked before 16 months so patients who seem to have good vestibular function at the outset show variable dysfunction later and some people say this argues for a progressive loss over time in those cases.

So vestibular problems are actually common to many forms of Ushers but not all.

So what does this mean in one with Ushers disease. Say have you profound loss. Your parents and your pediatrician will probably notice you



missed your motor milestones, that it's taking you longer to learn how to do the things moving around in the world. Other children learn at a slightly earlier age or much earlier age but the interesting thing is kids who miss their motor milestones tend to catch up so they are still clumsy and have difficulty with activities that require precise balance, but they catch up because of central compensation and substitution. And that's because of utilization of ankle and muscle inputs and vision. Then later in life with the onset of vision loss there is a progressive return of disequilibrium and balance. You are using what was natural for you to use and that is no longer appropriate. One of the senses you were relying on is no longer as useful to you in certain situations.

And so people have to seek new strategies. As they do the symptoms associated with their balance, loss of balance, start to resolve again. And so the key is to match the sensory input that you have available to you with the motor skills that you are trying to maintain.

How do we detect vestibular loss? Turns out there are clinical tools to detect this. And it is important to define the amount of vestibular function.

Early signs of classic Ushers Type I phenotype of hearing loss and vestibular loss, vestibular loss, is often complete and bilateral with early onset. Visual loss occurs latter. Some people argue if you don't have access to good genetic testing doing good vestibular testing is a way of getting an early clue if this person is at risk for Usher's Type I, but is the loss present or absent bilateral, complete or partial or is it progressive and static or fluctuating. Each type of loss relates to a different treatment strategy, so it is important to define those.

To assess this can you do a lot. If you went to see Dr. C she could give you test. most of what we can learn is with more sophisticated vestibular testing. You can detect problems with clinical test and they are activities you engage in like staring at something and if you can read when your head is shaking back and forth. If that reflex is not working, you can't. And there are technologies available in the laboratory that can define your vestibular function and help with your treatment.

Here is some of the tests that we use in the laboratory. This picture down at the bottom is a child sitting in the dark in a rotating chair and we would

watch this child's eye movements. Let's see if I can make this go. There he goes.

We would watch this child's eye movements as he's rocking back and forth and his eyes move because of the reflex that stabilizes your eyes when your head is moving. That reflex comes from the ear and not vision. It aids vision but it is not reliant on vision. So we can make the chair move in different ways to assess if the vestibular system is in tact, if it is working.

You can do this even with babies. You get the chair spinning and then you stop the chair and when you stop the chair the baby's eyes will move if the vestibular system is in tact. I think I can make this go. Let's see. There, this baby is not moving. He just stopped. Actually it is a she. She just stopped spinning. See how her eyes are moving? That only happens if your vestibular system is in tact and the eye moves, slowly dies away and that means the brain is holding onto this balance information for some time, which is good.

So we can test this even in babies, so we use this technology even in very

small children. And finally we assess your balance by putting you in a wobbling room. The walls and floor wobbles and your job is not to wobble and it is not easy. We can have you close your eyes and deprive you of information from your ankles by having the floor move, and we can trick you by having that world move to see how dependent you are on visual information.

All of this allows us to determine how much your relying on your inner ear, on your eyes and how much information you are getting from your ankles. And all of that information together provides you with good balance and good orientation. And you can have that even in the face of a loss of function from something as complete which produces as complete a loss in the ear as Type I Ushers.

Treatment options for people who lost vestibular function as a consequence of Usher Syndrome. Currently perhaps the best is vestibular rehabilitation, and that's generally performed by a physical therapist. You might say well, why is that important? You said your brain will make this will come to a solution all by itself. The problem is let's say you have lost

vestibular function and hearing. Your brain may decide the best solution is to rely on vision. As your vision changes that is no longer appropriate, so you can go to vestibular therapy.

You can develop strategies and develop a strategy that's appropriate for a variety of different contexts, and that helps you to maintain your balance in the face of changes to the balance organ in your ear. In the future there are many promising therapies. Gene therapy has been demonstrated in a model in mice to relieve both vestibular and hearing dysfunction consequences to Ushers. So that's, you know, that's on the horizon, and it is very promising. Hair cell regeneration is another route. And both of these maybe effective both hearing and vestibular loss in the future.

Currently or just around the corner there are other options that are become available. I just want to discuss one because we're working on it at the University of Washington. This is a vestibular function. These wires go off to the vestibular part of the inner ear. There are three groups in the United States who are working on these devices. Our group at the University of Washington, Harvard and John's Hopkins, and the intent is

to combine these so you can restore both balance and hearing.

With this device, instead of having a microphone to get sound information, it has gyroscopes to get motion, and they activate electrodes stimulating balance to the brain.

The trial is on going in Seattle and four patients have been implanted with this device, and it works. You can drive appropriate eye reflexes. So I can trick your brain into thinking your head is turn this way and force your eyes to go this way and I can change the speed your eyes move and the characteristics of the trick by stimulating different canals at different rates and the gyroscope does it's job. And patients who have this device, when you activate it, you can make this sway so they can maintain their balance despite the fact their vestibular is not working.

So you can activate this device, say the semicircular canal. You feel like tipping over backwards and when you combine these together and activate this device with appropriate sensor technology, peoples' balance is restored. So that's pretty cool and that's in in the laboratory now and in

patients.

Mark: We'll take one or two questions. I will start with David over here.

Speaker: What is the effect of cochlear implant itself on balance issues?

Dr. Phillips: Right. Yeah. So that's a very -- it is a very important question. And it's been looked at quite carefully. A lot of people who study vestibular end organs were concerned cochlear implant will compromise balance and farther injure the ear. And that turns out not to be the case. Most studies show it is rare. It does happen, but it is rare that balance is compromised in patients who received cochlear implant because of their, because of the cochlear or to say there is a change between pre and post implantation. Cochlear implants probably provided disorientation information, which is useful to patients who have a loss of vestibular function. But it is a very real concern.

Speaker: Thank you for that wonderful presentation. Question. Could you give a short summary of how the patients, the four patients are doing

and two, where do you get the funding for your research. Is there a need for additional funding? Thank you.

Dr. Phillips: Sure. The four patients are doing well. So all of the patients have actually this implantation was for a different disorders called Meniere's disease. And the device works in all of the patients and it will provide balance information in the face of loss of vestibular information.

We were very worried it would cause loud sounds or nausea, and that hasn't happened there. Only four, but that has not happened in any of the patients so far.

One patient had this device for a little over two years. Funding for this research comes from the national institutes of health at the NIDCD which is the Hearing Institute and it is coming from the, actually the manufacture of cochlear implants is providing us with implants, so that's pretty cool, so they are make our device.

And from the Culture Foundation formed by an instrument company for



bringing new medical devices to people and from actually a private gift from an individual who has vestibular disorder.

Mark: So we have time for one more question. I see Mitch over here.

Speaker: Thank you. Yes this is Mitch Turbine and thank you for the very interesting presentation. Going back to cochlear implants, as I'm sure you are well aware of protection of residual hair cells in the cochlear is a hot issue in cochlear implant surgery. How crucial is that for the future of the, you are talking about a possible future of hybrid cochlear implants and vestibular prosthesis. For those who have cochlear implants already, what is the likelihood we could benefit from the technology that combined auditory and vestibular functions?

Dr. Phillips: Right. I think for example there are hybrid cochlear implants which try to preserve residual hearing, natural hearing functions that provide stimulation. Any time you increase foreign bodies in the inner ear you are likely to decrease the survival of hair cells, so I think that's a very real concern if you have residual hearing.

And we won't know really until we move forward with this study and others in a variety of different kind of inner ear pathologies to know how long will hair cells survive. We performed lots of animal experiments, and including animal experiments in monkeys. We have done this and so has the group at John's Hopkins and in those studies hearing is preserved in most of the animals; however, in the patients with significantly damaged hearing, Meniere's disease, their hearing is already damaged.

Mark: Thank you. That was excellent.

So again we will have more time for questions a little bit later on. At this point in time, Krista, can you wave to me. Is lunch out there?

So here's the deal on lunches. The tables you are sitting at is where you are going to eat. The food is in the foyer. So can you go out, grab your food, and eat here. It will probably be logistically difficult, but we'll do the best we can, and hopefully this gives everyone time to spend, time and talk and network and meet some of the doctors and get some of your questions

answered as well. We'll get back together let's at all it an hour and fifteen.

So enjoy. The lunch is out through the back.

Mark: If we could get everybody to take their seats we're going to get started again. Before I get started, we have been working this year to increase funding and we just got word during lunch the language we submitted to congress has been accepted by the Senate. and the language says that this should be made a higher funding.

We have gotten a lot farther than a lot of other people, And I want to thank Susie, who has been doing a ton of work down in Washington D.C. to get that pushed through, so this is all very good news.

One thing that we talked about is having engaged families. Please watch this space. We're going to need you guys as this comes up for vote in the Senate and The House. Ask your representatives to support this language so it gets through. It is a big deal for us to get more funding for this.

So with that I'm going to introduce Karmen Trzupek to come up. Karmen is a genetic counselor. She spent time working at OHSU here in Portland. she is on the Board of Directors at Hear See Hope, and has been important to the research. So Karmen, it is all yours.

Karmen Trzupek: Thank you for having me here and giving me this opportunity. I think you guys have heard a little bit about genetics and having this be a little bit more interactive.

So, as I was saying. My experience with patient education events and conferences is that people often have lots of questions about genetic testing, so I do want to make sure, in particular, to leave some time at the end of this to take some questions.

You saw a picture of this before. I think it is helpful for people when they think about testing to have an underlying sense of what is being tested and what does this testing mean.

So we all have 23 pair of chromosomes, and you can see them here. At this level nothing looks wrong. You can see this in every patient. Unless they have a chromosome abnormality, it would look normal.

So within the chromosomes we have our DNA that is tightly coiled, and when you stretch it out, you see a sequence of base pairs, ATG and C, and they have several different, up to several different thousands pairs of genes.

If you look at this sequence of letters, it looks random. Here you see this sequence and it looks random, but it is not at all random. But it is perfectly ordered. And there is, in general, a perfect order for a perfect sequence to each gene.

Now that is not to say that any variation within it is detrimental because in fact, as Dr. Phillips pointed out, some are normal within all us for different colored eyes and how we look and in how our bodies act.

But there are many different changes within those genes that are

detrimental, and when there is a change within a gene and causes it to function abnormally, that is a genetic mutation.

It can look like it does here, a substitution of one base pair, and it can look like that and we get deletions or additions of material, but if the gene no longer has a normal function, we call that a mutation.

Usher Syndrome is recessive inheritance. The circles are female and the squares are male. So in this family of four siblings, and two of them are affected with Ushers Syndrome because you must inherit two genetic mutations to be affected.

The average chance for someone to be affected in a family that is carrying these mutation is 25 percent or one in four because, if both mom and dad are carriers, each one of these has two copies of a gene. IF one copy has the mutation, they have a 50:50 chance of passing that on.

So on average, one in four children in that family will be affected. It is not actually one in four. It is like flipping a coin, so it is an independent chance

every time. You could have all four affected, and some families you have no children affected, and in those families you wouldn't know it is being carried in the family.

So that is just a different way of looking at that. If you look at this particular gene here represented by capital R and lower case r, the lower case r represents that recessive genetic mutation. In order to be affected, you would have to inherit both.

So this is very much like inheriting blue eyes if your parents didn't have blue eyes. So I have mostly brown eyes. There is more than one gene for eye color, but there is a predominate gene, and I know I must have one brown and one blue copy because my daughter has blue eyes and she would have to inherited two copies one from me and one from her father. So it is the same in recessive where you inherit one from each parent.

Now as you heard today there are 11 or 12 identified genes for this syndrome. The total number are 15. And you see on a couple of other charts today where it will say there is a genetic locus or location. Mark

said when his daughter was diagnosed there were 8 but now there is 11 or 12. That gene is not fully discovered and characterized.

This chart is interesting. It shows the number of mapped and identified. This is not all inherited retina diseases. And today the number is even higher than what it shows here. That number is over 200. So there has been a huge explosion in what we know and understand about genes associated with these diseases.

So that, here are the genes associated with Usher Syndrome Type I, and you will see there are six different genes associated with Type I at present. One of them doesn't have an identified gene name yet. You heard earlier 1B, or MYO 7A is the most common. For Type I the most common genetic cause is MYO 7A. In certain populations you have other genes that are more common or more prevalent, and so if you fracture the acadian population you would have Ushers results from 1C. If you have Jewish ancestry and have Type I, it is likely you have a mutation in PCDH 15 but MYO 7A is the most common.



Type II there are these four genes, three are well known, and Ush 2A is by far the most common causes of at least 80 percent of all case of Type II. And Type III is a rare type in comparison to the other two and currently only known to be associated with one gene CLR N1.

I'm going to talk about genetic testing because this is a really interesting time to be involved in genetic testing because the methodologies have changed dramatically over the last three to five years.

So when genetic testing was done, you would test a single gene. What you do is look at an individual and say this individual has this particular genetic disease or I think this is the genetic disease and based on what we, from this person's symptoms and the testing we're doing, I predict it is most likely to be Type I and I think it is probably MYO 7A and that's what I'm going to test for, so you would test for some specific gene. If you were lucky that would come back positive because your guess was right based on a lot of good clinical information.

But what we learned over time is several things. One, if you have a

disease like Type I caused by many different genes, testing these one at a time these genes is inefficient particularly if you don't happen to have a mutation in MYO 7A, and if you don't how do you know what to order next? The way that genetic testing was done, they do what is called sequencing where they look at that sequence or those base pairs and look at the entire sequence to see if every single one is exactly what they predict or if something is abnormal.

So over time we realized this is not idea in a lot of cases for testing and then testing moved into what was called genome typing panel or chip testing.

And so what they did they took advantage of the fact people have been tested using that classic sequences testing methodology. So not just the gene anymore but what specific change within the genes pops up over and over again and you can test for. So we would have this test you can test for all Type I common mutation.

And then say you get that result back and you find they have one common mutation within 7A, then you can go back and sequence just 7A and then

you can do another test and know that's the gene to look at and you can go back and test all of 15. So it is a way to screen for the most likely gene and go in and look at every single base pair. So now we moved beyond that.

Now most of the testing that's being done is not only for multiple different genes, but it is looking at a sequencing technology that can look at the sequence of these genes for many different genes all at once, and this technology has gotten so much better over the last couple years. It makes tests all the genes at once not just the one type but all of the genes together. And that has multiple advantages.

And one of the distinct advantages as we learn more and more about genetics we understand that there's a lot of overlap. That one person may appear to have Usher Syndrome II, but they could have a mutation in one of the classic Type I genes or maybe here's a patient who looks like they have Usher Syndrome, but they develop symptoms latter on, so the clinical presentation doesn't fit. So if it doesn't fit, what are we going to do?

So finally I want to talk a little bit about whole genome sequencing. It is not something that is the answer today for genetic testing, but it is being used for research right now. Whole genome sequencing is looking at all 25 thousand genes and in that kind of testing, not only are they looking at all of the kinds of traditional parts of the gene that would be tested for, but they can look at the in between sequences, which we're learning more and more can carry genetic mutation. So this is not something that is you go back and get ordered from your doctor today, but it is very important in what we're learning about Usher Syndrome genes and about the interaction of different genes, and it is helping us to discover some of those mutation that have been very, very difficult to find.

So, these next two slides were loaned to me, and this one has a lot on it. But the point of this is to talk about the complexities of interpreting or annotating the data when it comes back from testing. The laboratory test comes back using this next sequencing technology may identify 50 to a 100 variants. It can be complicated in the lab to decide what is normal variation and what might be true disease-causing mutation, and that is part of what takes a little while in the lab, why test results take a while to get

back because there is a lot of interpretation that has to go on, but it also helps explain why people say they have a variant of uncertain significance. So that's what the VUS stands for.

So they find a genetic variation to decide whether that is a true mutation and then based on that they say that's clearly benign or probably benign or it is pathogenic, meaning disease causing. We have seen this and we can see the influence this has on the final protein. We know it is pathogenic.

Down from that, this is predicted causing the protein to not function but we have never seen it before. And the middle one is the uncertain significance.

Farther complicating genetic testing, you don't always find that a person's mutation is one of those used to find genetic mutations. So some individuals will only have one mutation found, so you order testing, you get the testing back and they find one mutation. What does that mean? They have two but we only found one and if so why? It can be as they are showing here.

Some individuals may have a deletion of material that is too large for the next generation sequencing test methodology to pick up or it could be in a region of the gene not included in this test because it has been thought to be a non-important part of the gene which we know is not the case anymore.

Or this is a red herring result and this person is a carrier for this type of Usher Syndrome. And this has been shown in several patients. This is the underlying complexities of getting genetic test results back and helping to interpret them.

So what are some of the benefits of genetic testing? it can help clarify diagnoses particularly if you have patients, many of them maybe children but not always children, if you try to decide if this is a syndrome form, meaning does this stand on it own or is part of a syndrome? Genetic testing can help predict the severity or lack of severity, how is it likely to progress, if it has been seen in lots and lots of other families, and they have a typical course that can help you provide information for the family.

And I can help qualify a person for a trial. I talk to a lot of people interested in genetic testing for this reason, and we're going to hear more about the current gene therapy trials going on and what is on the horizon. You need to know what gene is causing your particular condition.

Some families it can enable testing for other family members for preimplantation testing and it can aid in the research. Not all cases of Ushers follow the traditional rules. There can be a traditional syndrome Type II mutation that can cause a disease that looks more like Type I or vice versa. And sometimes there might be two disease-causing mutations in say MYO 7A and then another one and is that influencing the progression of that disease? And if it is, to what degree? And this can help aid the research.

With that I want to stop because I know there are going to be questions, probably too many to answer, so I will take what we can before we get kicked out of this and then we'll take more later.

Speaker: Thank you. This is Dorothy Watts speaking. You mentioned before Usher Syndrome Type III was rare. I'm curious. Are other people, are there other people who are not included in Usher III syndrome categories? Thank you.

Karmen: So Usher Syndrome Type III is from Jewish and Finnish ancestry, so sometimes people have a sense individuals of Jewish ancestry are cursed, they have all these genetic diseases, but that's not the case. But we know a lot about the diseases in that community, so any time there is a community that states together and marries within the same small community over many generations, you have disease more common in that group. And so Usher Syndrome III is a rare disease worldwide, but a couple of these tight-knit communities in Finland, it is more in Finland, but for the Jewish ancestry within the United States that live all over the place, but in someone with this ancestry, when I have a patient with that ancestry, I start testing depending on their symptoms as opposed to ordering a panel of test right from the outset because it is statistics. It is likely to get a positive test result.



Mark: Other questions? I see more.

Speaker: Your talk reminded me of stories I picked up through the years and I'm wondering years ago when I was first diagnosed I was from Switzerland and they had a database and a very large Eskimo population and also there was a Peter Humphrey in Ireland did a study of 100 people in the family, so are we still collecting that information, and have you heard of those groups and do you have any comments on them?

Karmen: So I think there is three components. One is the registry and this is why Mark is smiling, so I will let him talk about the registry? Oh, I will answer the other two. I don't know a lot about those other populations. So I tend to know more about the populations that affect frankly my patients here in the United States. So if it is not a population in the United States, I don't know as much about it, so I'm not as familiar like with the Swiss population, but there are certain pockets within all genetic disorders where disease is seen more frequently, and that's why it is important know that because it helps us focus on where to do testing.

But in terms of collecting all of this information, that's the purpose or one of the purpose of a registry so I'm going to let Mark take that.

Mark: So, just to give it some background, on the Usher Syndrome registry, I'm going to step up on the stage. So the registry right now is capturing information about basic contact information, but we have plans to be able to capture genetic information. We do ask people what type of Ushers they have and if they have been genetically confirmed, and we had a number of researchers contact us saying we're doing research on a particular type of Usher Syndrome. Can you put us in touch with people with that syndrome to see if they would be interested in this study?

And with the registry there is a Chinese wall between researchers and the families. Researchers have to contact the coalition and the coalition will let you know that these researchers are interested in talking to you and will pass on their information to you. Excuse me, pass on the researches, so your information is never handed on without you passing on the information.

I see one more question. So one more question and then interpreter switch.

Mitch: Thank you. This is Mitch turbine. I lost my voice. You talked about cases in which the clinical expression, the phenotype, might be very different from the genome type. What is likely be less effective in the clinical expression has been different, for example, you had someone who's genetically Type II, but the expression is more Usher Type I. You treated Usher II.

Karmen: I think that's a really, really important question. So first when thinking about treatments, most treatments that are being developed and targeted for inherited retina diseases are not gene specific.

Gene therapy is clearly gene specific. You don't want to give somebody a working copy of a gene they have, so you need to make sure you targeted your population to only those who have defects within that particular gene when you do gene therapy. There was different stages of clinical trials and I'm guessing we'll hear more about this -- no he's not going to talk

about that. He has other things to talk about but traditionally you have a phase I, II, and III that work out fine if you are doing therapy for diabetes, a really common disorder in a general population, but when you are treating a rare disease you don't have the numbers to have this big phase I, II, III study, so you combine them so you could do a I/II trial looking at safety and you have to utilize your numbers, The small number of people you have for that.

All clinical trials have inclusion and exclusion criteria. Based on that criteria you could have somebody who has two genetic mutations with an a typical disease course and you wonder about that. But if they meet the inclusion criteria and not meeting exclusion criteria and they are able to participate in your study, you probably want them because it is just hard in rare disease to find enough people to get a really good study. And so some of that variation, you just have to accept, and I think figure out as you go.

But they do try to make the criteria so that if somebody has a phenotype for a clinical expression that is different from everybody else in this population,

they probably wouldn't make it into the trial until a later stage of the trial where it is shown to work and now we're looking at dosage. What's the right dosage?

Mark: We have been talking about genetics and the phenotype with Usher Syndrome and how Usher Syndrome presents, but really what we, what most people are interested in are the treatments and one of the reasons we held this in Portland this year is because in the last year or so the clinical trials for Usher Syndrome began. And we are fortunate enough to have Mark Pennesi here today to talk about the clinical trials and other treatments related to Usher Syndrome. And I'm not going to give you more introduction than that. Everybody wants to hear from you; they don't care about me anymore.

Dr. Mark Pennesi: Thank you, Mark. It is really great to be here. And I have you for the next hour, so I hope you've got some coffee because we're going to be talking about a few different things.

For those following along in the handout, I added a few slides just because

there are so many exciting things going on, and I really wanted to include everything that I could.

Before I get started, I really want to acknowledge some people. Although I'm the one up here speaking, this is really a group effort, a team effort, and we're fortunate to have many great people on our team.

First and foremost is our chairman, Dave Wilson, who has been supportive developing therapies for these trials, and also my mentor, Dick Weleber, who taught me everything I know about retinal degeneration, so if I confuse you, he's here to clean up.

History. There is definitions going back to ancient Greece, but the first description in the literature is by a very renown German ophthalmology. We should probably call this Von Graefe disease, but Usher described 68 patients in 1912. Why we didn't get an understanding of this until the 1850's, that's when the scope was invented to look into the eye and make the connection between hearing loss.

This is a normal appearing retina on the left and on the right is a patient with Usher Syndrome, and you can see the changes and the pigment changes. And this where the name originally comes from.

This disease results from a degeneration of the rod and cone receptors in the back of eye, and these detect light. We use our rods in dim vision and nighttime and the cones are for daytime and color. We have gone through this and many of the speakers this morning gave excellent talks talking about the structures that are necessary and how the hair cells and photoreceptors share these structures.

And just for review, we generally classify Usher Syndrome into three types: Type I, II and III. Type I tends to be the most severe. Patients generally have onset before puberty and profound deafness and vestibular dysfunction. Type II, they are diagnosed a little bit later on in life often, after puberty, but now with genetic testing we are diagnosing more patients early before symptoms.

Type III is different. It starts off somewhat like Type II, but then it can

progress. One of the features I haven't mentioned in this slide, we do see some problems that is a new associated with enamel, but there is some role in the teeth as well.

This shows those twelve different genes and MYO 7A is the most common. Ush 2A is the most common and in Type III there was recently a second gene that was discovered.

These genes and proteins form complicated networks, and I'm not going into a lot of detail, but they all interconnect. They're six for one, and you lose any of those and you get Usher Syndrome Type I.

I want to talk about the tools we use to study this in patients, and this is because these tools are very important when we talk about therapeutic trials. And many of you have gone through the clinics and had some of these tests. And these tests provide us with a lot of important functional information about how much vision is remaining. These tools are very important as we move into gene therapy trials for understanding if they are actually working.



And usually the first thing we look at is family history. As Karmen told you this is autosomal recessive disease. There are multiple generations that are affected that might want be Usher Syndrome.

The other thing we looked at is just a photograph of the retina. We can look in and examine the retina looking for the changes we see such as decrease in the size of the blood vessel, a pallor of the optic nerve or pigment in the retina. We have fancy lenses that can highlight the pathology. This is a test called Autofluorescence, and it shows you this ring that is rounded and retina, so we can get a quick idea how much retina is intact in the patient.

One test that is very useful for us is the OCT and anyone with Usher Syndrome should have this test. What this test is is like an ultrasound but it uses light. And it let's look at the retina in cross sections so we can see the layers and we can see the layers of the retina here. Why is this in the Usher Syndrome? because we know a lot number of patients can get swelling right in the center here and these are cysts that are swollen that

can decrease the center vision. We can treat this with eye drops, and so in patients who have lost peripheral vision, if we can improve this, this is a big victory.

We can be quantitative about these measurements, and when we get into the trials we're actually using imaging more and more as an outcome measure. We can measure the thickness of the retina to see how much is preserved in an eye that we treat versus the other eye we might use as a control. We could plot those out as maps and we can get very fancy.

We have a new technology now at Casey Eye Institute. This is a man that has this really cool piece of equipment because it uses the same technology that ground based telescopes use to look at the stars, but we can see individual cells, so each one of these dots here is an individual cone photoreceptor and we can count those cells to get a sense of how many are there. And this is something we think will be useful in looking at treatment trials because we can count how many are left and how many have changed over time, and this is an example of that. We counted the cells and plotted out a density. And red means there is more cells in that

area and less in that area so over time we can look at the changes in the cells.

Many of you probably have seen this Electroretinograph. It is like measuring the electrical activity of the heart. This uses a special contact lens and we can measure the signals generated by the rods and cones, and this is useful for measuring how much residual function there is, so we can use it for diagnosis and as a functional outcome measurement, and this is something we're looking at in our trials to see if there is a change.

The multifocal ERG gives us a plot of the function centrally, and you can see this is unaffected patient and this is a patient with Usher Syndrome, and the signals are much lower.

And one modality is the visual field, and the visual field is going to probably be one of the more important outcome measures for trials, and patients complain about these because they are boring, but essentially what happens the patient looks into this dome and this area will have little lights moving across or appear and every time you see something you have to hit

a button. And from that we can plot out a map of the visual field for what the patient is seeing, and this is an example of a patient with Usher Syndrome, and you can see that there is an area in the center they can see and off to the side and you can see where they don't see the target and that tells us a lot of information about what is functioning and what is not functioning.

We can have more detail versions of this and we test very fine grids and get maps and then we can take all of this information and feed it to a mathematical model, and this is something we have created that allows us to treat this 3-D graph, and this is called Hilla Vision. It is a 3-D representation of your visual field and by looking at the volume which can get a quantitative measurement of how much you can see.

And this is an example of a patient with Usher Syndrome and you can see how this hill is much smaller. And when we start doing gene therapy we hope to see that actually increase and be able to measure a change in that.

We can then take all of these structural pictures and we can start to

correlate them with the functional measurement like the Hilla Vision and this is where we overlaid this graph onto a picture of the retina so we can see what parts of the retina are functioning better.

And why is this important? Because when we do gene therapy, at least right now, we can only treat a small area. So we want to pick the area where we think the cells are going to respond best and that area probably turns out to be in an area called a transitional area where you have healthy cells and where the cells are no longer functioning so we can target a specific region with the gene therapy.

So I'm going to shift my talk and talk about some of the treatments and future treatments we have for Usher Syndrome. And as you can see there are many different things and even new things that are popping up all the time. I'm going to talk a little bit about micronutrients and Mark mentioned this this morning and neuro protection and this concept of antisense.

Jennifer is going to come up and can tell you more about this and stem cells. and optogenetica and finally our gene therapy trial for Usher

Syndrome.

So most of you are familiar with low vision aids and these can range from simple magnifier and the iPad has been ones of the best things for the low vision community. It provides so many things in one device.

What about micronutrients and vitamins and this is one of the things patients ask me. Is there anything I can do to slow down my degeneration? And if you go and read in the literature you will read about Vitamin A. I will say there is a little controversy. If you survey all the specialist in the United States, some will swear by it and put every patient with Usher Syndrome on high dozes of vitamin A and others will say no, and there is some risk to it.

We tend to be neutral on it. We educate the patients and let them make their own decision, but when I say high dozes I'm talking 15 thousand international units, 20 thousand international units, not just eating some carrots.

With these high doses, you can get liver toxicity, so you do need to have your liver function tested once a year. Also, this is something you are going to be on your life and there a higher risk of osteoporosis in older patients, so it is important to get bone density scans. This is contraindicated in pregnancy and in other forms of retina degeneration. There is definitely a contraindications to it.

Lutein is another one found that we think could slow down degeneration. When you look at this evidence it is still small, but we do feel that at least the evidence for these was relatively good, and we don't think they are particularly harmful. Interestingly beta carotene is something that's popping up more and more in the literature and this is actually a precursor of Vitamin A.

There has been small studies looking at it. I don't think there's enough information to recommend taking it but it is something we're keeping our eye on as a potential supplement. And this is basically the idea of having a compound that would slow down the degeneration. And the reason this is appealing because it doesn't depend on the mutation. So, if you have

Usher I or II it wouldn't make a difference. They have types of devices and drugs are designed to work with any kind of mutation.

And one that has been looked is actually a growth factor called ciliary neurotrophic factor or CNTF, and the protein diffuses through the sides of this implant. And the implant actually goes right inside the eye here and here is an example of how big it has been. And there has been several studies looking at this device and I have to say that the results have not been terribly encouraging. There has been mild benefits seen from it, perhaps some preservation of the thickness of the retina, but we haven't seen it slowing down vision loss or visual field loss, so I would say the jury is not out on it, but it hasn't been a homerun. Maybe we need to figure out way to get the drug delivered differently. But now we have the technologies to deliver different kinds of medication to the eye. So, I'm sure we'll have lots of questions about stem cells. And I think this is a really large topic I could talk an hour about it just alone.

But just to sort of summarize it, what is a stem cell to begin with? There are many different types and if we think about the simplest when a sperm



and egg come together and create a fertilized cell, from that one cell the rest of your body comes. It can divide many times and become every organ in your body and that is a totipotent cell and it can become any other tissue. When you hear about embryonic cells, that happens later on. So the fertilized egg starts to divide and divides again and forms about a sphere of a hundred cells or so and there is the intercell mass where the embryonic stem cells are derived from. That's different from adult stem cells. We all have them in our body right now in a variety of places.

In your bone marrow there are adult stem cells that can develop into blood cells. In the skin you have stem cells and perhaps even in the eye there maybe some stem cells that exist there. There is the Muller cell that can act as a stem cell, and blood vessels, there are cells around the blood vessels that may have stem cell properties. Adult stem cells don't have the capacity to turn into every different tissues, but maybe a subset. But the advantage is these cells are your own cells so there is no problems with rejection and what might be possible is to isolate your stem cells, put them in a dish, fix whatever genetic problem there is, and put them back into your body. That's a very exciting concept.

Now, how exactly might my stem cells work? And this is an important concept. There are probably two different ways they can work. One, we put stem cells into the eye. And it may actually release neurotrophic factors like CNTF and slow down the retinal degeneration and that's all it does. It never becomes anything else but just releases protective factors.

What everybody hopes for and dreams about is the concept we can coax these stem cells into a new retina and replace the cells that have been lost in Usher Syndrome, and that may happen and I will show you interesting results.

These are the stem cell trials going on for the eye. There is one company called ACT that has been doing subretinal injection of embryonic stem cells looking at macular degeneration and other companies looking at a different variety of stem cells. And none of these have specifically looked at Usher Syndrome yet. They trials are still very early on and whether they work or not remains to be seen.

But there are some things that are very exciting. This is a paper that came out recently where a team in Japan was able to take embryonic stem cells and when they grew them in this 3-D kind of jello matrix, they were able to get a clump of cells to start forming in an eye cup, and you can see that right here, this clumping of cells that forms this eye cup. And this is going on in a dish. No other signals coming from the body. And what is more impressive, when they grow this out over time it actually starts to express the same kind of proteins and markers we would see in the retina, and this group developed a technique to isolated the stem cell from these eye cups and freeze them. They are hoping to do trials in the next year.

This is another interesting thing came out looking at how to deliver the stem cells and we think are we just going to inject them, squirt them under the retina. That's probably not going to work. We probably need to put them in a structured manner and they developed this device like a taco or burrito where you grow the cells on top of it, and you can see the cells here and then you role this thing up, inject it under the retina and it unfolds and acts as a support for the cells, and I think that's a really neat device, and so I think this is a very promising technology.

Kind of shifting on to other devices many of you may have heard of the Argus II it is an artificially based retina on a silicon chip and it is connected to a camera that you wear, and that camera looks around takes the data to a computer, which sends the signal back to this electrode, and this electrodes fires and there is a grid of 64 that stimulates the ganglion cells and they form the optic nerve and these electrodes activate these cells in a way that these patients can see a doorway or window frame or be able to orient themselves in space.

So going from nothing to being able to actually get around a little bit or see, find their way to the bathroom, is a big improvement. The second thing about this is that the technology is present to make even higher resolution devises and right now we're just limited by computers. Computers are not fast enough to process the information that comes from higher array chips, but we know computers, they just keep getting better, so it is just a matter of time, so this is an exciting option with patients with severe vision loss. If you have intact, vision this is not for you, but with severe varies loss this is potentially an option.

Moving onto gene therapy. So we reviewed a little bit of this, but I think it is important to understand some basic concepts for gene therapy. We are all made of 25 thousand different genes that code for every protein in our body. DNA codes for proteins that make up the cells in our body and what happens when have you a mutation in the DNA? Well two things can happen. The mutation can mess up the proteins such that you get no protein or it can create a property of the protein that makes it toxic or causes problems, and the approach for gene therapy is different depending on the mutation.

Where you don't have any functional protein, then the goal of gene therapy is going to be to replace that missing protein. In the case where you have a protein that gained some bad function, the approach of gene therapy is going to decrease the bad protein.

What is gene therapy? What exactly is it that we're trying to achieve? Well, what we really want to do is take a normal copy of the gene or the piece of DNA and get it into the cell to replace the mutated form of DNA.

We use a vector. You can think of a vector as a taxicab for bringing in that new piece of DNA.

There are different kinds of vectors. You can just have bare DNA or inject bare DNA into a cell. Now if we wanted to do that in the retina, that would be hard because we have to inject millions of cells with the DNA, so we need a machine that is going to take in the DNA automatically to the millions of cells and that's a virus. Viruses's job is to bring their own DNA into your cells.

And that's partly what makes you sick, but we can take advantage of a virus and strip out the parts of a virus that make you sick and instead put in our gene of interest and use the gene to take in the virus. The virus is not the only way to do this.

There is nano particles where we take small particles that binds DNA to the nano particles and release those particles such they go into the cells. Why do you need different techniques. It turns out that viruses have a limited capacity so just like a taxicab can. Fit a certain number of people

in it, and you have small taxicabs, and those van taxicabs you can fit more people. Viruses can only carry a certain size of gene. And that works for some diseases like one is a small gene, but when you start looking at other genes Ush 2A is actually big and it is too big for some of the viruses we have.

So this is just a picture showing the basic concept where we have a virus. It has a little bit piece of DNA taken into the cell, and injects this nucleus into the cell.

How do we physically get the virus into the retina? This is a surgical procedure. You have to go in and take the gel out of the eye, and then you stick a very fine needle under the retina and create a little blister of fluid with the virus in it.

Let me see if the video here will work. This is a video of actually one of our gene therapy surgeries going on. Doesn't look like it is going to work.

In essence this needle is tiny, about the size of a human hair. And you make a tiny hole, inject it and it creates this blister of fluid under the retina,

and you can see that right here. This is a scan. We're looking at the retina from the side and this is where we injected the gene therapy. After a few days that fluid gets punched out but the virus stays behind and the retina flattens out.

Currently we have trials going on at our institution. The first one we started with was Leber's congenital amaurosis RPE 65. That trial is coming to a close. We treated 12 patients and are hoping to report the results soon. Over all it's been a positive experience.

The two trials that have been exciting to us are the next two for Stargardt disease and Usher Syndrome 1B. I can't tell you an answer as to did it work or not, but I can tell you about the trial.

In addition, we have several other trials planned in the future, and it is not just us. All around the world people are doing gene therapy trials, so it is a very exciting time. Even though we're only treating one form of Usher Syndrome today, without a doubt in the next five years there's going to be other forms of Usher Syndrome that we will be treating.



So, Ush Stat is the name of the gene therapy trial. We heard about Type IB Usher Syndrome. It is a disease caused by a mutation and MYO 7A. These people have severe retinal degeneration, severe deafness and balance problems. This is a picture of one of our patients from the trial and you can see the changes all around the retina. This is showing the extent of the loss of the cells and how the retina is very thin.

The trial is sponsored by Oxford and this is a Phase I/II escalation study. Karmen talked about this a little bit. When you first start a new therapy you start with what is called a Phase I trial and you are really looking at safety. We never used this gene therapy vector before. We don't know if it is safe. We think it is safe. We tried it out in animals, but until you try something in a human you don't know if it is safe.

So, we start with patients who have had very severe vision loss because what if it were not safe? Already they lost most of their vision. Often we start with a very low doze that may not work.

And as we go on, we keep increasing the doze mainly to look for any kind of bad side effects. Eventually when we get to the highest dose and we treat enough patients to see if there is any kind of a hint of an effect.

We're collaborating with the Hospitalier in Paris. And this is a little technical jargon on the gene therapy, but I will translate this for you. This is using equine infectious virus. That's a fancy way to saying a horse virus. So we strip out all of the bad stuff and put in our gene of interest. This virus has never caused any disease in humans. It causes a transient anemia in horses. We tested it out and we didn't see any cancers or anything, but there's always risk when you are dealing with something new.

You can see this is broken up into groups, and we do this for safety. We start first just with three patients, a very low doses, and these are 18 years or older, and they are what is considered legally blind.

So, we treat it, first group, and then between every group you have a data safety monitoring committee that goes and reviews all of the data and these are independent people not at our institution, and they look for signs

of toxicity. And after that they give you permission. Okay, you can go on to the next group and treat three more patients, so the next group we do at a higher dose and we go through the same process. And we go to an ever high dose and finally, if everything is going well, we keep enrolling patients.

Now the very exciting thing about this trial is that we have approval if we're able to treat these 12 patients then there is possibility of going on and treating other patients. And when you think about it, that's where the excitement begins. We know gene therapy isn't going to bring back cells that are dead. It is going to slow down the degeneration, maybe freeze it where it is at, so it makes sense the earlier you treat with gene therapy the more effective it is going to be.

And if we can treat children perhaps we can treat them before they become very symptom.

This is just talking about some of the inclusion criteria in more detail with the different cohorts, and right now we're looking at 18 years old, legally blind, and have no detectable rod or ERG. As we go on this gets more

relaxed once we have seen enough patients we feel it is safe.

We're looking at many different things and I'll introduced you to a lot of these concepts including the vision field ERG, BCVA. Being involved in these trials is a lot of work. You have to come visit and it can take you two or three days to get through the testing for that trial, so it is a big commitment, and you might have to come several times in the first month. Usually it is a little bit better and starts spacing out over time. But when we look for patients it is actually difficult to find people that fit all the criteria that we want and are willing to come for all the multiple visits because people live far away and might want have the assistance of people to bring them.

So even though MYO 7A is the most common type of Usher I, it can be hard to find people and that's one of the reasons it can take a while for these trials to get completed.

Just to give you a sense of what we accomplished so far, we treated the first patient. We have a fifth patient planned but we're currently on a

pause and hoping to resume in a few months, so you can see here we finished the first cohort at the low dose and had a data safety monitoring meeting. They found no problems and we treat the one patient at the medium dose so in conclusion this trial, it is too early to tell if it is successful, but it is really exciting and this is just the first step in many more trials to come for Usher Syndrome, and it is really the beginning of a new era for this, so I think everybody should be very excited about this.

So, I will just stop right there and answer questions. Thanks.

Mark: Okay. So I have a suggestion because I know there is going to be million questions right now. Why don't we take a 15 to 20 minute break, and then we can do our Q & A with all the speakers.

So why don't we take a break, it is 2:38. Start at 3 o'clock and come back and we'll do our Q & A at that point.

Krista: Excuse me everyone. If we can start taking our seats in the next few minutes we'll have the Q and A session With Dr. Weleber

Mark: So I have, first I want to thank Dr. Pennesi for the talk he gave and thank want to take all of our speakers here today that were so great. We have a new person up here in the front this is Dr. Jennifer Lentz who is doing fascinating work with Usher Syndrome, so we have a great number of people up here for you to ask questions to. You have been saving up your questions. Please ask anything you want.

That's Bella. Bella wave. That's Camera. If you would like to go over there and introduce yourself. That's Bella, in case you missed.

And one more thing before we start I hope you all caught the perfect symmetry of this conference which started with a picture of Bella on a horse and ended with an equine virus. So do you have any opening statements?

Dr. Richard Weleber: First, thank you very much for the opportunity to participate in this. I think all the speakers have been fantastic, and I have learned a lot and they have learned a lot from each other as well.

This is your time to ask questions. I know you all come with questions that were not necessarily addressed by any of speakers, and so with that in mind perhaps we should start with Dr. Pennesi's presentation because that might have the most clear in your mind at this point and see if there are any questions from Dr. Pennesi about his presentations. So we have questions?

Speaker: Hi. I'm Susie and I would like to ask Dr. Pennesi what you showed us here where you are in the trials. Is this a Phase I, II considered Phase I/II together. Yes. And what is the time frame, so when it will go on and where will get it from there?

Speaker: I'm going to be shuffling the mic back and forth.

Dr. Pennesi: This is what we call a Phase I/II combined trial. The reason the FDA actually allows you to do trials like that for orphan diseases, which Usher Syndrome is, so we can do those two together. And so yes. The next stage would be a Phase III trial. Which would

probably be a much larger trial hoping to enroll a greater number of patients. I think this current trial is around 18 patients total. And as far as the pace goes, we have the capacity to essentially treat one patient a month. And what we're doing is alternating with Paris so we treat patient one month and they treat one the next month and we go back and forth.

In reality, it takes longer finding people who fit the criteria and a lot of things can disqualify you from a trial. It could turn out we go to collect your liver function test and they are high so we can't enroll you even though you fit the other criteria. Sometimes there are things that may disqualify you and often times we think we have a patient and bring them in and go through screening and find out there is some reason we can't enroll them and so the reality actually takes longer than what you see on paper.

Speaker: Any other questions?

Speaker: My name is John. You mentioned in your presentation the viral vector you are using to deliver 7A integrates into the genome but causes less damage. Why is that? Is what unique about this vector.



Speaker: The big concern that people have with a virus integrating into the DNA is that you could disrupt a gene with normal function. And when it does that, there is always the potential to create what we call a gene that might predispose it to a cancer. And that is a theoretical possibility. What we found is that when you look at how the virus integrates, it integrates randomly so some viruses actually have a preference to integrate to certain parts of the genome and in fact there are viruses that specifically put you at risk for cancer because of that property. If you think about the human papillomavirus that cause cancer because they have a predisposition to integrate to an area of the genome that actually will create a oncogene or cancer causing gene.

Now when have you something that randomly integrates, there is no preferential spot, so the odds are it will integrate in the same spot in the two differential chromosomes is low. Remember, we have two copies and usually you need to knock out both genes to get an effect so we think because of that non-preferential that is low.

Speaker: And there is another issue and that is we're delivering the gene under the retina. And so if for example you were delivering something systemically and that was the administration that created some mischief for activating oncogenes that was for deficiency genes or genetic disorders and then you were giving the vector, basically a very, very rapidly proliferation cell, so you were giving much larger bolus. It is going to actively divided population of cells more likely to run into a problem of integration where there could be a problem.

When you take a vector and administrator it into the vitirus ,you are reduced by a thousand of an extra ocular event under the retina. You increase it by another factor now a million times less likely to get an extra ocular event. And this is a virus that, where the gene itself doesn't cause human disease. It is then tested now and then for several years and treatment of Parkinson's disease and now Usher Syndrome so in all three of those, and actually there is a fourth one and that's the delivery of a anti, the wet form of macular degeneration. It has a very safe profile.

Mark: Thank you. Another question?

Speaker: My name is Carrie. I have us Ushers Type II and know you talked about the various testing that is currently being done. Are you aware of any testing forth coming for people with Type II?

Speaker: I haven't seen any specific clinical trials that I know of in the next six months. There are people very interested in looking at Type II Ushers, especially Ush 2A because it is the most common mutation that we see in the clinic. And as I eluded to one of the difficulties is the size of the gene, there are different ways to deal with that.

One thing our collaborators down in Florida are looking at is making the, breaking the gene into pieces and putting it into two different viruses and then actually having them combined once they get into the cell. And I think that's a very exciting concept for larger genes. I don't, I think they've gotten it to work in sort of experimental conditions, but I'm not sure it is at a point of being ready for clinical trials, and as I mentioned, there are these other delivery methods that people are looking at.

Oklahoma is looking at the nano particle delivery where you compact the DNA onto a nano particle and the advantage of that, you can take a very large piece of DNA and deliver it and there are other methods that people are looking at for delivering these large genes, so I think it is a technical issue right now. I don't think it is something that we can't overcome with enough effort.

Speaker: Can I add to that? First of all the Usher 2A gene, and it is a very large gene. It is larger in full length ISO form than MYO 7A but there are two transcripts or forms. Usher 1 is a longer form and one is shorter and they are both present. We don't know which ones are more important or might be more important to rescue the retina or prevent degeneration, but those studies need to be done before they can make a decision as to whether they can reduce the size of the portion they might want to put into the existing vectors. There is one question in the back of the room there.

Speaker: I'm Angela and I have two questions. How long is the trial? And if it works, I'm sorry -- how long is the trial? And I'm wondering is the trial happening solely in Oregon or all over the country and is that

coordinated? And if it is successful, when will the FDA approve it.

Speaker: Well first of all, the trial is an observation for one year, but after that the patient is continued to be examined for several years after that because they go from the very close monitoring, as was mentioned during the first year, to monitoring every six months, but they are still closely monitored. Thereafter and so that trial will continue to go on for a period of four years. Is that right? And after that there is a long-term registry for which goes on for another 10 to 15 years. So they monitor these people for extended periods of time.

Now you asked whether it is taking place anywhere else. It started in Portland and right now that's the only place that has treated any. They had some little difficulties getting the French regulatory agencies to give them final approval. They have gone through most of the hurdles and had acceptable conclusions so that so as soon as this pause is lifted in the next month or so they will start entering patients and dosing the retina so trials can go in both centers at a fashion that will get them completed sooner. So maybe that answers that question.

Speaker: I have two young children with Usher Type 2C. How often do you recommend getting the tests? And my other question in addition to being registered in the coalition I contacted NIH but anywhere else that could meaningfully exploit our genetic material for research that would be best place to use that.

Speaker: There's three agencies that are helping to fund Usher Syndrome research. One is the Coalition for Usher Syndrome Research, NIH, and and Coalition for Blindness, and they all have registries of some type. So if you wanted to be inclusive in all of them. you could do that.

Speaker: Question inaudible.

Speaker: So the question is, in general, usually after the child is somewhere around seven or eight years ever age, they can be tested unседated. So one could make an argument for holding off until they are seven for the second one.

It would be nice to have information about the ERG. And at other points but is it worth the minimal risk of sedation to do that. It couldn't be done without a protocol to propose to the institutional review body, but in the case of impending trial they probably want the ERG and that maybe three to five years away for Usher Type II, both your kids might be in the range they could be done unsedated and in general the ERG is stronger without sedation. And so it could be a better baseline for future studies. Would you agree or disagree with that Mark?

Speaker: Yeah. I think that's reasonable.

Speaker: I'm Cloie from England with a daughter three and a half with Usher 1B, and my question is related to a slide showing increased blood supply, and I just wondered is it possible or would it be helpful to stimulate the blood to the cells to preserve function? And a second question about Vitamin A. You mentioned maybe not using that so a lot of multivitamins have Vitamin A, so should we stop that?

Speaker: The second question about vitamin A. When they, when the

original vitamin A supplementation studies were done they were actually looking at giving, there were four groups vitamin A, A plus E, E and then nothing.

And you know, as I mentioned earlier they're having some criticisms about the statistics of those studies, but one thing that fell out of the multigroup analysis was that it seems like the patients who were on Vitamin A did worse than the patients who were not.

Your other question? I forget.

Speaker: Blood supply.

Speaker: Oh, yeah. So the really interesting thing you have to ask the question why does the blood vessel shrink in retina pigmentosa. And I think that if you look at animal models for the disease, it is probably because the cells are dying off and the blood vessels aren't needed. So early, a hundred years ago. there was a theory that retina pigmentosa was caused by the shrinking of the blood vessel. I think we know now it is



probably the other way around. The blood vessels sort of shrink because they are not really needed. And you know, the question is will they come back?

Say we were to deliver new stem cells under the retina. Would the blood vessels come back? And I think they probably would. I think it is more of a dynamic type of process. Blood vessel can grow when they are needed and I haven't seen anything to suggest they are permanently destroyed. I don't know if anybody else has questions on that. Mitch?

Speaker: So my name is John and I'm from Seattle, Washington. I would like to ask two questions. My first one is for Dr. Weleber and for Karmem Trzupsek. Several years ago I had blood drawn and my father told me it wasn't going to work. The DNA screening wouldn't work. But I wasn't quite sure what was wrong.

Speaker: Was that specifically related to testing for any of the trials? for example, the blood screening?

Speaker: It was related. I'm not sure what kind, but it was for the research. The screen was being done for the research.

Speaker: Because we have been testing some patients to see if they qualified for the trial. Usher 1B trial and those were people we don't know what the cause, the genetic cause of the Usher Syndrome was. So that's what I suspect was done was that we may have tested for which gene you have and if we only looked for, if that was during the time we were only looking for the gene that was associated with this particular trial, then it became negative that would be consistent with or they didn't find any mutations or changes that would be consistent with what sound like you were told where they didn't find anything that were particularly related to the reason that particular blood sample was drawn whether you my qualify or not for the MYO 7A. Does that sound right, John?

But the question. We can go farther saying if you were interested in knowing what your gene actually is, regardless of whether it is the one that is with the trial, it sounds like it is probably not through one, but the other option would be to do what Karmen was talking about would be a panel of

genes where the full, like the next generation screens where sequencing would be done for all of the Usher genes and that would probably have a good chance of detecting the existing known genes as whether or not they were contributing to your condition.

This leaves us, if that testing was negative and didn't give the answer, we would have to be saying that maybe you have a different kind than is known at this point.

Speaker: So if it is not, if the blood screening is not successful, what would be next step be?

Speaker: So, I'd like to help clarify the answer and this is probably broadly applicable. There are probably many people in this room who participated in some testing that was not helpful in identifying the underlining gene and there could be a number of reasons for that.

Even five years ago it was probably be done under a research study and that study may only have been looking at one gene or a couple of genes

and sometimes individuals get results back from search studies and sometimes they don't and that's related to what the findings were and how much testing they can do.

If you participated in a research study before, that is not going to now reflect and get you testing for all of the different Usher Syndrome genes. That would be something you need to revisit. Genetic testing now is significantly better than it has been in the past and probably worthwhile in many people who had negative test results in the past. If you have genetic testing done now using next generation sequences and you are still found to be negative, on one hand that could be very disappointing because now have you done the best testing and you still don't have an answer, but you are helping the research more than you could have before.

Now what happened you have been tested for every gene we know and that means that you are in a group of people where that population is enriched for individuals who are most likely to help us to discover novel or new genes because we're not testing this population of people anymore for those genes that are known but they just didn't get tested for. So, it's

helping you but it is also helping the research effort. Really.

Speaker: My name is Lucy DeFrancis and we have a daughter, five, who has Ushers 1B, and I have two questions. One is for Dr. Pennesi. Could you expand on your comment regarding deficiency and enamel? And do we have to be concerned about adult teeth? And the question for anyone who feels appropriate to answer it, we haven't gone into a lot of detail about the vision loss because we don't want to change about how she feels about her future especially because she is not systemic right now. But anyone, how we can best approach that topic?

Speaker: I might try the second question and let other people answer the first one. With regard to what you tell your child, you can wait until she's asking questions and then answer them in ways that you can answer her direct question without anymore detail than she can process. And most of the time she will say oh, thank you and go back on playing.

The main thing is if she, for example, complains she is not seeing at night, you can say that's normal for you. Or that's what is expected because you

have some difficulty with night vision. And so, keep the information at the minimum level. Don't necessary to go into deep explanations, and if they have more questions, they will come back to you and say no, I want more information than that.

And as she gets older she wants to know the consequence and at this point it is worthwhile talking about, you know, what happens with the retina and the fact there is a tremendous number of researchers working on trying to modify that and improve the situation, and we are all hopeful this is going to be something that will become a reality soon, so you are giving a little dose of reality but a larger dose of hope. But not, you know, you don't want to make it that it would be unrealistic hope. But I think it is important that you balance those things.

Mark Dunning: If I could add on to what you just said, this is probably the only question I might be able to answer. I think he said it perfectly. What I recommend to families you talk about Usher Syndrome a little bit and you talk about it a lot. What I mean by that, the way we deal with Bella and talk with her about it if she want to go out with friend and go trick or treating

for Halloween we say go do what you want.

Remember, you have Usher Syndrome that you might have problems seeing at night and that might bring up questions so we don't spend a lot of time dwelling on it, but we talk about it often in our family, and it is just who she is and to Dick's point, Miah is five, so she doesn't understand much of anything at this point.

My daughter is now 14. What I realized from my daughter being 14, 14 year olds think if you reach 40 you are near dead. So she has no concept of what 30 looks like. And so to try to say to her you know you might have severe vision problems when you get into your 30's or when you are 50, God forbid, you might want be able to read the newspaper at 50 is way beyond anything she can comprehend.

And to Dick's point, talk to her about little things when the lights are off in the house maybe you shouldn't run around because you have Usher Syndrome and you could have problems seeing at night, but you don't need to get into the genetics and talk about what Jennifer Phillips does.

But when she is 14, 15, 16 years old Cameron, just sat through this presentation and I'm sure she understood a lot of it. As they get older they will ask the questions and you don't need to offer it up. And then Kathy is going to comment on this, too.

Speaker: For the kids who can be expected to have earlier vision problems, sometimes having the school vision specialist touch bases with the kids can be helpful preparing them, and in Washington state not every school has a specialist but we have a dual state specialist, and that can be helpful for them.

Speaker: Yeah, and the enamel question. I don't think we have a lot of information about it. If you go and read a lot of articles on Usher Syndrome they don't mention it, but I actually dug through the dentistry literature and there are some articles on it. I think it is something we don't know does it affect all the forms of Ushers or more in one mutation and not another. I started asking all my patients now how many cavities they had just to try to get a sense if there is some kind of pattern to it.



I think often times this is how we learn about diseases is that patients tell us things and we say oh, I saw that in another patient and you start keeping track of it and after a while you have enough information to actually figure it out. So it is something I'm interested in.

Speaker: Hello there. My name is Vince. I'm a deaf individual I use ASL in my professional career and my parents are here sitting in the back and they learned ASL. There are wonderful benefits to learning ASL, I think there is for Usher people here Usher Syndrome here use ASL. And I have a master's degree as well. And Dr. Sie, what is your recommendation? It is not on the list at the Children's Hospital. What is your recommendation to learn ASL and why is it not on your list? Is ASL not a good choice? Do you feel it is a negative thing to have as an option in your center? Thank you.

Dr. Sie: Thank you for the question. I'm not aware of a list we have. I did preference my comments with the fact that in our hearing loss clinic we try to support families in whatever communication decisions they make and we're strongly supportive of ASL. ASL is a language onto itself unlike

some of the other manually coded languages, signed exact English, so we're very supportive of families able to do that and you are fortunate you have learned ASL and your parents have done that and embrace that.

What we find over 95 percent of deaf children are born to parents of normal hearing. And so the parents with normal hearing tend to communicate with a spoken language and it is hard for adults to learn a second language. And particularly adults with young kids they typically have young families so they are very busy so it can be challenging for these parents to embrace ASL in a way that allows cognitive development of their children.

There are a lot of studies talking about the importance is really language and cognitive development, which is what I said at the outset of my talk. Learning ASL, it doesn't matter what type of language you use as long as you are enrolled in early intervention by six months. That is going to optimize your outcome so whether it is ASL or English or French or French signed language. So, we're very supportive ASL. I think for kids with Usher 1 who have bilateral congenital profound sensorineural hearing loss,

it can be challenge for families to make that decision, and so giving kids as much sensory input as possible as early as possible tends to be the decision the families make. But it is not the right decision for everybody, and as long as families do their best to make language accessible to their children, that's what is important.

Speaker: Hello. My name is Karen Tenon from Seattle. I have Usher Syndrome Type I. I have two questions. The first question is for Mark Dunning and the second is about gene therapy. So Mark, I was wondering about the statistics with the registry, for the networking. All of the contact information you collected how many people have been involved in that so far globally and how many people have responded to that request to be on the registry?

Speaker: So the second question was about gene therapy. I was wondering when you get the shots in your eyes, how many times do you have to get those shots in each eye?

Mark: Okay. I will answer the first question. I don't know about the

shots in the eye part. That's not my expertise. So the Usher Syndrome registry we have over 450 families at this point in the registry. They are from 23 different countries. And we have been operating on a shoe string and not promoting it yet, so we have families from 23 different countries without much promotion.

The family network has several hundred families from around the world of different walks of life from different ages to young adults, older adults so the family network we have basically connects you with any person through that and the shot in the eye is you Dr. Pennesi.

Dr. Pennesi: So currently this is an early trial, we're only doing one delivery of the virus. Now we don't know how long the effect might last and that's something we won't know until we studied it so it is possible we may have to treat somebody more than one time.

Also, when we deliver the virus currently we're only treating a small area and it may be that you need more than one shot to treat different parts of the area. We don't know yet. The other thing is right now the way we're

doing the delivery is we're doing the shot under the retina but I don't think we're going to have to do that for all of the time. we're actually developing ways now where we can just inject into the gel area of the eye and the virus will be able to go down to the retina.

And if we can develop that technology then it might be possible to treat the entire retina with just one shot so that would be the ultimate goal is just to make it into one shot but I think it is still too early to know whether you would need one shot or more than one shot. We just don't know enough about that yet.

Speaker: I know there is some questions out here but before that we have Dr. Jennifer Lentz up here who didn't talk today, and could you just talk a little bit about the work you are doing because that might change some of the questions out here if they hear what you have been working on.

What she is going to talk about is a very different way of treating a genetic disease and that is not with replacing an entire gene but actually direct correcting.

Dr. Jennifer Lentz: I'm science researcher at Louisiana State University in New Orleans and we focus on research on Type 1C Usher Syndrome and have developed an animal model that contains the mutation responsible for Usher Syndrome Type 1C in our Acadian patients and we recently discovered a new therapy that works well for our animals.

And so we're at the very beginning stages and have shown that we can treat our animals and treat their deafness and their vestibular defects and are currently working on determining whether this will work for their vision problems as well.

And we're very excited. The therapy in our animals works very well for their deafness and their vestibular defects. And we're very excited to see how it will work for their blindness and the therapy is a genetic therapy, but it is a little different from the gene therapy. It doesn't target the gene but what the gene expresses just before it gets made into a protein, and so it is something that we deliver with an injection and it finds this intermediate molecule that is not the gene and not the protein but the messenger so that

forces that messenger to make the correct protein. And so, we consider it a genetic type therapy but it is a little bit different than the classical gene therapy.

So we're also hopeful that we'll be able to translate this into other types of therapy for other types of Usher Syndrome.

Speaker: Thank you very much. I'd like to ask for a show of hands all of the, you, if you are willing to do this, who have Type I Usher Syndrome. Can we see a show of hands? And how many with Type II? Clearly almost twice. And type III? I got in the range of about 28 to 30. It is almost twice.

Type III. And we have how many just one or two? two. Great.

That would fit the the seven percent, the seven to eight percent. I'm just trying to see if we're pretty much represented as to the proportions of Usher gene types and I think we're pretty good. We have a good representation of the different types of Usher Syndrome. So with that do we have

additional questions.

Speaker: This is Mitch Turbine with Type III for Dr. Jennifer Lentz here and she described her research, so I got that one covered. The second is a follow-up to that and it would sound like your research, Dr. Lentz, could be particularly pertinent so those of us who have it, so are you considering looking at a mouse model of Usher III to continue your research on?

Dr. Lentz: Yes. So, one of the reasons why we have been able to progress to where we are today is because we have a clinical model, a model with an animal with a mutation that actually patients have. So, we're able to test new therapies and relate them specifically to a type of mutation that a patient has. And we are very interested in making more clinical models through mutations that other usher patients have to see if this kind of therapy would work for those mutations as well.

And I wanted to add briefly to a previous question that I failed to mention earlier. The question was are there other places or other websites you go to, to make your genetic information available to the research community?



And there is a company that's called Corell that creates cell lines from patients that have mutations in human diseases, and these cell lines are useful to us researchers because in addition to testing our animal model with new therapies, we can also test cells from patients, and it is a simple blood draw that can be sent to their company and then the patient information is removed and the only information associated with these cells and the type of mutation that they have, and they are made available to us researchers so we can learn specifically about this mutation and whether therapy might work on these types of cells. So it is a tool in the research laboratory that is useful to us.

Dr. Jennifer Phillips: Mitch, I wanted to add more about the mouse. They made a knock out mouse and deleted a large portion of the gene and that mouse does have a retinal phenotype. They are making a mouse model of a particular Ush III, a human mutation. They haven't gone public with the researches of where they are recently, but I know it is happening, so please do stay tuned on that. If you watch our blog and the minute they say anything about it, I will write it up for you guys.

Speaker: Hi. I'm Hillary my niece has Ush 2A and I wanted to clarify. Dr. Weleber said realistically it was three to five years for trials for Type II. Is that correct?

Dr. Weleber: At the very earliest. I think it could be more than that.

Speaker: And is that for gene therapy and stem therapy and does the same hold true for drug therapy?

Dr. Weleber: Stem cell therapy is much farther and I wouldn't want you to hold me on that five years because it could be easily ten. First they have a lot of things they have to find out how to package this larger gene and how to monitor the course. Each one of these genes is going to have it's own difficulties and problems and packaging and regulating the gene so that just the right amount is produced and getting to the target cells of interest, which are the core receptors.

Speaker: And I wanted to know, I know this is not necessarily your area of speciality but any drugs therapy trials that would be sooner or does that -- I

guess I'm wondering which horse is in the lead on this?

Dr. Weleber: Not I'm aware of for usher type II.

Speaker: My name is Meghan and I have a seven year old boy with Usher 1B and I have two questions. As a parent we decided on wearing hats and transitioning lenses and eating a healthy diet. What else can we do? And second it mentioned gene therapy targets parts of the retina that are still healthy, so how did this play with younger patients getting better results?

Speaker: So to answer your first question, and we can can get the doctor to chime in here. I think the concept of sunglasses outdoors is very justifiable particularly if it makes the individual more comfortable. Of course if they are trying to do things that are at dusk or shadow, that could be more problematic. A good diet and nutrition and a health lifestyle are all important issues, and having them eat well as children will probably carry over, and they will have a good diet when they are adults as well.

With regard to anything special that can be done, Dr. Pennesi has gone over the concepts of antioxidants and DHA. I tend to emphasize food groups that contain those other than supplements mainly because a good number of studies that suggested there could be a benefit for age related degeneration, which is the only diseases that it has been looked at with adequate associate studies, it appeared the food groups were the ones that identified what particular compounds were in them. Mark you want to comment about the other question?

Dr. Pennesi: I would just add that one thing that I think that is important is to not smoke. And also stay and way from second hand smoke. There is evidence out there that smoking will make the progression faster, so get back to the healthy lifestyle type of thing. But if I have patients that smoke. I really try to get them to quit. And I'm sorry what was your second question again?

Speaker: In younger patients in the therapy.

Dr. Pennesi: Yeah. I think that as you said before gene therapy is not

going to bring back dead cells, so once the cells have died, gene therapy will not be able to resurrect them. However, if you look at a very young patient, they still have a great compliment of cells, so gene therapy, the earlier we can treat the better. There are limitations to that because of the FDA. We have to start in adults before we can start in children.

Speaker: And we have to also demonstrate efficacy in the adults before we can move down into the pediatric range.

Speaker: And the other thing diagnoses often times it is not made until later but we're getting better and better at that so with improved genetic testing now. I had a patient with Usher Syndrome the other day who was three years old and had been picked up because they were deaf and got genetic testing at two years of age and found out it was Usher Syndrome and, you know, being able to identify people early so that when we do have these therapies, it is going to be an important component as well.

And one other concept I just wanted to bring across, which I didn't give in my talk, we talk about one therapy but I think in reality it is going to be a

combination of therapies. It is really going to be kind of like chemotherapy where you have many different things like a neuro protective drug that you take. Gene therapy to slow down the degeneration. It is not going to be one magic bullet; it is going to be a combination of different treatments.

Speaker: I just had a quick question. If you took all the people in the world with retina pigmentosa does that raise it out of orphan status and what is being done that could be applicable to Usher Syndrome II? If something helps one subset it may help the others. Wasn't sure if there were more people with RP from other forms of genes.

Speaker: I will take that question. First of all the vast majority of the genes for Usher Syndrome relate to the ciliary structure. And there are other things, retina pigmentosa, for example, some of the other syndromes form that also are associated with either another disorder or some syndrome disorders where they are also related to defects of that particular structure. So one them is a gene SEP 2 90 which is an master organizer and it maybe that when that comes to a trial for gene therapy in the future, what is learned from that trial may be applicable to the Usher genes for

example. Dr. Phillips, would you consider that a possibility?

Dr. Jennifer Phillips: Yes. That's your answer. Yes.

Speaker: I had two questions. You said that you were doing testing on rats and mice and monkeys and curious if the testing was similar and if you drink too much coffee does that affect your vision decreasing sooner?

Speaker: We don't. There is no evidence that drinking a lot of coffee will decrease your vision, and I'm sure that's a relief to those of us in the Northwest because we really like our coffee.

Speaker: As to the different animal models that are used, it is good to have options as far as that's concerned in my opinion. I think that we can learn a lot of things from one animal model that maybe another animal model might not be well suited to.

I think in a perfectly ethical world the closer we can come to approximating what is happening in a human, a nonhuman system would be very

beneficial and educational, but it is not technically possible to do that in a lot of cases so we have instead developed a number of different animal model systems that can fill in the piece of the picture for us. And with a lot of people working in parallel on that, I think together the researchers are filling in a lot of information that can be useful for human medicine, with Usher Syndrome in particular, but in general for a lot of different diseases as well.

Mark: I think that's going to be it for us for today.

The first if you borrowed one of FM's, when you leave the room and go out into the foyer, go to the left and drop off the FM system. And then second thing is stick around in the foyer where we have our reception. There is drinks and a big cookie thing for kids, and kids will be running around out there and an opportunity for a few more informal discussions, so until 5:30 you are welcome to hang out there thank all of our excellent speakers here today and Jennifer thank you for joining us here.

And start making your plans for next year at Boston Harvard Medical



School, my home town and I won't have to travel. I will be more lucid and I look forward to seeing everybody there. So thank you.