

International Symposium on Usher Syndrome July 21, 2018



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(Irmgard Reichstein) Dear ladies and gentlemen, I'm very proud to welcome you here to a very challenging event. Goal of our patient day is a transfer from actual scientific research results from scientists to patients.

We all know how difficult science can be, and we appreciate very much that we can welcome scientists here who will transfer their knowledge using a clear and understandable wording. Conference language is English. And we kindly ask the speakers for today to speak very loud and also slowly.

This is to achieve a good accessibility for all participants. And we offer a lot of interpretation for this. So we offer you simultaneous interpretation into German via headset and conference receiver. And if I look around, everybody is following my words. So is there anybody who cannot follow the conference? Are you all fine? Please give me a short sign, are you all fine and can you hear me? Would you please give me a sign that you can all listen to this conference? You can, you can, you can also?

That's very important for us to lose nobody. And so we also offer American sign language and speech-to-text

IRMGARD REICHSTEIN

interpretation in English on the left screen in front of you, and we offer German sign language and German speech-to-text interpretation on this side of the conference room. All people with these needs have been placed before the conference started, so hopefully the communication situation is clear for everybody. You will also see Lorm interpreters for deaf blind people, and you will see tactile sign language for persons, and also a lot of persons with personal assistants for orientation, but also for communication.

We offer a lot of induction loops, and they have been used by much more people than we knew before hand, but we could cover that. So we are very happy that everybody who needs an induction loop really got one. For the blind people: we missed the guidance lines in this very big hotel. But we have assistants. So if every blind person needs an assistant to go to the toilet or for every need they have, please give us a simple sign with your hand and assistants will come to you and help you in that situation.

Also we will offer a livestream for those of you who want to follow the event on their mobile device. After the conference we will post all talks with subscription in German and English language, and we will provide you and everybody who cannot attend today and is interested in the new scientific results with a protocol of this conference to read this slowly at home. Please forward this information to all of your friends who cannot be here today. We kindly asked the speakers to help us with the protocols. All

IRMGARD REICHSTEIN

speakers will receive the protocol to make comments or corrections. If you have problems during the conference, please use our accessibility desk in the back of this room. We will do our very best to help you and to answer your questions.

Please also make use of the free assistants we have here. We have five free assistants. May I ask them to stand up? Where are my assistants? They are all in the back of the room. Okay. I guess more than 30 % need these kind of accessibility offers we made here. In total this day will cost us about €150,000. And €120,000 of this large amount are needed for accessibility.

I would like to note that here, because I need to thank all the sponsors who made this possible for us and for you and all of us. So you see in the back all the sponsors we have, we needed a lot. And I really want to mention the most important sponsors for accessibility. This has been Aktion Mensch from Germany, the Usher Syndrome Coalition, the AOK Rheinland-Pfalz-Saarland - a health insurance - and the National Institute of Health, NIH. Without that support we would not have been able to offer this kind of accessibility.

I also thank the organization team, I'm part of it, but I really want to thank the University of Mainz which did the complete organization work, which was really a lot. You see we are more than 200 attendees here today, and that's a very big success for this conference. I guess it's the first time that the patient day has been so full. So

IRMGARD REICHSTEIN

thank you very much for coming to this event. And now I wish you a very interesting and pleasant day with hopefully helpful information for you, and I kindly ask you also, you will have the possibility to give us your feedback. We have a film team going around taking pictures, and just if you leave this room on the right side you can give us a feedback. If you would like to do that, we would be very happy, beginning with the lunch break. Okay, so now I will give the word for the scientific part to Mark Dunning, who will introduce the program for you. Have a good day, thank you very much. (applause)

(Mark Dunning) Hi everybody. Wow, look at this crowd, this is awesome! My name is Mark Dunning, I'm the chairman of the Usher Syndrome Coalition, and I'm also the father of a 19-year-old daughter who has Usher syndrome type 1B.

So this is, I am not just one of the speakers, I am also one of you guys, one of the families here. And my job today is to kind of introduce what the purpose is of the meeting here and what we hope to accomplish. I also want to let you know that you will see on your chairs, there are flyers about taking pictures for the Usher Syndrome Society.

MARK DUNNING

We would love to get people's photos. You have probably seen the pictures out in the lobby area. We have a fairly well-known photographer here taking pictures, portraits



of people with Usher syndrome. And you can do that upstairs in room E6. But if you need guidance getting there, we have four people here who will guide you upstairs where you can have your photo taken.

I hope you use that opportunity, you use the breaks or any other time you have to get up there and get your photos taken. So welcome. This is the 10th time, the 10th annual family conference that the Usher Syndrome Coalition has helped to organize. And this is the first time we've done it in Germany. And I can tell you based on this crowd, we'll be back, because this is pretty amazing to see all these people here. I want to thank Irmgard, who is up

MARK DUNNING

here handling the accessibility, Sebastian, who has done a ton of work with organizing the family side of things, and of course Uwe and Kerstin, who organized the whole area here and did a ton of work on this and are running around quite a bit. So I want to thank those guys for everything that they have done. (applause)

I suggest giving each of them a kiss when you see them. So the purpose here today really is to try and build an usher syndrome community. And there is a lot of reasons for needing to do that. We are all here, we are all interested in treatments, I know you are all here to learn about the science. But the truth is that none of us are really concerned about going deaf, excuse me, being deaf and going blind.

09 What we are really concerned about is being socially isolated. And that's the real problem with the disease is that it separates us from the things we want to do and the people we want to be with. And that's what we are trying to overcome with these treatments. So the medical side of it is really important, because it gives us access to this other thing that we really want. So the way for us to get to these treatments is through you guys. You are the source of everything that happens in research. You are the source of the genotypic information that we found.

So we know about the genes, because we know people with Usher syndrome. We know about the phenotype, what happens with the disease, because we know people with Usher syndrome. You guys are the sources of funding

MARK DUNNING

for all the research that has happened, whether you have written a check, or you have run a fundraiser, or you have just simply lobbied your government or lobbied a funding organization. That's where the money comes from. It comes from you guys, whether directly or indirectly. Money is a critical component defining this research, finding treatments.

You guys are also very important though for the next step in moving these treatments forward. You will hear in the science talks today that we are getting pretty close to bringing stuff out of the lab and into the clinic. But that next step is the big step. It's the most expensive step, and it also really requires you guys, because to be able to get something from the lab to the clinic requires us to do clinical trials, that means trying this in humans for the first time. And clinical trials are not a guaranteed thing, in fact, only one in 12 clinical trials results in a treatment in clinic. That doesn't mean that they all fail, it means that a lot of it is trial and error.

So you have to go through a lot of clinical trials to be able to get to the point where you have treatments for the entire community. And to be able to do all those clinical trials you need a lot of people. And that means we need a big community, we need the community to participate to be able to move these things forward. But we have a problem with that. The problem is that we are not in touch with enough people with Usher syndrome. There are hundreds of thousands of people in the world with Usher syndrome, and we are only in touch with a small fraction,

MARK DUNNING

with one or two percent of those people. So we are going to need just about everybody to be able to move these things from the clinic into treatments. So events like this, where we get to meet people and connect with people and hold onto people are incredibly important for us to be able to make it to clinic and get things to the clinic.

You guys are also an important factor in motivating pharmaceutical companies to invest in usher syndrome research. Because pharmaceutical companies want a market. They want a place where they can sell their treatments. And so the more people that we can say we are in touch with, the larger a market we can present to them, the better the chances are that they will continue to invest in the research for Usher syndrome. So the community is important on those levels just to be able to deliver any sort of the treatments we are going to talk about today.

But remember, ultimately what we are trying to cure here is not deafness or blindness, it's social isolation. Well, look around you. This is why we need this community. Okay, you guys literally are the cure. There is no social isolation in this room today. There is 250 people here. And this is really what we want out of the community.

In this room you are not alone. In this room are people who understand you. There are people going through the same thing that you are going through. There are people in this room who share the same fears, who share a lot of the same goals. This is what we want. This is the challen-

MARK DUNNING

ge to social isolation is building this community. So there are treatments coming, and they will be here soon. And in the interim we want the community so that we have each



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other, so that we have this, and we have opportunities to be with people who love us, to be with people who understand us.

There are people in this room who understand me better than my own family, because my aunts and uncles, they love me, but they don't know what it's like to have a child with Usher syndrome. But people in this room do. I have connections to people in this room who I have never met that are deeper with them than with my own family, and so that's what we want to really build out of this. That's the goal of this community is to fight that social isolation. And the best way to do that is to be together and to hang

MARK DUNNING

together on this stuff. So we have the means to find treatments. And you will see that here over the course of the day today, there is a lot of wonderful stuff coming. But in the meantime, we need each other.

And so we don't want this to be just a one-time thing where you guys just come out today and then we lose touch with you. We want to maintain contact, we want you to join the different parts of the organization that help to maintain accessibility between each other, and we don't want to lose touch with you. We don't want to meet you for one time and then not see you again. And I know that that's not the case.

I'm looking over here at my friends from Australia whom I see on a regular basis. I have friends from Austria whom I see on a regular basis now. And so there is lots of people that I've become very close to simply because of going to these conferences. We want to maintain that connection, we want to maintain that community. Okay? So that was all I wanted to say. I also have the great pleasure of introducing one of my heroes, Christina Fasser from Retina International, who is going to come up and talk to you a little bit more. I want to adjust the microphone before you... It's right in front of you.

(Christina Fasser) Thank you very much Mark. I didn't know that I was a hero, so I learned somet-

hing new today. Ladies and gentlemen, dear friends. I feel very honored and privileged to give one of the introductory talks at this usher syndrome conference.

I thank you very much the doctors Kerstin and Uwe Wolfrum for having invited me and the organizing committee to speak to you on behalf of Retina International. Retina International is an umbrella organization of 43 organizations, patient-led organizations that promote research into retinal degenerative diseases such as retinitis pigmentosa, Usher syndrome, macular degeneration and similar conditions, as well. I think that's one of the most important things, to foster mutual support of each other affected by one of these diseases. As Mark said: First we have to live it today. We have a wonderful future to come, but today is the day we have to enjoy. And having retinitis pigmentosa myself - I'm blind in the meantime of it - but one of the biggest supports in my life were my role models with retinitis pigmentosa and all my international friends within Retina International community.

That's one of the biggest pleasures for working for Retina International that you meet friends that you would never have met otherwise. So I met a very long time ago already Sebastian Klaes, an usher person here very important for the organization. Of course also Dr. Reinold Funkischitz-

CHRISTINA FASSER

ki who was one of my peers in the very beginning up to the late age of today. And I think just learning from each other, it's the best thing that life gives you with Usher syndrome or retinitis pigmentosa. Now just coming back to what we are doing at present - what are we concerned about? Retina International's objective is to make sure that every patient with a retinal degenerative disease gets the latest information about ongoing research and information that is validated. To make sure that patients know what is important and what is quack.

When we are affected by a degenerative disease for that at present no cure is available, then a lot of quacks show up, and we see that for instance at present in the stem cell area, where FDA just has issued a very clear warning letter. Stem cell research is an interesting research. It's already done in some human clinical trials which show first very positive results. However, these are very first results. Every stem cell treatment offered economically, you have to pay for it, is trash and might be even very dangerous for you. And I think these are the kind of messages we have to give. On the other hand Retina International and its member organizations represent more than 1.6 million people affected by retinal degenerative diseases. And that's a huge amount. Compared once again to the overall estimation of people with retinal degenerative diseases it's about 10%. But 10% is a big number which can change the world. And how can we do that?

The first gene therapy has been approved last December in the United States by FDA, and very luckily it has also

CHRISTINA FASSER

been very quickly reimbursed by the health insurance. We do hope that in Europe EMA will issue a positive opinion within the next weeks or days - we don't know really - and hopefully will register it by the end of the year. And then we will meet the cultural differences. Europe is divided into 26 countries. And within the EU the authority to decide what is reimbursed or not reimbursed stays with the member countries. That means discussions have to be done in 26 countries to get it reimbursed.

To do this, we will need a lot of lobby. And we will need the patients and also you with Usher syndrome to go out, because the Usher syndrome at the moment we have three clinical trials ongoing, among them also gene therapy trial. If they should be successful, then it's also your concern whether it's reimbursed or not. Therefore it's so important that we all tell the insurers why it is so important that the treatment or a gene therapy is paid for for the patients and that we do have access. Access to therapy is a human right. All European countries and a lot of other countries have signed the United Nations' declaration for the right for people with disabilities. In article 5 of this declaration it is stated that each person with a disability has the right to access treatments that lower the burden of our disease. And that means we don't need cure, hundred percent vision.

I think it would be wonderful if we got treatment that is slowing down the progression of the disease or preservation of the disease. And for this Retina International has also taken up the cultural differences between Europe

CHRISTINA FASSER

and other outside US countries and FDA. In our countries the health payers are asking what the extra value for the patient is. What is really important for us. And there we



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need the help of all of you. I am a person that has lost vision completely. And I do know how helpful it was when I only had night perception and could direct me myself toward a window or follow something, or even when I had a very small visual field that allowed me to read print.

For health payers sometimes this is no difference. So we patients, we are the experts, and you with Usher syndrome, you are the experts, too, to tell the payers what is important to you, how good it is to see a little bit better at nighttime. How good it is to have even a small visual field preserved, and how it helps you for social integration and to stay in the labor market. Economists always want fi-

CHRISTINA FASSER

gures. And of course staying in the working place means we are there, integrated in our social lives. Please stand up. We as patients, we are taxpayers, we have the right to complete inclusion into society, and we just have to call for it. We don't beg for it. And on the other hand, take your most important strengths. You as a patient, you as a parent, you as a sister or a brother or an uncle or nephew of a person affected by Usher syndrome, you know what it means to live with Usher syndrome.

Go out and tell the people that it is not a lost case, that we have lives that are worth to live, to live from day to day and that we all are part of the society. We are ready to give our part, and we wish and we ask for our integration. And just start to be the expert today. Learn from each other, and also share just laughter and fun, because that's also important in life. I wish you a wonderful conference, a lot of new persons to meet and perhaps some new friendships for a lifetime. Good luck to all of you.

(applause)

(Mark Dunning) Thank you Christina, that was wonderful as always. I also wanted to introduce Dominique Sturz, who is a mother of a child with Usher syndrome and also had a big hand in hel-

DOMINIQUE STURZ

ping to organize this event. Dominique?

(Dominique Sturz) Thank you Mark, thank you for the kind introducing words. So welcome to you all, and a warm welcome from my side. Today one of my most important dreams of my life has come true.

We all have many dreams in our lives, but this is really one of my most important ones today. So this is a unique event which I have been working for to have this connection of Europe and the US international Usher syndrome community today here. It means a lot to me personally as a mother of a young adult daughter with Usher syndrome subtype 1B, and also as a patient advocate for Usher syndrome and rare diseases coming from a small country, where there has been no expertise for a long time on Usher syndrome at all.

So next to my dreams. Dream number one, and maybe many of you share this dream with me - dream number one as a mother of a young adult woman born deaf in 1996 and implanted bilaterally very early with cochlear

DOMINIQUE STURZ

implants. One of my most important dreams and also a dream of my husband has always been that one day she might be able to be as everybody is, to be not as everybody is, but to be able to lead a happy and fulfilling life like everybody else. So I'm sure many of you share this dream, all the parents who are here in the room. And now I can say, today I can say that this dream - despite the additional diagnosis of RP she is a happy young woman with friends, who completed her school career, she is a law student, has a boyfriend, and she has turned out to be a genuinely good young woman.

So dream number one in my life has come true. But there is also another dream that has come true today. Dream number two. Dream number two in my life has been that one day we would have some Usher expertise in our country, in Austria, which is a small country, and it is difficult to have expertise on rare diseases there. So and I've learned, my family has learned so much from organizations abroad, when my daughter got diagnosed with RP in 2005. And first of all we didn't know where to turn. So we have learned so much, first of all through Pro Retina Germany, through Retina international. Then I met Stefan Suchert who connected me to the Usher Syndrome Coalition and to Mark Dunning.

Then I met Sebastian Klaes and the team of „Leben mit Usher-Syndrom“ in Germany. And what I wanted was to give some of the knowledge and the expertise back to people in my country, in Austria.

DOMINIQUE STURZ

And today we have some Usher expertise and some medical university centers in Austria, so that patients who get diagnosed and their families get a more adequate and



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professional consultancy and management of the disease. Much better than it was in 2005 when our daughter was diagnosed. And we also have an organization for families and for individuals diagnosed with Usher syndrome, where they get support and where they can give each other mutual support and exchange their experiences. So this was dream number two.

There is also dream number three. And this is the most important one for today. Having connected Europe and the US, and having here patients, families, experts, scientists, researchers from all over the world in one room - and I'm really impressed to see the room full of people, I

DOMINIQUE STURZ

mean it's a huge room and it's really full - has been also one of my most important dreams. So why is it so important to have the international community connected? The part of that has already been said by Mark and by Christina. I know exactly, my family, my husband, I know we feel, we know how you feel when you have a diagnosis. It's so important to have the feeling not to be alone, to know where to turn, to know to which organization to go, where you get your support, and also to know where the experts are.

And it is also very important, gives you hope and much motivation and strength to be there for your children if you know that there are hundreds of researchers, scientists, clinicians, patients and patient organizations, all fighting for the same cause, and fighting to find solutions, to find treatment, maybe not cure, but at least the treatment and maybe a cure one day.

So to have the feeling you are not the only one, and also to have the feeling that you get support, and also to have the feeling that you don't miss anything. Because you are connected to the community, you know what's going on on national and international level, and you know what to do if maybe a therapy comes up, you exactly know where to turn, if you want to get it. So this is a really very important day to me today to see you here.

And I hope you all have inspiring talks, you get interesting insights in scientific, medical, psychosocial and other aspects. I'm very happy to see many familiar and also new

faces here, and I'm really looking forward to catching up with you also during the breaks. So I wish you an inspiring conference. (applause)

(Mark Dunning) Thank you Dominique. So we have one more speaker for just a brief period here, before we get to the science.

I promise there will be more than enough science for you today. So I would also like to introduce Rebecca Alexander from the US. You may know Rebecca, she has written a book called „Not fade away“ about her experience with Usher syndrome, and it's actually available out in the lobby. And so, Rebecca? (applause)

(Rebecca Alexander) Okay, good morning everyone, thank you so much for having me. So it's so wonderful to hear parents share their experiences and talk about all the work that they have done for Usher syndrome.

REBECCA ALEXANDER

Particularly as a woman living with Usher syndrome, I'm 39 now. I was diagnosed with retinitis pigmentosa at 12, and at 19 I was diagnosed with Usher syndrome. At 19 when I was diagnosed with Usher syndrome they said yes, Rebecca, you have Usher syndrome, but we have never seen it as it presents itself in you. And fortunately, because of the research that is being done and all of us in the community, we were able to connect with researchers in Finland, in Helsinki Finland. And it was with my family's blood work and with these researchers and of the population in Finland that to the identification of Usher syndrome 3A became possible. So we now know of 88 people in the registry who have the type of Usher syndrome that I have.

24 This is part of what Mark so eloquently spoke about in terms of the importance of having people registered. If you know people, particularly in the community who have not been genotyped just yet, that is probably the biggest thing we can do in terms of research. More importantly, living with Usher syndrome requires you to be vulnerable. Being alive requires you to be vulnerable. So I encourage all of you living with Usher syndrome, one of the most difficult things that I found for me in my own experience of progressively losing both my vision and my hearing was asking others for help.

And what I've learned is that the more I've been able to ask people for help, the less isolated I felt, the more included I have become in my community, and the more of a sense of community I have created, not just with people

REBECCA ALEXANDER

within the Usher syndrome community, but with the sight-
ed and hearing as well.

And lastly I'll say that when you ask someone to help,
when you tell them that you need help, when you own
what you have, that is vision and hearing loss, you are
able to create a sense of empowerment within yourself,
and you empower others to want to help you. There is
nothing we want more in this world than to know that we
matter. And when you ask others for help, you let them
know that they matter. Have a wonderful day everyone,
and I would love to meet as many of you as I can while I'm
here in Germany. ^(applause)

**(Irmgard Reichstein) Okay, we
lost a little bit of time, but now
we will start to summarize the
scientific conference from yester-
day.**

And I will find only very few words for that. We have the
organizers involved in that summary. So we will hear
three summaries from Dr. Margaret Kenna, she will start,
and also from Gwen Geleoc, both are from the Children's
Hospital Harvard Medical School, and also from Prof. Uwe
Wolfrum who is from the University of Mainz, and I guess
all of you know him very well.

MARGARET KENNA

I will make this very short not to lose time, but I will mention you will have the possibility to ask one or two questions afterwards, due to time we cannot allow more. Please be so kind and prepare really clear questions which are of general interest. If you have questions more or less related to your personal situation, we kindly ask you to use the lunch time, the breakfast and all the breaks we will have during the day. Thank you very much, and here is the first scientific talk. (applause)

(Margaret Kenna) Is this on? Can you hear me? Thank you. My name is Margaret Kenna, I am a pediatric ear, nose and throat doctor in Boston.

And I get to do this, and I'm really privileged to be here, because we diagnose babies with hearing loss at birth. And so because of that I've learned a lot about the causes of hearing loss in young children, and this is certainly one of them.

But before I get going I want to thank the planning committee. Gwen and I are the US version, but really it's the people here in Germany that did all the work as everybody has said, and we really appreciate it. I also want to thank the interpreters.

MARGARET KENNA

When we did this in Boston, we were still looking for interpreters an hour before the conference started, and I know how much work this is, all the different types of



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interpretation and translation and access. I know this is a lot of work, and I've been watching interpreters and reading written text, and it's, they are really good! So anyway, thank you very much for that. (applause)

And finally, and of course without the patients and the families there would be no reason for us to be here. I've been to many of the other family conferences. We are going to need a bigger room the next time we do that, so it's all good. So I'm going to just summarize very briefly some of the information that was presented in the first day about the diagnostic part of Usher syndrome. And obviously as many of the previous speakers just said, without the

MARGARET KENNA

diagnosis you wouldn't all know each other. And when we come to clinical trials or treatments, you won't know that you are eligible. So there is a whole bunch of reasons to do this.

Many of the speakers on the first day, including Dr. Kimberling who was part of the team that discovered the very first Usher gene, Myosin 7A - and I'm assuming he is in here someplace - and then many of the other people that are listed here talked about different aspects in the genetics of Usher syndrome. Many other people talked about treatments or the way the different genes work together. So the truth is, this is really from everybody in the last two days.

So, Bill Kimberling, as I just mentioned, really came up years ago with seven steps to treatment for an inherited disease. And when he did this, we weren't very far down this pathway. And it was really starting with finding and the genes that cause a particular disease. We are very far down that path now with Usher syndrome. There are other genes that we don't know about, and the way the genes work we are not completely sure about, but I think one of the things that is really key and that Rebecca just alluded to is: get your genotype done if you can.

Figure out what the gene is. Make sure you actually have, if that's the case, Usher syndrome. There are a lot of other things that cause hearing loss and vision impairment, and so having a correct diagnosis, what ever the diagnosis is, really matters. Everybody knows there are at least

MARGARET KENNA

three types of Usher syndrome, but as Rebecca alluded to, some of the presentations are rather atypical for what we know from this little box up here.

So it's entirely possible to have Usher syndrome type I and look like you have type II or have type II and have type I, or have Usher syndrome III and look like type I. So there is a lot to be learned based on the genotype. And there also is a wide variation in the way patients present. So this is the reason we get testing. These are the known genes, but almost certainly there are other genes that are also an underlying reason to have Usher syndrome or genes that interact with these genes.

And depending on how you play with the genes or what you do to the genes really may result in the clinical changes that we are all talking about and hoping for. So here is the other reason we need genetic testing. These are two of my patients. The one on the left, GJB2, that is Connexin 26, this child presented as deaf. The patient on the right, MYO7A, USH1B presented as deaf - same hearing test. And looking at a baby, when they present they look exactly the same. For us to figure out what to do with them, we have to do genetic testing.

This is a patient with MYO7A USH1B. This patient has a profound hearing loss this is a patient with USH1B, MYO7A, this patient does not have a profound hearing loss, at least not at the beginning. And so both of these patients have mutations in the same gene, but they didn't have the same mutations, and their clinical presentation

MARGARET KENNA

wasn't the same. And actually the second patient here, this patient walked on time, her balance is pretty good, she wore hearing aids for years, and then her hearing loss progressed, and now she has cochlear implants. So same gene, different mutations, very important to figure this out. Bill Kimberling talked a lot about the history of genetic testing, and there are probably people in this room without research testing. And if they only have one gene and they are not entirely sure, all these other things now that are available, common mutation testing came next, followed by single genes, followed by deafness panels, where we have 120 or 30 or 60 genes, vision panels that are similar. What we probably need is a combined vision and hearing loss panel, so we are not missing anybody.

And then now we are talking a lot about testing whole exomes, that is the protein part of the DNA, and then whole DNA testing. So things are progressing really rapidly, but each step has the good news and the other news. And it's the other news that we have to be careful about. So why knowing? Why does this matter? And when you call the insurance company in the United States, they say exactly what our first speaker said: why do you have to do this, how is it going to change, why should we pay for it? Well, to get a diagnosis helps a lot. And then once there are interventions that will also help.

We also want to know how the genes interact, how they affect both hearing and vision and balance and things that we are not really looking at very hard, but we should be. And some genes only affect the hearing or the vision,

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not both. Or some mutations in the same gene. And if you change this gene over here, it's like those little toys you push this box and the other boxes move, like what happens over here. So anything that we do to intervene we have to make sure it doesn't make things worse. Other genes we don't know about, Almost certainly there are genes we don't know about.

And so for example USH2A, which is a really big gene and one of the common causes of Usher syndrome. There are a lot of different versions of USH2A. Which ones do you treat? Which ones do you worry about? How do they look clinically? So, and finally, do you actually have USH? And I know that sounds kind of silly, but there are people who do have vision impairment and hearing loss, but they don't have the clinical diagnosis of Usher. And that would guide them down a different pathway.

And this really gets to talking about what we consider Usher syndrome. It's a particular type of vision impairment, a particular type of hearing loss, and there may be other things. So what else can we learn from other people about when they study cilia, which are the little cells, the little hairs - they are not really hairs - but maybe there are other genes that have to do with cilia, microtubules. We actually heard from two other really excellent speakers in the last two days - Matt Tyska from Nashville who talked about the gut. Well, how does that affect the ears or the vision? But the system in the gut that he is looking at is very reminiscent of what's going on with Usher syndrome.

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So maybe there is something that we can learn from that. And then Fred Schwaller from Berlin talked about the skin. And once again, lots of similarities. So there are other organ systems that we can learn from, and maybe they are even involved in Usher syndrome. So the other thing is better genetic testing. Anne-Françoise Roux talked about finding the second mutation or even the third mutation and how that affects the diagnosis and then the interventions.

Are the mutations in places in the DNA that we haven't looked? Like in the introns, which is part of how the DNA gets transcribed, or in the splicing which turns out different types of genes, so different versions of the gene. Is it really dominant or is it recessive? So are there to possible causes for the hearing loss or the vision impairment? That happens. I know that sounds rare, but it's not that rare once you begin to look.

And then, of course, most important and as everybody before me mentioned, we need registries, we need to be able to find the patients and families so that we can do better networking, - although we are doing a pretty good job of that - and then better treatment as things come down the road. How will knowing the genes really help? Well, where are the genes expressed they don't all start out at the beginning. What type in mutation is present? What kind of intervention is it going to be making the genes bigger, better, smaller, different, replacing them, are there going to be medications?

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Yesterday there was a very eloquent speaker on using something called Baclofen, which is something we use for tight muscles. And maybe it will help with vision and hearing. So I think we don't know, but without knowing the genes, and when the genes express themselves we won't know what to do. And then when to treat? So say you assume you know the gene, and we know that when the genes are expressed at different times. So when do you do something about it? When do you do something about the hearing loss? When do you do something about the vision impairment? And if it turns out there are GI symptoms, when to do something about that? And we can test prenatally now for genes.

I have patients or parents coming to me, and their baby is not born yet, and they know the baby is going to have something that affects their hearing or their vision. And they want to know what that's going to turn out like. And is there something they can do before the baby is born? So these are tricky questions, they are ethically tricky questions, and yet they are very exciting questions. And it's sort of what all of these people, the families and the patients and the science folks together, are going to figure out. So anyway, thank you very much. (applause)

(Irmgard Reichstein) Thank you very much, Dr. Kenna. We just decided to bundle the questions.

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So please write your questions, note them down, and at the end of the three talks you will have time to ask questions, and we know then how much time we have for that to be on time. So the next speaker is Dr. Uwe Wolfrum from the University of Mainz, and you will hear now the second summary from the scientific program.

(Dr. Uwe Wolfrum) Thank you very much for the introduction. I'd like to welcome you here in Mainz, and we are hosting now the scientists first, we have hosted them for two days, and now you as patients come and join and can get the discussion going on on Usher syndrome with other goals.

I would like to summarize a little bit what we have heard about the cell and molecular biology of Usher syndrome. When we look at the Usher syndrome, we have 10 different genes, and I guess it was introduced to you now from Margaret, and we have 10 different Usher genes, and they are all expressed in these two cell types, hair cells and photoreceptor cells.

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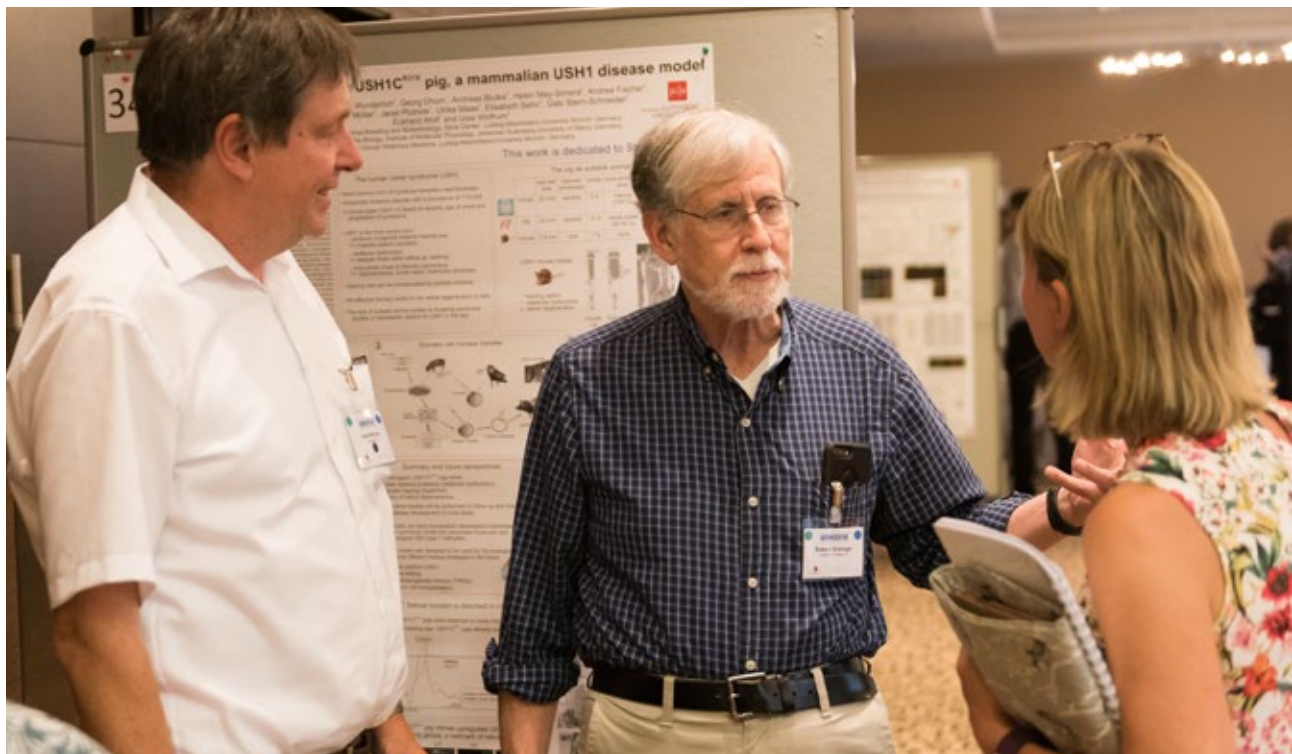
Therefore, when we have to keep the touch to the cellular mechanisms, we have to look at these cells, maybe to other cells, maybe also to intestine cells sitting in the gut, and maybe also to the skin. And we would like to understand how these molecules are functioning. And I think it's very important to stress that we have to decipher the molecular and cellular function of the disease, of the Usher disease, the disease molecules related to the Usher syndrome, to develop an effective therapy. This is all about what we do. The goal is the therapy for you, but we have to understand the molecules to get an effective therapy developed.

The first thing we and others show is that all these different Usher genes are interconnected in the cell and they are functioning together. Like we are functioning as a society, they are functioning together in the photoreceptor cells or in the hair cells. Let me go to the hair cell system. The hair cells are sitting in the inner ear, all of you know that. And here we have an image where the hair cells are sitting. These are the hair cells in the cochlea. And when we look from above on this cochlea, we see that there are some hair bundles of these cells. The name is coming from these hair bundles. And they are important, these hair bundles, we call them also stereocilia or stereovilli, because they have a cytoskeleton, ecto-cytoskeleton inside. Okay, okay. You may hear me now better? Okay.

But it's important to understand that these hairs are important for the stimuli of these cells. A stimulus is a bending of these hairs. And then there is a depolarization

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of these neurons occurring, and then hearing can occur. Still problems? Okay. We and others, and there was also a big contribution from the French research team around



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Christine Petit, to figure out where these molecules are sitting in the hair cells which are affected by the disease. And the localization of these Usher molecules is shown here in this cartoon. There are different molecules sitting at the base of these hairs during the development. The so-called anchor links, they form some fibers linking these little hairs, these stereocilia. And in addition, these are the molecules related to Usher type II sitting at the base and forming anchor links.

On the other hand you see up here that during the development also some other molecules which are related to Usher type I, they are present at some membrane links

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between the stereocilia and the tips of the stereocilia and forming also some connections between these stereocilia. And this is during development. And when we have defects in Usher molecules as a developmental effect leading to deafness from birth or during the early years of life. When we look now to the mature or the adult cell, then these molecules related to Usher syndrome have a different function. One function is to get an interconnection the so-called tip-link structure. And this is important for the signal transduction, because this tip-link is related to the mechanosensitive channel. And this channel has to be open to get a depolarized cell. And this tip-link is the important structure leading to the depolarization of the hair cells and hearing.

Now we have two different problems, when we have defective hair cells our molecules related to Usher syndrome. We have a problem during differentiation.

We see that these hair bundles in wild type, in the normal mouse cochlea, for instance, are well structured and really nicely orientated. On the other hand this is a MYO7A Usher2B deficient hair bundle. And you see that this is not really organized. These contacts between the stereocilia are not functioning. Then we have a defect in usher molecules. But in addition also defects occur in the mature hair cell, because we have not this system of the tip-link formed.

We heard yesterday also that it's also important to have molecules related to the Usher syndrome at the synapses

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of the hair cells. Aziz was presenting data, very new data, that Clarin-1 is necessary for the contact to the neurons, which are projecting towards the brain for hearing. And also this we have to take into consideration.

Now it was already mentioned today that these molecules related to Usher syndrome are not only present in our ear and the eye, but they are expressed all over the body. And you see for instance some molecules also present in the gut. And the two guys here, Matt and Mingjie, they are studying these molecules and the proteins forming network complexes in these different organs, predominantly here the brush border and microvilli of these cells in the gut.

And they see that there are parallels between the stereocilia tip-link complexes which I introduced to you, at the tip of the stereocilia, and the molecules sitting in the intestine cells. And if they are defective, then we have also problems when this complex is not effectively working.

We have the problem which we can see here, we have not any longer the number of the extensions of these intestinal cells present, these microvilli, and we have these mice are suffering. There is a defect in this intra-microvillar adhesion complex in the intestine. They are smaller, and there is a decrease in growth, probably due to the nutritional deficiency of these mice. And we may observe this also in patients of Usher syndrome that there is a problem with the nutritional deficiency.

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Okay, now let me go to the eye. This is also a very very important part of my presentation here, that we have to see where these molecules are found and what problems they may cause in the eye. And we see here the retina and the photoreceptor cells, cones and rods are sitting here in the retina, and they are connected as the hair cells to other neurons. And we found out that the photoreceptor cells are containing the Usher molecules. These symbols are indicating where in the photoreceptor cell we find the Usher syndrome molecules. We have here the outer segment, where the visual transduction cascade is localized, and we have here a little link a so-called connecting cilium, and you see here that they are associated at this base of the outer segment, the molecules related to the Usher syndrome.

And we have the inner segment, and there the inner segment of the photoreceptor cells, it harbors the molecules for biosynthesis of molecules necessary for the signal transduction, for instance, the visual pigment. And we have a synapse, a contact to the other neurons. You see that there is a distribution all over the cell more or less, of the Usher molecules, but we have here a localization present at the base of the cilium.

And this we have studied, and Jun Yang was presenting new data on this. And there we see, for instance, the Usher II molecules are sitting right at this place here at the connecting cilium, and they are forming some connections like the hair cells between membranes, right here in this little pocket. And these are molecules related to the

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Usher type II. Based on other findings we think that this is the function of this complex is related to the transport of the molecules.



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For instance, we have to transport, as I mentioned, opsin from the place where it is synthesized in the inner segment to the outer segment, and this is the pathway here shown through the inner segment first and then through this little tiny bottleneck, the kinocilium, and to the outer segment. And there the molecules have to function, and we can detect some light with the visual signal transduction cascade. And if this transport is defective, we may have also a defective visual system. And right here at the linkage between the inner segment and the outer segment, we find the Usher molecules related to Usher type II.

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But we learned also that we are not mice, when we started the Usher I molecules, because we didn't see any degeneration in these mice, or only mild degenerations which were not representing the disease. And therefore we also ask - and when I say we, the scientific community ask - what is the difference between the mouse and the human. And when we look at the photoreceptor cells, we see prominent differences. They are a little bit larger, our cells, but we have the so-called calyceal processes.

And right there in these calyceal processes, these are extensions and projections of the inner segment. Right in these calyceal processes we find the Usher I molecules, but also some Usher II molecules were observed. And right here we have big differences between the two cell types. This inspired Aziz, for instance, Aziz El Amraoui, to test the hypothesis that these calyceal processes are important for the photoreceptor function.

Therefore he tested this in an animal model. And the animal model was the frog, *Xenopus*. You see here some data, this is a photoreceptor cell, and these are the tiny extensions. There is Protocadherin-15, Usher 1F sitting in there indicated. And when you look at the deficient frog photoreceptor cells, these are absent. Without Protocadherin-15 we don't have calyceal processes. And if we look also a little bit more closer at these photoreceptor cells, they are bent. The outer segment is bent. These calyceal processes may support mechanically the outer segment. And right here you see that this, there is another phenotype. The outer segment discs are over growing and are

really not in the correct shape like in the normal condition. And these calyceal processes, they have also an actin filament sitting in there.

Again a parallel, which is the molecular parallel to the hair cell stereocilia. We also are looking for other models to see whether we can do some research on these issues. And we thought on a larger animal model. And the pig. And you see here a pig photoreceptor cell, and you see also these calyceal processes. And right now we are in the progress of generating an Usher pig. This is a consortium from Munich together with Mainz, and we are teaming up to get an USH1C pig model, which will be good.

We decided and have generated it, and now we are trying to get the animals around to go for gene therapy, read-through therapies, we will hear about therapeutic options later today. In the next slide I like to introduce again another strategy, which is in our lab that we look for interacting partners. We have Usher network working, I introduced this in the hair cells, but we found out that other molecules may also interact.

And when we identify these, when we have identified your friend - tell me who your friends are, and I will tell you who you are - and then we can really see what kind of function these molecules have in the cell. This is an important thing. And we go for proteomics. We found out that there are several other relations between these molecules related to the Usher syndrome. We have endocytosis or gene regulation, also related to this and with this

slide. And we will have to do a lot to figure out how these molecules are participating in these cellular functions. And with this slide I would like to thank you for your attention, and you are very welcome to address questions to me also during the entire meeting. And I would like to dedicate this presentation to two families, the Suchert family and Steffen Suchert, and the Thomas Welp family, and with this I'd like to thank you. (applause)

(Irmgard Reichstein) Thank you very much for this clear information. Thank you also for speaking slowly, that was very helpful for all the interpreters here.

So I welcome now Gwen Geleoc. She will say us something about the new therapeutical possibilities we have, and I guess this is also a very interesting issue for all of you.

(Gwenaëlle Géléoc) It is my pleasure today to give you a summary of the different presentations we had during the scientific symposium related to new therapies and the work that is being pursu-

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ed right now to develop new therapies for retinal degeneration and Usher syndrome.

So in my lab I actually also study Usher syndrome, but at a basic level. And understanding the role of the different Usher proteins, and also looking at how we can use novel technologies to recover hearing or protect the ear from degenerating and eventually collaborate with the labs that are focused on the eye. So today is a very exciting day for me, because we held this conference in Boston where I am from, working at Boston Children's Hospital in Boston. We held this conference four years ago. And there were maybe a handful of clinical trials that were on the way.

But today, four years later, the science has progressed so much that we have about 40 clinical trials going on. Not all for Usher syndrome, but all for retinal degeneration. And some more focused on Usher syndrome genes more precisely. And this is really exciting. But the other aspect which I want to touch upon is that there actually is the first clinical trial which started in 2006, was approved in the United States, the drug was approved in the United States in December 2017.

So when you think about Usher syndrome, and I don't have to reintroduce the basic of Usher syndrome, since Uwe did such a wonderful job, but as you understand the-

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re are at the moment at least we think of 10 genes which are associated with Usher syndrome. And many many mutations that affect the expression from the gene to the



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protein. So if the gene is disrupted, you may not get any protein expressed, or you may get a shortened protein, so a very short protein which will not be functional. And what we have learned through the years is that these Usher proteins form what we call an interactome, they interact with each other.

You can imagine a tree of Usher proteins that are assembled and play a role, structurally and functionally. If you take one of these proteins out, that tree falls apart. The sensory cells of the ear will eventually degenerate. The photoreceptor cells of the eye will eventually degenerate. This is what's going to lead to deafness and blindness. So

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where can we interfere with this mutation? How can we go beyond that and restore functions? So there are lots of different approaches, many of them which are associated with - okay, a little bit more slowly.

I'm sorry, I tend to speak fast. And I am French, but I speak fast in French and in English. So we can think about what we call gene augmentation therapy or gene replacement therapy, in which case we basically add more copies of the normal gene. There is current work going on looking at gene editing, so using small molecules or different novel proteins that have been discovered recently to correct this gene. We have potential correction of translation, and I'll talk a little bit about that, which basically allow for correct reading of this gene sequence.

Right? Like you are reading a book, and instead of reading the word with a spelling mistake in the middle, you are actually going to correct that. Or there is a slow progress looking at molecules and using pharmacology mostly to limit the degeneration of the sensory cells. So during the scientific meeting we had a lot of different talks: on gene augmentation therapy by Alberto Auricchio, Gene editing by Carla Fuster Garcia.

Some of those were invited speakers, and others were selected from the abstracts they submitted. We had work presented on antisense and translational read-through therapy - I'm going to touch upon that - and also looking at small molecules and pharmacology with Yoshikazu Imanishi and Alaa Koleilat, and also potentially using

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stem cells, mostly at this moment to understand the disease. That is a part of all these different put-ins, but also to derive stem cell organoids, so basically reproduce the retina or the ear in a dish from patient-derived stem cells.

So from your cells we can learn a lot. We can put these stem cells and force them to become a mini-eye or mini-ear. It's not quite like your ear, but it's a system that we can use to tease apart those different molecules. And it's extremely useful, and we've learned a lot from it. So I want to start with this amazing story of this clinical trial which is not for Usher syndrome, it's for LCA. It was started in 2006, and it took about 10 years for them - Jean Bennett was one of the main investigators who was involved - to go from lab results and the beginning of a clinical trial to a drug that was just approved.

47 So that was approved on December 19th, the drug is called Luxturna, and it is, basically what it does is gene augmentation therapy. So it allows to give back the normal copy of the gene for patients who are affected by Leber's congenital amaurosis or LCA, which does lead to retinitis pigmentosa, which is also something that we see in Usher syndrome. And I'm not sure if this is going to work. I'm going to try to play this. We have the sound, right? Let's see if it will work.

(Video) LCA stands for Leber's congenital amaurosis. It's a rare form of retinitis pigmentosa...

(Gwen Geleoc) Ah, it's not showing. Do you know how it

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can show?

(Video) Usually the babies are significantly impaired, and it's devastating, because not only is their vision terrible at birth, but it gets progressively worse with age, as the cells in the retina die off. A dog born blind with these very same conditions. So the puppies that were born blind cannot see their way around the room. (Video is stops)

(Gwenaëlle Géléoc) The video is not showing, we're going to try to... It's not... Yes, okay! Should I start from the beginning? It's only a minute and a half.

(Video) LCA stands for Leber's congenital amaurosis. It's a rare form of retinitis pigmentosa, which is a progressive blinding disease. Usually the babies are significantly impaired, and it's devastating, because not only is their vision terrible at birth, but it gets progressively worse with age, as the cells in the retina die off. A dog born blind with these very same conditions. So the puppies that were born blind could not see their way around the room, and we tested the possibility of restoring vision for the puppies by delivering the normal copy of the gene which is defective. That's called RPE65. And lo and behold, these dogs began to see, and so those results led us to propose to test this same approach for treating blindness in young children.

For these individual patients it's so gratifying to see what they now can do that they could not do before. There are two things that are really going to be important from this.

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One that we will move forward with this particular disease and get approval for the drug that we've been developing. The other outcome that I think is really important is



that this could be a steppingstone for developing a treatment for other blinding diseases. (end of video)

(Gwenaëlle Géléoc) Let's see if I can go back to my presentation. (sound of another video)

Oops, sorry! (sound of another video) Sorry! Sorry about that! Technical difficulties. Thank you. Okay, That's all right. Sorry about the technical difficulties. Now I went too fast. Okay, so I have about 10 minutes to go through the scientific presentations we had, and I apologize to the speakers who are here, I may have to go quickly through your slides. But one story that we heard during this meeting is

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actually a very important progress that we've made in the labs, because one of the issues with some of the Usher genes that we've been looking at is that they are too big to fit into the tools that we currently have.

So we have to design alternative strategies to package basically these genes to re-express the correct proteins. And so one option that we have now and that's really becoming, it's working quite well, is basically really chopping the gene into little pieces that we can package into our little vacuoles, and then provide them to either the eye or the ear. And so it's basically chopping in this case, this is an example of chopping the gene into two pieces, and having little pieces overlap, and then we can get re-constitution of the gene and expression of the protein in the cells.

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And so this work was presented by Alberto Auricchio from Naples, Italy. And he validated the use of this dual, we call it that dual adeno-associated viral vectors. It's a virus which is innocuous, so it would not make you sick, it serves really as a vacuole to bring that gene inside the cell. And in this case Alberto was targeting the USH1B gene, which encodes for MYO7A. And so he showed that he could get the gene into the retina of pigs and get the gene expressed. And he also showed that he could get recovery of the morphological feature of the retina.

So while the mutant mice, for example, here that he was using which I call shaker mice, it's a model again for USH1B, while he was seeing mislocalization of structures

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called melanosomes, he was seeing accumulation of rhodopsin. But when he treated with this dual vector, he saw recovery of that morphology. So it's very encouraging, and we think that is going to be, you know, really changing the way we think about treatment. We'd end up often being the most affected, because there are a lot of more places where those mutations can occur.

That's the case for example for USH1B, that's the case for USH2A, and USH2B as well. So, yes so that's just the recovery of the morphology. And the goal is really now to go to clinical trial, so Auricchio told us a little bit about the work he is doing, developing a clinical trial using a dual AAV viral vector to target this MYO7A mutation. And they are working together with the Foundation Telethon and have a lot of participants which are involved in the development of this clinical trial. So that's one story.

The next story I'm going to talk about briefly is work done by Jennifer Lentz. She's from Louisiana, and she's been seeing and working with patients who all are affected by a specific mutation in the USH1C gene. And these are patients, they actually are French-Acadian patients from Louisiana. And what this mutation in the gene leads to is the expression of a very short truncated protein.

So instead of the very long protein which is called harmonin, in this case she sees a very short protein which is not functional and in this case leads to retinal degeneration and hearing loss as well. So what she designed here is to bypass this error that she sees in the gene, is to use so-

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mething called antisense oligonucleotide. And again this is to skip that mistake in the reading frame of that gene, and it actually is very potent, it works very well.

And she demonstrated a few years ago, that by injecting this viral vector into mice that she designed to have that exact same mutation that the patients had, she can recover vestibular. So the mice have a normal vestibular behavior, they recover hearing, and they also recover vision. So I actually worked together with her at the different ways to apply this drug in a systematically or locally transmembrane application on a transmembrane or through the round window. And she is now working on the vision using local intravitreal injections. I'll just show you this quick video, I hope this time it will work well. So what we are looking at, it's very interesting, and I know a lot of you suffer from these vestibular balance disorders, and in the mice it's pretty pronounced.

So when a mouse has the mutation in Usher 1 gene, it's typically associated with a very typical behavior of repetitive rotative movements, very active rotative movements. You'll see that here. So here in this case on top we have two controlled mice. One that was injected with inoffensive drugs, and this one was injected with control drugs. And then this one was injected with the antisense oligonucleotide, we call it ASO29, and then a mutant, so this is the one I'm really going to be looking at. A mutant that's not treated, and a mutant that's treated.

And now you can look at their behavior. So you see the

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mutant mice are really spinning, you know they rotate like that all the time. And in fact they actually are typically a lot leaner because of that, they are very active. But you can see that this mouse that was treated here really behaves like the normal mice. They are rotating, they are moving around the chamber, but they are not doing this repetitive motion behavior.

And so any of the treatments that we've done, local or systemic, really led to this recovery so it's pretty pronounced. We also saw recovery of hearing and recovery of visual function. I won't have time to really go through this data. But it's very encouraging. Okay, so I'm going to have to go a bit more quickly, so this is - no I mean, not quickly but just skip some slides, that's what I mean. Not to speak faster. Don't worry. I just won't tell all the stories that I have, but I will try to skip and to keep it slow. Erwin from the Netherlands is looking at again the same kind of approach using antisense oligonucleotide, and this is here for Usher syndrome 2A. And he has validated his approach in zebrafish and also patient-derived photoreceptor progenitors.

They are actually starting a clinical trial with a company called ProQR, and they started a clinical trial to target LCA. In the process of starting a clinical trial targeting mutation in USH2A. This one should be starting by the end of this year. So it's very very encouraging. Kerstin used a drug, I call it TRIDS, they target in-frame nonsense mutations so this is a typical aminoglycoside, which in this case do not induce hearing loss, but also can allow

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correct reading frame. So this is also a drug that's been very promising and importantly again that she validated in patient-derived fibroblasts.

You guys are really part of this science, you are part of this progress. And the patient cells that we can get to work on in the lab can really bring us, you know, many steps further. That was really evident throughout our talks, so for anybody who has doubts, this is really important for the science and eventually for the development of therapies. And again there is progress with the use of these drugs that she has been studying, and she is really hopeful that there will be a clinical trial very soon targeting Usher syndrome. Finally, I will finish with a short story about retinal organoids. And so again this is using stem cells and using them to make a mini-eye and eye cup in a dish. And again this has been very informative.

Mike Cheetham from London reported a lot of his exciting work looking at the development of retinal organoids as the disease model. Not only to understand the disease, but also to assess different drugs and in particular, for example, small molecules to restore the maturation and limit the degeneration of the photoreceptor cells. And so there was also a story from Yoshikazu Imanishi from the US, which again is assessing different molecules.

He has a system for screening a lot of molecules on these tissues, to really find molecules that are non-toxic and can really have an effect on the photoreceptor cells and then assess those drugs really in the mouse. So I will

wrap up by saying, the future is in our hand, it's in your hand, to shine a light on Usher syndrome we need you. As scientists today, this day, this meeting is so important for us, it's so important for us to know that what we are doing matters, and for me to see where we've been from four years ago to today is absolutely mind blowing.

And I know when we see you again in three years - hopefully - it's going to be again another story, and it's really wonderful, and I thank you for being here. And I want just to finish with the main thesis of Usher syndrome. There is a lot of us, and I now it's not everyone, it's just some of us here. You are not alone, we are not alone, we are all working towards understanding the disease and finding a cure. Thank you. (applause)

(Irmgard Reichstein) Thank you very much, Gwen. We are perfectly in time for breakfast.

So I kindly ask the speakers to stay with me here, and if you have urgent questions, please come to us. I don't want to shorten the breaks for all the people who really need the break. The coffee break will take place on the right side, if you pass the registration, you will come to the coffee desks.

And if you need assistance, or if you need interpretation, please come to the help desk, we have there interpreters

which can help you and we have there also assistants which can help you. We have also microphones, but I would say everybody can go to break, and everybody who has a question will come to us here, so that we don't shorten the break for the people. So I wish you a good break, and all questions will be answered here directly from the speakers.

(Mark Dunning) So, looks like everybody has just about settled down. So, if everyone can just grab a seat and we will get started with our next session.

Uh, as I know, I saw a number of you catch Margaret and Uwe and Gwen at the break. Again, if you guys want to grab them at any time and ask any questions, I know that they will be more than willing to answer those. And our next session is going to be on... hold on. I have the wrong day, I have my thing upside down. Where are we, 20th, 21st? There we go. So, sorry, I had my paper upside down. The next section is gonna be on therapy in focus. And our first speaker is Isabelle Audo from Paris. And she is going to give us an update on the USHStat MYO7A and other the clinical trials. We have a bunch of stuff that is close to clinical trials or just about in clinical trials. So, this will be good stuff.

ISABELLE AUDO

(Isabelle Audo) Thank you, Mark! So, thank you very much for this very exciting meeting and the opportunity to share with you some of our data.

Actually, I am just going to give you few examples. And there is a lot of very exciting talks coming up with all other therapeutic developments. So, if you want to have therapeutic approaches, and I am going to talk essentially about retinal disease. I am a retina specialist. So, I am going to talk essentially about the retinitis pigmentosa part of Usher syndrome. If either you want to try to stop the progression of the disease or to restore vision.

To stop the progression of the disease, there were very exciting developments in the past years, aiming at treating the genetic cause. So, that could be gene therapy. Either by replacing the gene, the defective gene by new normal genes or correcting the genes. And you will hear in other talks about oligo and high sense nucleotide, about CRISPR/Cas, about readthrough drugs other things in order to correct the disease.

So, regarding Usher, the problem is: if you want to bring the normal genes to replace the defective genes, you need to have a vector that will deliver the genes to the target cells. So, you usually use viral vectors. And the first

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viral vectors that were used are adeno-associated viral vectors, called AAV. And fortunately most of the genes that are mutated in Usher are too large to be packaged in AAV. Or they need to have some special tricks in order to be delivered by AAV.

So, there is one trial in which our centre in Paris is involved which is sponsored by now pharmaceutical company, Sanofi. This trial has been using not AAV, but lentiviral vectors that are able to package larger genes up to 10 kb, which is quite large. Some Usher genes are even larger than that. So, the idea is this virus, this lentivirus vector, it's the virus, it's called EIAV. It's the virus that cause anemia in horses, and it is not pathogenic in humans, we are not horses. And there were pre-clinical studies that documented the safety of the delivery of this viral vector. And currently, there is two trials, that aim at packaging and delivering a normal gene through this lentivirus.

One is for ABCA4 and it's another disease, which is called Stargardt disease, ABCA4 is the long gene. And the other one is MYO7A. As you know, MYO7A mutations cause the most common form of Usher Type I. So, prior to that, there were experiments in animal models and this is a slide as an example of what was performed in monkeys. If you want to use a viral vector, you have to prove that you are indeed able to infect the targeted cells. So, what Sanofi did, is on non-human primates. They delivered the viral, the EA1V viral vector subretinally and then the virus was not expressing gene to be treated, but a gene that made a protein that could then stay in the cells.

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And by doing that, they were able to show that there the EA1V was indeed able to infect cones and rod photoreceptor and also RPE. What they also did, is they performed subretinal injection in non-human primates in one eye. They injected one eye and subsequently the other eye, or they re-injected the same eye and they could document that it would not lead to major inflammation. So, that's when the trial started.

So, the trial is called UshStat, and is really aiming at one single injection underneath the retina of this viral vector delivering the normal MYO7A gene. This is a trial that is taking place in two centres, Portland, Oregon with the Casey Eye Institute in the US and our centre in Paris. So, this, the design of the trial is dose escalation. So, it started by with vision that had severe disease with the lowest dose, because the first point is to document that it is safe. That it doesn't lead to major side effects, because that is not what you want. Although, it was safe in the pre-clinical test.

So, the first patients had very severe retinal degeneration, linked to MYO7A mutations. And then, the dose was increased while we were documenting safety. So, so far 9 patients have been involved in both centres, and with a nice safety profile, which is provided by Sanofi - I have got to say I have no income interest or am paid by Sanofi - and 9 patients involved. And there were several side effects and actually one side effect in the latest patient was panuveitis which means after the surgery, there was inflammation in the vitreous. So, after this inflammation,

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everything was resolved and most of the patients recovered. At least, the vision they had prior to the surgery to the subretinal injection. But when the Independent Safety Committee discovered that there was one case of the 9 patients who had developed severe inflammation, they wanted to pause the trials.

Up to now, the trial is on pause, Sanofi did further tests and the safety profile was re-studied with half of the highest dose. And the trial should re-start at the end of 2018. So, the good thing is, we have limited data so far on this patient. As I was telling you, this is mainly looking at safety. But there is some efficacy that are evaluated, based on visual acuity and visual field. And on these slides, I put some results of the visual field for the 9 patients. All the patients that were treated, recovered their baseline visual acuity. And even some of them have after the surgery and after some, you know-in this graph, some patients were followed for 150 days. Some patients are starting to have a difference between visual acuity in both eyes, but very little patients. Yeah, sorry?

(change of speaker) Can you slow down a little bit?

(Isabelle Audo) Ah, excuse me, yeah, sorry, I will slow down. So, these slides were to show you, that the majority of the patients recovered their visual acuity. The visual acuity that they had prior to the injection. And then, we followed these patients and what we would like to document because only one eye has been injected, is to see, what the follow-up- whether the injected eye behaved

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better, based on visual acuity and visual field. And, in some patients we are starting to see some differences, but it should be taken with caution. So, again, the trial has been on pause for a year now to have more safety data on the pre-clinical side. And it should resume before the end of this year. So, that was for MYO7A gene replacement and you hear about other gene therapy approaches later on.

So, I wanted to now touch upon few other trials that are either at a pre-clinical stage or will be starting very soon or already started. One is independently of the gene. You want to stop the disease. You know that for the retina, the rod photoreceptors are degenerating first. Then the cones, the cones are more precious photoreceptor because they are responsible for our daylight vision or reading or colour view.

And one other approach would be independently of the genetic cause: Can we save the cones, can we stop the cones to degenerate? And this is some work that was done by my boss, Professor Sahel, for a long, long time. His idea was that not-not always in Usher but in other type of retinal degeneration, the mutation is really carried and expressed only by rod photoreceptors, but the cone degenerates again early.

And his idea was, that not only rods are important for night vision. But they are also able to synthesize to make factors, proteins that are really critical for cone survival. And when a rod degenerates, then a cone degenerates.

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So, there was a huge research going on in our institute to identify this rod-derived conveyability factor. And one was published in 2004.

It was shown in different animal models that it was indeed able to stop in few animal models with rod-cone dystrophy with retinitis pigmentosa. It was documented that the cones could be- the degeneration of the cone could be slowed down or stopped. And even that the structure of the cones, the morphology of the cone was even improved. And there would be a clinical trial initially in a selective genetic group of patients starting in 2020. The group of patients that mirror the pre-clinical studies on the animal models.

But we hope that with the proof of the concept that we are indeed able to deliver- by delivering this trophic factor RdCVF, we can stop the cone to degenerate. Then it should be wide-spreadly tested, including in patients with Usher syndrome and retinitis pigmentosa. So, that was the axis of stopping the disorder. Either by gene editing, gene correction, gene therapy with the current MYO7A clinical trial or protecting the cones. But now you know there is other type of therapeutic approach to restore the vision, when you no longer have photoreceptors and especially the cones to degenerate.

So, professor Zrenner will speak about artificial retina. So, I will just very briefly speak about that. And the idea of artificial retina is: When you no longer have photoreceptors, only photoreceptors are able to be activated by light

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to generate an electrical signal at the optic nerve towards the brain. And, so the idea of the artificial retina, and another approach I will mention later on, is to restore the fact that no longer cells of photoactivable and able to send information to the other retinal cells. Other retinal cells, such as the bipolar cells, that are connected directly to the photoreceptor. Or the ganglion cells that are the third neuron forming the optic nerve and sending the vision to the brain. And these two types of cells usually are not degenerating during artificial retina.

So, there is different types of artificial retina, underneath the retina. But underneath the layer of support the retinal pigmented epithelial, or subretinal, or on top of the retina. In our group, especially the group of Serge Picaud in our institute, has been working with Stanford and Professor Palanker to develop a special artificial retina with little diodes here, that are completely independent from each other. And this idea of these diodes is to be subretinally placed surgically. And then with the camera, the camera looking at the environment, coding the information and sending back the information to these micro-diodes by infrared light to encode the vision. And this is something that- So, you see the implant underneath the retina.

This is something that has been tested in primates. And, so this is a bit innovative in a way that there is no connection for this little chip with diodes because it is just activated by this infrared light. And there is currently a trial which is not yet for retinitis pigmentosa. But we hope it will come in geographic atrophy in two centres: One

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in Paris, one in Pittsburgh, Pennsylvania on geographic atrophy. And the idea is geographic atrophy in age related macula degeneration. And the idea with this little chip



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that can reach a thousand electrodes, is to prove, that we are able to restore fine vision in these patients that have only macula involvement. Because if we can do that on patients, who have only macula involvement, then you can also restore that when not only the macula is involved, but also the peripheral retina.

The last trial I want to mention is optogenetics. So, what is optogenetics? So again, when you have retinitis pigmentosa, you lose the only cells that are able to be activated directly by lights into the retina. The idea of optogenetics is not to restore photoreceptors, but to transform the other bipolar cells or ganglion cells that

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are not affected by the disease and to make them photosensitive. And the idea is: You have some protein in algae, you know, ancient protein, in algae in the sea, that are able to be activated by light and directly open a channel and initiate a signal into the light.

So, there are two types: one is halorhodopsin and one is channelrhodopsin. So, the idea with optogenetics is, it is a sort of gene therapy. It will be injection within the eye, it doesn't need to be underneath the retina because you want to target either the retinal ganglion cells or the bipolar cells to inject the genes of this channelrhodopsin, this protein that are able to be activated directly by light and generate the signal. Unfortunately, this channelrhodopsin can be activated by natural light, so this type of approach will need to be coupled with specific goggles that will transform our environment and generate light for this. The approach is developed in Paris, this will be red light in order to activate this photo-pigment that will be in the ganglion cells.

So again, the group of Serge Picaud has performed testing on mice showing that they were able to indeed infect ganglion cells and generate an electrical signal by stimulating this channel. It was also performed in macaca, in monkeys. And the intravitreal, it was proven that just injecting inside the curvature of the eyes, not underneath the retina, but inside the eye in the vitreous, the channelrhodopsin was distributed quite widely. So, it could give larger vision. So, the trial is supposed to start anytime soon. And it has been accepted in France, there will

be other trials, other centres in the UK and the US and we just got the approval. And so, the idea was, one single injection in the eye. And testing this device with the goggles to see, if there is any possibility to photoactivate and restore some vision at the cellular level. It is a sort of similar approach than the retinal implant. But you really go directly to the cells, trying to have maybe, hopefully a better refined visual restoration.

So, there is also a very exciting development, in the group with the mathematicians that work in Paris and in Pittsburgh, is to try to combine optogenetics or implants with a precise coding of the visual signal by a specific camera in taking into account, how our brain is able to analyse the space with the contrast and the speed. And to try not only to improve the device that is delivered to the retina. But also improve the way, the information is treated by a camera and sent to this different approach. So, this is going to be continued. And I want to thank you for your attention! (applause)

(Isabelle Audo) I am sorry, I spoke too fast.

(Mark Dunning) So, thank you Isabelle! As I mentioned before, you know, Isabelle is available to answer any questions that you might have. We have a slight change in the schedule. Thomas Lenarz is coming, but he is going to be running a little late. So, our next speaker is going to be Eberhart Zrenner from Tübingen, Germany, who is going to speak about retinal implant and electro-stimulation. Welcome!

EBERHART ZRENNER

(Eberhart Zrenner) So, first of all, I would like to thank very much the organizers for the invitation. I'm very glad and happy to be here. And I will have two topics. Both are about electricity.

Electricity can be used to stimulate neurons and to provide vision. But electricity can also be used to tickle certain cells, to release endogenous growth factors to protect cells from further degeneration. This will be part two of my lecture. I would like to start with the retina implant and I also would like to thank to Isabelle, because she has given a wonderful introduction already into the different types. The subretinal, epiretinal and the subchoroidal type of electronic implant to restore vision.

We have to be aware that gene therapy and other therapies you learn today, are only applicable in patients, if patients still have cells, if they still have vision to rescue. You can treat only something that is present. If cells are gone, you can't treat them. And the only way presently available to patients, to restore vision in case of blindness or light perception only, or very low vision, extremely low vision are retinal electronic implants. There is nothing else.

There are two types of implants. The Argus II from Second

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Sight that you have seen a moment ago and the Alpha AMS from Retinal Implant in Germany. One is epiretinal, the other is subretinal. And I just would like to start with the Alpha AMS which we have developed in Reutlingen and Tübingen, since most recent 20 years old, so to say. These are both on the market and in Germany and other countries, repaid by the public health system. So, the target disease is clear, it is retinitis pigmentosa. You have learned this already about epi- and subretinal.

So, I will go into more details into the subretinal approach. How is it working? Essentially, it is a little camera chip, what we are using, like the one you have in your mobile phone from outside. But inside, it is very different. But the size is the same: 3 mm × 3 mm, it has 1,600 pixels, that is not much in comparison to what cameras have. But Argus II has only 60 pixels. Each of the 1,600 pixels has a photodiode, like the photo cell in the eye. It has an amplifier which amplifies the light point by point. And it has an electrode which forwards amplified current to the bipolar cell layer. Remember, you have these different layers in the cell. All the other layers in retinitis pigmentosa are still functioning pretty well. It's only the photoreceptor layer which is missing function.

That is, what we are doing: we are replacing the natural photoreceptors with artificial technical photoreceptors. And the iris's camera chip, it is in the back of the eye. That's where the photoreceptors had been, when they are still functioning. So it's under the retina. The retina is transparent. So, the regular picture through the lens, like

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in a camera, falls onto the back of the eye, goes through the transparent retina, falls on these 1,600 photodiodes, and an electrical image of this picture is produced and forwarded to bipolar cells.

I just show it to you on the picture, where they are. These are the bipolar cells here. And then, it is processed. So, the processing is a natural processing. There is no computer, like in other approaches which you have to have in the pocket. There is no camera outside in the face. It's all in the eye, it is moving with the eye. And nothing is to be seen outside, except the little coil back behind the ear, like in cochlear implants, where power and signal control is provided. So, it is processed and sent to the optic nerve to the brain. And this has a number of advantages: we can utilize all this remaining network. We can use the fixation of the eye, because if you have a camera outside the goggles. You need to move your head and look, what it is doing, whatever the eyes are doing. But, normally we are used to find objects, where we are looking at.

So, the fact that the implant is right below the phoria, helps us to use this particular pathway from the phoria to the brain to fixate things and to find something, much easier than with the camera outside. And we can use wiggling eye movements, which we normally have, so to say the micro saccades, which help us to refresh the image. If you have a camera outside, you have wiggle the head all of the time in most patients, to refresh the image. If you have the chip under the retina, the normal eye movements are helping.

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Okay, now you have understood how it works. And Dr. Stett in the afternoon will tell you more about the technique, the technology about that. Of course, we need a power supply and other things, which we will see in a moment, like here. So, behind the ear, there is transmitter antenna kept with a magnet. Below the skin, there is a coil that receives the signals from a little box, the patient has in the pocket for its batteries. And you can adjust sensitivity and contrast, like in the old black and white TV.

You may remember football in 1954 you have seen how everything was happening in Basel, no in Switzerland, Bern, Bern, sorry! That was not much to see, but it was as exciting as nowadays with the HDTV. I think, I wasn't there. I heard it on the radio nevertheless. Okay, so then from below, from the implanted coil below the skin, there is a cable that runs from behind the ear, under the skin towards the eye. It enters the eye with a very tiny thin foil, you know, with like in computers, the thin foils with electrical gold wires, printed wires, and it goes into the little camera chip, the AMS, Alpha AMS camera chip, which is implanted under the eye.

The question is now, how to get it there? That is not the greatest place to put something under the retina. And there were many experiments, meanwhile we have operated more than 60 patients and you see them here. So, first a little window is made into the eyeball on the side. You don't see, it is on the side of the eyeball. And then, a little foil, a small foil is advanced through this cut on the side, where the muscles are, and advanced to the phoria.

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So, it is a tunnel which is made in a way. And this foil protects the retina from damage. And then behind the foil, the implant is advanced, so you see, it is elevated a little bit and behind the foil, behind the protected retina, now you see the chip coming forward, until it reaches a place right below the phoria.

There it is, and you see the gold foils in this catch which provide power and control signals. Each of these dots is a pixel. And the size of the visual field is 15 degree. 15 degree is not too much, but you may have had or still have 15 degree of vision and that is pretty good, pretty good to come around, I think, with moving the head and looking. So, 15 degree is not much, but it is absolutely sufficient, even to drive a car actually. Because when you go Porsche on the German highway, these things on the side are going so quickly by, that your visual field is 15 degree or even less. That is why highways are always straight because you may not easily go around corners safely. Okay, that wasn't intended to be discussed.

Okay. Now, what did we do so far? We started in 1995, developed the implants, all the pre-clinical experiments in rats, in pigs in rabbits, until we really understood how everything is working. We did a pilot study with eleven patients. And there was one particular patient: Mika.

He was the first patient, where we put the implant under phoria, before we always had it in the periphery, that was not sharp enough. And he looked on day at his name which we had written with chalk on a little black board, 4

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centimeters or up to 8 centimeters in height, little white letters on the board.

He was sitting there and saying nothing first. Then he said: „Do you think I am a formula 1 driver?“ So, we asked him, „Why do you think so, that we think that?“ He said, „Mika Häkkinen“, which is a very famous formula 1 driver, „he writes his name like M-I-K-A, the way you have written it.“ „But my name is M-I-I-K-K-A.“ „So, you have made a mistake.“ So, we were very happy about this mistake because this was the really proof, he could see and read properly.

Imagine our joy in 2010, when we learned that the patient told us that we have made a spelling error. That was great. So, we did a few more studies together with other people - Oxford, London, Dresden, Budapest, Hongkong, Singapore - with 29 patients with the wireless chip, the first generation, we call it the IMS. That was very much looking like the present version and it worked pretty well, but it didn't work so long. It was only 9 to 12 months or even less or more in some patients. That is not enough. If you want to have something implanted, you want to have it longer. But there were problems with cable, there was problems with corrosion. But for this time, they had it, the patients were pretty happy.

I show you, what we did with them. And then we developed a new chip. I will tell you at the end: The Alpha AMS, the second generation which I have tested meanwhile in 15 patients. It is on the market and that comes at the

end. But what first of all: What did we do with the patient? We put them in front of a screen, we show them light, we show them gratings, we show a Landolt ring, you know, this C, where is open, left, right, up, down. So, we learn about visual acuity, learn about light perception.

And then, we do daily life activities. We put a plate on the table, a spoon, a knife, a cup. Then we ask the patient: „What do you see on the table, where is it?“ „How many items on the table, what is it?“ These are the questions. And then, we score. And the score is 0 to 5, actually 5 points, 0 to 4, 0 to 1, 2, 3, 4. If patient sees nothing, it is 0. If he says everything is correct, it is 4. So, what did the patient do? I just tell the outcome of the early study which ended 2013. Roughly 3 quarters of the patients had benefit. Some had very good experiences.

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Even reading, telling that there was a Vapiano restaurant in large letters or something like that, or finding the ADAC, which is the German automobile club something like that, but that were just experiences. Some found it useful, but not to that extent like reading. But still finding an object on the table makes a difference from not finding an object of a table. So, you would grab something and your arm, and the hand is in the potato salad. You would like to avoid that, and that helps.

And for a quarter of patients, it was only light source. But also this is helpful, if you see nothing anymore, you are very happy, if you see the window, or a lamp, or a moving car light, something like that. In 8 patients, there was no

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effect because some didn't want to learn very much. It is a bit like skiing, you have to train it properly, and in others, in 4 of them, the implant failed. This is a clinical trial and we learned enormous things from these 29 patients which allowed us to create the next generation.

Still, these 29, just to abbreviate, 72 % reached the primary efficacy endpoint which was significant improvement of activities of daily living and mobility. And 86 reached the secondary efficacy point, like visual acuity of grating vision. So, we were happy, we said: „Okay, let's go on, let's provide something which really can be available to patients.“ That means development, engineering, material sciences, physicists, surgeons, everything had to be improved. I skip something, and we came out with a new subretinal implant Alpha AMS. So, here is the implant, same size with the gold foils. It is implanted the way you know it. It is here with a cable below the skin. And this is a box, the patient has, it has two knobs for brightness and contrast and to switch it on and off, that's all.

And then we started this with 15 patients, just published 2017, results with a Multicentre Trial with a subretinal implant Alpha AMS. And I show you a patient from Oxford who - for the very first time, when it was switched on - looked at the table with the items and she was very touched. So, maybe there is a little - can you give us some audio, please?

(video is played)

She tells us that there is a knife, there is a cup. But you

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cannot hear it, in a moment.

(woman in the video) Yeah, yeah. Yeah.



(Eberhart Zrenner) And she looks around to find the egg cup.

(woman in the video) Here, I see a cup, that is clear.

(another person in the video) Is it clearer than yesterday?
When you were looking?

(Eberhart Zrenner) Okay, and if you look at all these patients together, then we see, if the implant is switched on, which are the green bars, in comparison when the implants are switched off, they are doing much better, signi-

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ificantly better with all the screen tasks over this 12 month period with light perception, with light localization, with seeing the grating acuities, or on the table tasks with finding the items, I just showed. Or also where the items are. They are not so good, what the items are exactly, they may mix a spoon and a knife. But that is probably not so important. I show you a few movies from the patient at home, because the engineers go home to the patients, in the near-vision area. So, the patient looks at a laptop.

(women in the video) Versuchen Sie es mal zu zeichnen.

(Eberhartt Zrenner) Can you like to draw it? So, he nicely draws the borders of a square. So, that works. Or another implant, it is the same one, sorry! Grayscale! The patient sits in front of grayscales between white and grey and black. And he describes exactly which way it is around, where are the whites and what is in between, because the vision patients have is blurry, of course. It is low vision, it is 20 over 500, it is not much. But it allows to see a bridge, a car, a scarf or a hat.

And some patients even were able to see others smiling, because the teeth are pretty bright contrast against the face. So, that helps, and now the movie, again. I have problems with the movie. So, plate on the table to find, patient looks around, looks for various items and right away sees it. I skip this one. Okay!

So, now you know the important things you need to know, I think, you may like to hear about the implant. The ques-

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tion is, when can it help to regain some vision? Clearly, it is too late in pigmentosa. But light perception or worse that makes no sense, if you still are able to recognize a face or something to do it. If you are an Usher patient and you have a hearing aid at one side, it is no problem to put a retina implant on the other side. Reading must have been possible earlier in life.

So, the brain develops ability to recognize and if it is not done in the childhood, then it cannot be developed later on. Still some retinal in a layer must be there, no macula holes, optic nerve must still be functioning and of course a proper picture has to go back to the eyes or if you have a trauma of the lens or cataract, it has to be first corrected. And no serious systemic disease like infection diseases or so. And we are very grateful to our people who have worked in our teams to develop this in Kiel, in Oxford, Singapore, Budapest, London, Hongkong, Dresden. If you are interested, you can contact any of these centres or ask in Tübingen, in Germany.

This was the first part, the second part is: What can we do to help the neurons in the eye to survive longer? And if you had looked a moment ago very carefully, you may have seen that over the time, a patient became even better a little bit with the power switched off. So, this is an effect of a well-known - and also described by other groups - point, namely that electrically stimulating Müller cells or RPE cells, they do release all kinds of factors that are good for the cells. So, secretion of growth factors, they change the BCL-2 level. And this has been studied in

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many, many investigations in rats. In a number of studies shown here since 2001. And there are nice reviews that say: „There is a role of electrical stimulation which can help therapy in olphalmic diseases“, published in various archives.

This is an example for the specialists: If you take a rat, you stimulate it with alternative current, very tiny currents, 300 micro Ampère for one hour, the antiapoptotic expression of BCL-2 is measured in Western blot, goes up within six hours. And then in 7 days it wears off again. The apoptotic cells are the ones who provide the death signals to the cells - they go down. Casper3 does nothing and growth factors - ciliary derived neurotrophic factor and brain derived neurotrophic factor - after one hour of electrical stimulation of the eye with the electrode, you know, like in the ERG.

But not measuring the current, but putting current it into the eye, increases the level of growth factors enormously. And there are clinical trials for various kinds of optic nerve diseases. And we also did a clinical trial in weekly, cause you saw that it keeps active for 7 days.

So, we did a weekly stimulation for 30 minutes for 6 weeks in the first study. And we saw that those who received a certain dose of electricity had an increase in visual field, while those who were sham-treated, so they didn't get a current, they had a slight decrease. And also lower dose had a decrease.

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Then we did a second study in 52 RP patients randomized over one year in 3 groups. And it turned out they had very similar effects. Also, especially the electroretinogram, the b-wave increased and implicit time shortens. Then we did a multi-centric study with this device in 105 patients. And again 2 years, 30 minutes a week, we saw in the stimulated eye a significant increase in the best corrected visual acuity. Not in all patients and this with many treatments, like glaucoma, it lowers the pressure, but it doesn't help all the patients. So, there is - the device is not shown here.

So, how does it work? It is called OkuStim, it is like glasses. But instead of lenses, you have tiny fine, little spiderweb wire, electrical conducting. You put that onto the eye. The spiderweb type wire is in the lower lid, and you have a box that provides the current, where you put the plug-in to, and you sit there for half an hour. You may get a little bit of tickling, the eye may be a little bit dry for one or two days afterwards. So, you get some regular wetting drops into the eye. So, we learned that it has in clinical trials significant improvement. It is safe and well tolerated by patients and the German health insurance has now acknowledged that it has potential benefit.

We think, that is a very important point that the German healthcare system - that was difficult to get - says: „Let's to do on the expense of the taxpayer in Germany a big trial with 250 people and look on the long-term effect.“ So, we hope that in the next 2, 3 years, we will be able to get these 200, 250 patients cost-free for the patients

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into the trial, financed by the German healthcare system. That's where we are.

Finally, I would like to show you our new hospital, new clinic. Only one in Germany, we are a full-fledged research institute with 110 researchers within the same building with a hospital with 72 beds. And in the same building with an ENT department. So, we have a special Usher clinic Wednesdays. Katarina Stingl, my senior physician, is running it together with Anke Tropitzsch. And if you are interested, I have put here the e-mail, where you can write to Katarina, if you want to join this special clinic for Usher patients and other rare diseases that affect eye and ear together. Thank you very much for your attention! I was speaking a little bit slowly and overdoing it for two minutes. And if you have questions, I will be there during lunch. Thank you! ^(applause)

(Mark Dunning) Thank you very much, Eberhart! So, our next speaker is Darija Udovicic Mahmuljin, am I even close?

(Darija Udovicic Mahmuljin) Close.

(Mark Dunning) You can come up here and pronounce your name afterwards, so we get it right - from Perkins International. She is going to talk about 'Steps Toward Better Life', improving access and quality of education for deafblind children and youth through partnerships.

DARIJA UDOVICIC MAHMULJIN

(Darija Udovicic Mahmuljin) So, good afternoon everyone! Do I need to do this? Good afternoon everyone, thank you for inviting me here! I will be talking about improving quality of life from a different angle that you have been hearing until now.

And that is through the improving access to the high quality and appropriate education to the children and youth who are deafblind or with additional disabilities.

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I come from Perkins International and that is a part of Perkins School for the Blind. Just a second, yeah. Perkins School for the Blind was the first school for the blind in the United States that was established nearly 200 years ago. And it was also the first school in the world that educated a person that was deafblind. And that was not Helen Keller, that was Laura Bridgman, even 50 years before Helen Keller. And I would also like to mention Helen Keller, as well. But not the way that you would think I would.

I would like to mention her with her teacher that was Anne Sullivan, who was mentored by Laura Bridgman and who had a strong believe that Helen could learn. And her dedication and her quest for the ways that Helen could

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learn, actually brought Helen to what she has gained later on in life. And Anne Sullivan remained her teacher, as you all know. But I want to stress that because that is what we



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in Perkins do and that is what we are good at: The expertise of teachers for children and youth who are deafblind and with additional disabilities. We do think that quality teachers with the right dedication really do make change in their life.

So, Perkins International was established in 1989 - the Perkins School for the Blind - to support the development of that quality education through the world. Our mission is to ensure that all underserved children and young adults with blindness and additional disabilities and visual impairment receive and have access to equality and appropriate education. We work on our goal through

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the partnerships with orphanages, schools, universities, ministries, family organizations at local, regional level. So, wherever we find a partner that truly believes in our course and that is willing to do a change. We want to break the isolation and neglect these children fates, transforming their future through the power of learning.

But, so, Perkins International today, we work in 70 countries throughout the world, through Europe, Asia, Latin American and the Caribbean, Middle East and North Africa, building capacity at local, regional and national level to develop independent and sustainable educational systems that will transform the future of those children.

We do those trainings and those partnerships, even on a grassroot level. Even if there were programs, we build partnerships, programs with only two children and one teacher, with family organizations we only wish to make a change. And sometimes, even those programs with our support and other support, made a huge change and impact to the society and local community. Because every child counts and we think, all of these children and all of these possibilities add up to bigger change and bigger impact to the society and community there.

But, we have a challenge, and the challenge is that according the World Health organization, there are 6 million children and young adults from 0 to 24 in the world that are deafblind and or with additional disabilities. Unfortunately, the majority of that huge number is not receiving the education, they would need. So, we consider them as

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the world most vulnerable children. For too often, they are excluded from the education systems. Instead of going to school, they are left at home. And unfortunately, in many cases, they are left in orphanages and children's homes, where they are being isolated and neglected. And for those children who are lucky enough to go to attend schools inadequate teacher training is a fundamental issue. Because teachers do struggle, if they do not have the special skills, how would they meet the unique needs every and each of those children have.

Thankfully, the world community has acknowledged needs for solutions. So, with sustainable development goals, disability education is a renewed priority. Global leaders have committed to providing quality education for all children, including those with disabilities. That was that sustainable development goal number four, quality education for all until to 2030, it provided us a window of opportunity to create a systemic change to achieve that goal.

So, Perkins International with its expertise is committed to make quality education accessible for that vulnerable group of children. Further on, U. N. Committee on the Rights of Persons with Disabilities, had a declaration where they said, „Inclusive education is a human right, including those with disabilities.“ And in that declaration, the committee specifically identified individuals with deafblindness and multiple disabilities among those, who are most at risk of being excluded. So, we do have to do something about it and build on that momentum.

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Perkins has designed a global strategy to achieve quality education for some of the world's most vulnerable children. We had consolidated 97 years of global teacher training with it since 1920. And we launched a global campaign in 2017 in the United Nations through Perkins International Academy to help governments to meet their commitments for the Sustainable Development Goals.

We designed Perkins International Academy to be implemented in partnership with governments, universities and NGO's. The course establishes international competence standards for teachers working with children with multiple disabilities. There are four levels of education finishing with 'Train the trainers' which is a blue print of how we can reach a bigger number of children.

Our strategy is not only through the courses, but also - as I have already mentioned - through building, through partnerships model programs, centres of excellence, that will be models for best practices, training and application.

The communities need a place where children and their families can go for quality education, for resources to support their children at home, for inclusive settings, to get the resources, how they could meet the needs of their students at a best and appropriate way. We also do have technical systems and support through our country representatives, where we do on-site mentoring and trainings, government agency support, NGO support and of course, a lot of it to family organization support.

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And as a final thing, we do have an International Educational Leadership Program and that is 9 months intensive program that supports international educators from all around the world, where they learn best practices at Perkins and Boston College and disseminate them in their native countries.

The history was in late 1920, when we started this teacher program, but it became solely international in 1989. So every year, 15 teachers around the globe come and get their skills and when they come back to their native countries, usually they are at the forefront of change in the education system and policy systems in their country. Because not only that they learn skills, but they witness the power of change that really appropriate education has to life of children, and youth, and their families. And they really become the major ones that do the change and our partners in their countries.

So again, of this short presentation, I would really like to emphasize that knowledge and skills are the cornerstones that create good practice model programs and policies for children with disabilities around the world. But also attitudes. For too often, we have been encountered with the situation that we couldn't even believe that was coming from even persons and organizations, we would not expect it.

And that is, at the heart of the issue is often deeply-seated misbelieve that children with especially profound disabilities and multi-sensory impairments cannot learn.

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And whatever we do, we have to have that in mind and we have to change the attitudes and perceptions, because without that, we have to change it not only with policymakers, but also with teachers too many times and also with families. So, we have to have that in mind to change it, because in their attitude and perception of that they have powerful ability to determine, whether these children can achieve a good quality of life or not.

We believe that all children can learn and thrive. We believe that education enriches lives of individuals and prepares them for active roles in communities, in their families and schools. And we have worked on that and we believe that all children have the right to be given a chance to learn new skills. Because only, when learning new skills, that is the way to get a sense of accomplishment. And we all need a sense of accomplishment to feel recognized and we feel recognized and that we accomplish something. That is how we get to be a part of society and that is what it gets us to lead a more fulfilled life. Thank you! (applause)

(Mark Dunning) So, thank you, Darija, for that! That was excellent and very important stuff. Is Thomas Lenarz - did he make it here? Is he available to speak? Yes.

(Mark Dunning) Okay, okay, excellent, okay. Well, welcome! So, now I have to find where you are in here. Kimberley Smith, excellent! So, we have a change in the program. Kimberley Smith from Uxbridge in the UK is going to talk about ,Psychosocial wellbeing and health-related quality

of life in the UK population with Usher syndrome'. Once, she gets her headphone on here. Is it good? Thank you for doing this at short notice.

(Kimberley Smith) Okay. Would you like my laptop? I have it on there, as well. I have had this before, it has been damaged. And it has been damaged because of one of the - if we go down - Okay, I have got it on my laptop. Oh, yeah. So I know where the stick is. Is that my one? Yes, yeah. Sorry! Oh, no, that's alright, it is actually on the physic- Oh, it is on the laptop itself. That's okay.

(Mark Dunning) Hi! Hi, ooh, sorry! Hi, sorry! We have a little bit of technical difficulties. So, thank you to Kimberley for stepping in at the last second. If we can have everybody's attention, we are ready to get started again. I just want to give you one more quick update on the schedule. Thomas is here now, so, he is going to follow Kimberley and then we will have lunch. We gonna delay lunch just a little bit. But we will pick up the time on the backside of it, okay? So thank you, Kimberley!

(Kimberley Smith) Thank you!
Okay, can people hear me okay? I got the worst spot, nobody wants to have the spot before lunch because all anybody can think about is the food, they are about to eat.

KIMBERLEY SMITH

So, I try and get through this as quickly as I can for you. So, I am here to talk to you today about 'Quality of life and psychosocial wellbeing in Usher syndrome'. To give you a little bit of background about myself: I am a lecturer in health psychology at the University of Surrey. But prior to working there, I worked as a lecturer at Brunel University London. And I taught on the master's in health behavior and psychology.

And it was while that I was approached by a student called Gavin Dean who has Usher syndrome himself, who really felt very strongly about doing a project around psychological wellbeing in people who have Usher syndrome. So, I think, before anything else, what I would like to get across is, this is very much Gavin's project and I am here representing it on his behalf. Gavin himself wrote a blog for the limping chicken website. And that blog gives you a really nice insight as to why he feels that this was an important project to do. He says, having Usher syndrome himself since he was a teenager, he often found himself in many situations where his deafness and blindness left him feeling depressed, anxious, isolated, hopeless and frustrated because of the many challenging and uncertain experiences that he encountered in his everyday life.

He felt that these feelings came from barriers in communicating with other people, barriers in mobility, barriers in accessibility and also a general lack of understanding and appreciation and even acknowledgement about what Usher syndrome is and how it effects the people throughout their lifetime, both physically and psychologically.

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So, by undertaking this study, it allowed us to get some - he calls it - ,hard scientific evidence in the public eye on the impact of Usher syndrome on psychological well-being'. And we published a paper on his work in 2017 in a journal called BMJ Open. And, anybody can access it. So, if you feel that you want to, you can go and download the study that myself and Gavin did. But before we get into the study, I would like you all to think about what health is.

If I was to ask each one of you: „How would rate your one health on a scale that runs from excellent, very good, good, fair or poor?“ „How would you rate it?“ And then think about, what is it that is influencing how you rate your own health. There are lots of different things that are influencing how people think about their own health. There might be physical issues that are happening, but with other people it might be linked to functioning, not to being able to physically do, what they want to do or need to do. For some people it is social, they can't go out an engage with people, as they want to. For some people it is much very much linked to how they feel psychologically. And this is reflected in the World Health organization definition of what health is. It is not just the absence of disease or infirmity.

It is a state of complete physical, mental and social well-being. So, when we bare that in mind, and we know that health is this really multi-dimensional complex thing, why is it that - and no offense to any other Usher researchers here, who do this - so much Usher syndrome research is

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focused on the biology of Usher syndrome and finding a treatment. And there is no doubt that this is incredibly important. But Usher syndrome is not just biology. Usher



syndrome is something that is affecting people. And it will affect them psychologically and socially and it will do more than affect them just biologically.

It might have an impact on something, that we in health psychology call 'quality of life'. And this broadly is the satisfaction a person has with their own life. And it is influenced by lots and lots of different things. So, it is influenced by our psychological wellbeing, how happy we are, whether we feel depressed or sad. It is influenced by our environment. This work is showing that, if you are in an area where there is lots of green space, that is better for your wellbeing, than being in an environment that is very

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built up and polluted. Spirituality will have an impact on people's quality of life, as well. Spirituality can really help enhance people's quality of life. Another thing that can influence is the level of independence, whether you are able to do things for yourself or not. When you actually ask people, „What is the main thing that influences your quality of life?“, social relationships will often come out as the top thing.

We are social creatures, we need to be around other people and so social relationships do explain a lot of quality of life. And finally, physical health is a part of quality of life. But it is not all of quality of life. So, when we consider - wrong way - quality of life and what it is, we can see that, well, there is lots of things that are on that diagram that might impact people who are living with Usher syndrome. So, let's consider a few of those. Firstly, level of independence, will be something that might affect people who live with Usher. And Watters-Miles did a very nice thesis a few years ago, where they talked about something called ‚independent dependence‘. Where to maintain quality of life and to maintain independence, sometimes people would have to ask others for help with certain activities.

Something else that might affect level of independence in Usher syndrome is change and uncertainty. So, Usher syndrome is very different depending on the type that you have. But it is also something that changes over time, the longer that you live with it. There is a lot of uncertainty around, how that change might affect you. And there is a

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possibility, that as the condition progresses, that it might have an effect on level of independence. But ability to personally manage goals is associated with a better quality of life in people with Usher syndrome. And adaptation in particular, is something that can really help. So, there is research out there that has been done, interview studies, where people have almost prepared themselves for the fact that they might lose their sight.

So, they teach themselves Braille and they adapt to what is going to happen, so that they can maintain independence. And these ways to maintain independence without - I don't know - I totally lost my train of thought here, I got up 4.30 this morning to catch to the plane. And my brain is completely fried, I am really sorry. I just smoothly go on to the next slide. So, environment is something else that can impact quality of life. So, navigating environment is gonna be a key thing. When you look at interviews that have been done in people with Usher syndrome, uneven pavements can be something that can be hard to navigate, branches that hang down, cyclists, these are all things that can impact on quality of life.

Lighting is something that has been shown, can improve quality of life in people with Usher. So, something as simple as turning the light on in an indoor environment can really help. Communication is gonna be key, as well. So, not everybody will be able to communicate with sign language. And that can be quite difficult, when out and navigating in a new environment. Assistive equipment is something that can be really helpful, so there are vari-

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ous things that can help you use computers, people can find that canes can help, when they go out. Change and learning skills will also help, as the condition progresses. Adapting to and learning new skills will be important to help you to navigate your environment.

In terms of physical health, a lot of people with Usher syndrome have balance difficulties, which will invariably impact on their ability to go out and about. There is also work showing that fatigue and headaches can be issues, as well. And that is proposed to be linked to the fact that you have to concentrate so hard, to think on things that it can be really, really tiring, when you have Usher.

And there is also associated co-morbidities. So, some people might also have intellectual disability. Psychologically, there is work showing that Usher syndrome can be linked with higher rates of depression. In particular, depression is linked to the diagnosis, when you are told that you have this condition. That can be really hard for people. And also as the condition progresses and you start losing independence. So, I think, not being able to drive anymore for a lot of people is a key event that can lead them feeling quite depressed. There is also anxiety, stress and fear that can arise, as well. This is linked a lot into the uncertainty of what might happen in the future and the progressive nature of the condition. But it is not all about news.

If you look at interview studies, a lot of people with Usher syndrome have an incredibly positive outlook, they see

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it as a challenge. Something they can - they try - like this diagnosis empower them, rather than beat them down. So, there is work that shows us, that is not all doom and gloom. I think, that is one thing, I really want to get across here. A lot of researches focus only on the negative for some reason, but there is positive stuff out there, too.

Usher syndrome also has a big impact on social relationships. First thing that will come to most of your minds, will be communication. Whether you can communicate with other people and how you do so. People with Usher syndrome can also report feelings of loneliness and isolation which are linked to deafness.

But again, it is not all bad news. When you look at what is out there, people with Usher syndrome, peer connections, having friends, who also have Usher syndrome can be a really beneficial thing. To have someone else there, who understands what living with this condition is like, is good. And then your friends and family and social support networks are something that will really help improve your quality of life. It is something that will also have an impact on your family, as well. So, when somebody is diagnosed with Usher syndrome, they often are worried, about how it is gonna impact on their family, on their ability to look after their parents, when their parents get older or their ability to look after their children.

So, in terms of relationships there is a lot of work that showing that Usher syndrome and social relationships are linked with wellbeing. So, when we go back to this quality

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of life figure, we can see there is a lot of things that influence quality of life in people with Usher syndrome. So, myself and Gavin - (someone sneezing repeatedly) - bless you, I hope you are okay.

Really, we want to look at everything, but you can't look at everything. It is really ridiculous to expect people with Usher syndrome to sit down for two hours and answer question after question for you. So, we decided to focus our study on two main areas that we are interested in. Social relationships and psychological wellbeing. We wanted to see, how these were linked with quality of life.

The aim of this study that we did was to determine whether psychosocial wellbeing is associated with physical and mental quality of life in a UK-resident population of adults with Usher syndrome. We asked for people to take part, who had a diagnosis of Usher syndrome, were aged 18 or older and also lived in the UK. And, Gavin had links with SENSE, the charity in the UK. He had links with meet-up groups, as well. So, we were able to advertise through a lot of deafblind charities, through magazines advertisements, meet-up groups. We managed a 120 people, that said that they were interested and we had 90 people who ended up completing the survey for us.

The first thing that we measured was called 'health-related quality of life'. We looked at mental quality of life and physical quality of life. And we wanted to see what predicted these in people with Usher syndrome. So, we looked at their characteristics, their age, their gender. We

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looked at health-related characteristics, sight-registration status, deafness level and associated co-morbidities. We also measured depressive symptoms, we measured loneliness and we also measured social support. So, apologies for the next table, but I will just tell you about the main things to take away from this. In terms of age, most of the people that we had in our study were around 36 to 45.

60 % were of our sample were female, more women than men took part in our survey. And most people, 43 %, were employed or self-employed. Most of our sample had Usher syndrome Type II, just under half of the sample reported having that. But 11 % reported that they didn't know or they hadn't been given a type of Usher syndrome. Most people had severe hearing loss, 63 % of our sample. 70 % were blind or had a severe sight impairment. And most reported, that they did not have other disabilities or illness, 63 % had no other illnesses or disability. So, when we then looked at physical quality of life, we found that this was linked with how depressed people felt. Whether they had another chronic illness or disability and being older. So, this meant that the higher people's depressive symptoms were, the poorer their quality of life was.

Those people who reported having another chronic illness or disability were more likely to have a poorer quality of life. And those people who were older were more likely to have a poorer quality of life than people who were younger. When we then focused specifically on mental quality of life, we found that this was predicted by depressive symptoms, social support and loneliness.

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The higher somebody's depressive symptoms, the lower the mental quality of life. The more social support they had, the better their mental quality of life. And the more lonely they were, the poorer their mental quality of life. So, depression and loneliness, we found, were linked with a poorer quality of life and social support with a better quality of life. And I don't think, these results will surprise anybody in the room. But, what we really wanted to get across was that psychosocial wellbeing seems to be important for quality of life in people with Usher syndrome.

So maybe, it is time to start thinking to about health more broadly in people with Usher syndrome and to start thinking about psychological wellbeing and their social relationships. It has been good points to the study, we did. This is estimated, that there are around 10,000 people in the UK who have Usher syndrome. So, the fact we managed to recruit 90 people, I think, is a really good sample size. And we had a wide range of ages who took part, too. But we can't necessarily take these results and apply them to every single person who has Usher syndrome.

A lot of the people in this study were employed, a lot of them were female. So, we probably had an overall better functioning Usher population, than you might normally find. These were also self-selected people, there are issues with that, too. People who have more issues tend to put themselves forward for studies, where they can talk about those things. The questionnaires that we used, were short and self-report.

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To get a clinical diagnosis of depression, you are given an interview by a psychiatrist, and obviously that wasn't feasible for what we did here. So instead, we used a symptoms questionnaire of depression, where people would rate different symptoms. So, we might have overestimated depression slightly. And this is also a cross-sectional study, which means, it is a study that was just done at one point in time. So, we don't know, what it is leading towards. But I think, the main question is: Can we improve quality of life for people with Usher syndrome? And something that comes out of the literature quite a lot is that we need to promote the positive.

As all of us move through our lives, we are gonna encounter transitions that will affect us psychologically and socially. And for every single person, resilience is one of the main things that we can build up, that will help us to cope with these changes, as we age. Coping is gonna be really important, too. So, having a problem-focused approach to coping, has been shown to be much better for psychological wellbeing, than having what we call an 'emotion-focused coping strategy'.

And empowerment is really important, too. If you feel like your independence has been taken away from you by this condition, it is really important that you try to empower yourself somehow to improve your quality of life. So, take up a new hobby, do something that makes you feel good. Redirecting goals and adjusting is going to be key, too. So, it's not just Usher syndrome. All of us as we age are going to find that we can't do certain things.

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So, we might have to readjust our goals and adjust because of that. The key thing is: Don't just focus on the negative. Now, I am a researcher who has made their



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living looking at depression. And I am as guilty of this, as everyone else. But as researchers, we just tend to focus on what is bad. And I think, if we are going to improve mental wellbeing, quality of life, we also need to look and really focus on what is good. And peer and social support is one of those things that is good. It comes out time and time again, as being really important for the quality of life in Usher syndrome.

There is also a lot of work, showing that cochlear implants can benefit people in terms of quality of life, too. So, what we need to do as researchers, we need to take a more positive psychological approach. I think, this claim „seek

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and you shall find“, applies, when it comes to psychological research. If you look for the bad, you will find the bad. But if you look for the good, you will find that, too. So, we need to take a more balanced approach to how we look at this. We need long-term work. Most of what we have in psychological wellbeing in Usher syndrome is cross-sectional. But this is a condition that worsens over time.

So, how does that impact people psychologically? We need more work to tell us about that. And I am aware, that I have just talked about Usher syndrome, as though is one condition. I am very aware that there are very different types that affect people very, very differently. So, doing more work across different types in severities of Usher syndrome and looking at, how that is linked with quality of life, will also be really important. I think, the key message, I want you to go away with, as you go to lunch, is that health is more than physical. It is not just biology, health is how you feel psychologically and socially, as well. So, finishing off, I just liked to firstly thank the UsherVibe Group. They very kindly gave us root money, so that we could do this study. SENSE played a really big role in helping us to recruit people. Gavin, thank you so much for allowing me to do this study with you on Usher syndrome. And finally and most importantly: Every single person who took part in this study! And thank you all as well for your attention! (applause)

(Mark Dunning) So, thank you again, Kimberley! Not only was this a fantastic presentation, but I know, we kind of put you under the gun there. That was fantastic, so thank

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you very much! So, we have one more speaker, before we go to lunch. Thomas Lenarz from Hannover is gonna talk about cochlear implant technology.

(Thomas Lenarz) Ok, thank you, thank you very much for inviting me to be here and speak to you, on cochlear implant technology.

I want to briefly mention what hearing loss is. And what a cochlear implant is and what we can achieve in patients with Usher syndrome. So, when we look on hearing disorders. There are basically different types how hearing can be affected. This one is a so-called conductive loss where we have a problem for sound being transported from the environment through the outer ear and the middle ear to the inner ear. Any disorder like wax or perforation of the ear drum or on the small ossicles will cause that.

Now the true sensory organ is the inner ear where we have specialized sensory cells so-called hair cells, that transform the acoustic vibration into the action potentials of the auditoral nerve. So, it is a kind of mechanical, electrical transformation. And these hair cells are affected in so called sensory or cochlear hearing loss. Most patients with hearing loss have this type of hearing loss. Now hearing is also taking part of the brain starting with the nerve going through the brainstem, the midbrain to the cortex.

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There are different areas of the brain which are assigned to hearing. Now, we call this retro cochlear or neural loss. There are also combinations between sensory and neural, but this number of patients is smaller than this one. Now in Germany there are approximately 15 million people who are affected by hearing loss and about 12 million are affected by sensory hearing loss. So, one fraction of the hearing loss is congenital and hereditary - You can't see this, sorry, ok, good, then you can see this one, ok.

For the congenital hearing loss, which means we have some inborn reason for developing a hearing loss or you are already born with it. In children the prevalence is between 1 to 5 out of 1,000 children being affected. Now 70 % are genetic, there are some other reasons like infection, etc. but 70 % are genetic. And out of them 30 % are syndromal, so they have not only hearing loss but also other associated symptoms such as in Usher syndrome loss of vision. Now, for Usher syndrome it is important that we have the sensorineural hearing loss and the retinitis pigmentosa. The prevalence 1 to 20,000, there might be also some other disorders coming along with it and most important is, that we look not only to the loss of vision but also to the sensorineural hearing loss.

Now, before I come to this further just how can we treat hearing loss? Well, the good news is that hearing loss can be treated quite efficiently by different types of technology. Which type you use depends mainly on how severe your hearing loss is. So, when you go from mild to severe and profound then you probably need hearing assistance

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for mild loss of hearing. Or hearing aids if it is more moderate. Now, if it is severe that means that you have probably no benefit from hearing aid, then cochlear implants are the best treatment available. And this treatment can be very efficient depending on how early you give it to patients who are affected.

Now, Cochlear implants restores hearing by taking the function of the inner ear. And it is basically a two-component-system, one is the external part which is worn at the ear level. It is a microphone, it is a processor, that transfers the sound into a sequence of electrical pulses. There is a battery for the power supply. Then there is a transmission coil which transmits the electrical pulses through the skin to the internal part, which is implanted behind the ear. Then from this internal part there is an electrode cable or bundle that goes through the bone behind the ear through the middle ear, into the inner ear and there is the electrode located inside the inner ear. Now we look more in detail on this situation. You see here again the inner ear, - sorry, excuse me - the inner ear. Sorry. And you see here the electrode with different contacts.

Normally the ear analyzes the incoming sound in a way that high frequencies, high pitches are displayed here, middle pitches here, and low pitches are here. So, it is like a frequency analyzer. The cochlear implant now rebuilds this type of frequency separation. And the high frequencies are presented by for instant this electrode contact, middle frequencies by this contact and low frequencies by this contact. And in doing so you can activate different

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parts of the auditory nerve. The auditory nerve as you can see here, so, you see now, the different frequencies are going to the different electrode contacts. And with this the cochlear implant presents the different frequency information to the auditory nerve.

Now, the auditory nerve normally does not degenerate. This is true also in Usher syndrome where the sensory cells, the hair cells are degenerating but not the nerve fibers. So, the nerve can take these artificial electrical pulses and then give it to the central part of the hearing system in our brain and the brain can then take this information and the recipient can understand for instance speech. Now, there is a success story behind this Neuroprosthesis. There are more than 500,000 patients worldwide who have a cochlear implant. 50,000 are in Germany.

But you see, there are many more patients who could benefit from a cochlear implant, but so far have not being implanted due to many different reasons. So, when we look on the history in the late 70s of the last century, cochlear implants started with very basic technology. Patients could understand some sound. Today most of the patients who have a cochlear implant can understand speech. So, there is a true development behind it. And you see that it is just how many words a patient can understand, and this is the time the development in technology from the 80s until today, and you see there was a constant improvement by technology advances over the decades. It means today patients who get a cochlear implant are able to understand speech.

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The important thing is that of course you will get this cochlear implant as early as possible, that means as early as you need it. Because the brain must have this information right in time to understand the speech. And especially in children, in young children, it must have this information very early in life so that these children, who are born deaf can develop speech and language, can develop the ability to understand language and also to produce language. That is different to adult patients. Adult patients who already have acquired speech, they don't lose this ability. And then the cochlear implant can be given to them and they just can build on their memory what they already have learned.

So there are two groups, the one, those who are early deaf need the cochlear implant very early on to learn speech, pre-lingual as we say. Then we have post lingual deafness where you probably can reactivate your language memory by this cochlear implant any time. Ok. Now due to this development in technology it is possible to give a cochlear implant not only to people who are completely deaf but also to people who have still some residual hearing.

We see here a so-called audiogram, that means a diagram where you can display how good or bad somebody hears. This is measured by presenting tones, different tones from low frequencies, middle frequencies, high frequencies, and then you just present a tone with increasing loudness. And at the loudness level, the patient does hear then you make a cross and then you get this kind of

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threshold as we call it, a hearing threshold. Then you can measure how much is somebody affected by a hearing loss and then you can decide which treatment a patient should get.

Now, we see here a patient who still has some hearing in low frequencies and mid frequencies, but nothing is left in high frequencies. And today we also can give cochlear implants to those patients, who are not completely deaf, but who already have quite severe hearing loss. And they will get information back for instance high frequency information, which is lost due to the progression of hearing loss.

So, you see here the electrode replaces the hearing for instance in the high frequencies, the low frequencies are presented by hearing aid and the patient, so to say, can use both together on one ear, so-called hybrid systems. Ok, now in Ushers disease there are different types and depending on the type, the cochlear implant has a different role. Usher type I is the clinically most severe, it is basically starting when the child is born. Often there is congenital severe to profound hearing loss which means if the child does not get a cochlear implant early in life, that means during the first years, this child won't develop speech and language. And then will basically rely on some other communication channels.

Our goal is that we detect hearing loss very early which can be done by neonatal hearing screening, that means every child is tested for hearing right after birth and later

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on again during the first years of life. And once you have detected there is a hearing problem, then you can also do early cochlear implantation. The goal is audio-verbal communication based on language and on hearing and social integration. Now, you see here just three patients from our Hannover population of cochlear implantees.

Here, that is one child that had been implanted early, you see at the age of 1.6 years and this child with the cochlear implant does understand single words or sentences very well. 70 %, 90 % correct. That is very good. This person can use the telephone and communicate verbally with other people who just speak to them.

Now here you see other patients who basically did not get the cochlear implant early in life but at the age of 30 years, or here at the age of 10 years and so what you see is, they basically, they are not able to use the cochlear implant for speech understanding. It was too late for them to get this type of treatment. In Usher Type I.

Now we look on Usher Type II. There is a later onset of hearing loss. It starts at the high frequencies, I showed you this audiogram. Loss of vision starts during adolescence. And basically these patients are diagnosed with hearing loss while this hearing loss develops in their life. And here, we also want to give them a cochlear implant as soon as the hearing loss is severe, so that hearing aid does not provide enough speech understanding anymore. Here we want to avoid the loss of communication abilities. So, somebody who already does use language,

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he should be able to do this even in the future and not convert to some other communication channels. And this also of course will then avoid social isolation, so that goal



of treatment is preserve societal integration. Now we see here a group of 15 patients we did follow over a longer time and you see these patients have either got the cochlear implant on both ears or only on one ear.

And again, you see that many of them have very good and high percentages of speech understanding. So, it means that in Usher Type II, cochlear implant is very effective to preserve speech understanding and the use of speech for communication. Well, Usher Type III is very rare, it is mainly in Finland. They also have hearing loss starting in childhood with progression. Large variability of disease and here it is basically the same as in Usher type II con-

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cerning cochlear implants. The patient should get it once the hearing deteriorates, and the patient has no benefit from the hearing aid anymore. Usher Type III, you see again here, very good scores for speech understanding in these patients. And then there is a kind of mixed Usher Type, where we also have normally good results with the cochlear implant. So, in conclusion cochlear implantation is a successful treatment option for hearing loss in patients with Usher syndrome. Early diagnosis and treatment is mandatory to achieve the treatment goals. Usher Type I, audio verbal speech and language acquisition is possible and is the goal.

Usher Type II, adequate timing of cochlear implantation to avoid loss or disruption of communication and the social isolation and Usher Type III is basically like Usher Type II. Ok, now in the future there will be other possibilities coming together with a cochlear implant. We want to basically tailor the treatments to each individual patient, so that we can make the best choice for everybody meaning to go to precision medicine. This means that all the diagnostic information we have from one patient is audiometry, the information we get from imaging, that means the computer tomography and magnetic resonance imaging. On genetics this all will be taken to make the right prediction how the hearing will develop and what the right time and type of intervention is.

Now, this means that we also use data from many patients in order to build up comparative data base. A cohort of hearing impaired patients, among them are also many

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Usher patients and taking this information from other individuals we will be better in predicting what the individual patient will need. And then of course you also can become very precise in for instance how you do a cochlear implantation, when are you doing it and how deep you for instance insert an electrode and while you insert that you also don't damage the inner ear. And we do it like in a robot system very precise. So, that is something which will come very soon.

There are other treatment options that will be added to the cochlear implant and we call it advanced auditory implants, that means we want to have a better contact between electrode and nerve. Means, that for instance the nerve can regenerate and grow directly onto the cochlear implant electrode. This will improve the hearing with the cochlear implant. That means many more information channels. Now, this can be probably achieved by adding stem cells taken from the patient during surgery, stem cells which are brought onto the electrodes. We also can put on drugs. Drugs that stimulate this nerve regeneration.

We also can put on genetic information, gene therapy so to say on the electrode. Here you see those coated electrodes where stem cells from the patient have been taken in order to protect the nerve, protect the residual hearing and also modulate immune response to this foreign body. And this, you heard already about, will come along with already running gene therapy studies where we try to stop the progression of hearing loss for instance in Usher Type II.

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So, the gene therapy will aim not to grow new hair cells, but to preserve the still existing ones. And this is the next step that will be taken. Ok, so Kant, a German philosopher said, „Not to see means that we are separated from things, not to hear means that we are separated from people“ And that is basically what we already can tackle in also Usher syndrome patients. A lot of research is going on for this purpose. Here in Hannover, I just want to mention the members of our team, who are doing this kind of research for the auditory system of the future and those who are interested, we have very soon a conference, where also some of this work will be shown. Thank you very much for your attention. (applause)

(Mark Dunning) Thank you very much, Thomas, ok, so we are going to take a break for lunch, lunch is - you go out the back door and you take the left back where we had the coffee break. You will find the food there. We are going to take an hour break for lunch, so we are trying to have everybody back here by 2.30 timeframe. And one other thing we are asking for people to make statements, if you walk out the door and take a right, you can make a statement about how things are going here. Yeah, 2.30, yeah.

(lunch break)

**(Sebastian Klaes) Ok, let's start.
Please take a seat. We will go on**

MARIYA MOOSAJEE

with our next session. Inclusion through innovation.

When we started with the first planning for our symposium, maybe 2 years ago, there we thought we should create a platform for companies and upcoming products with interest for us Usher people. So we decided to start with our session, or to create a session inclusion through innovation.

Now we have four companies, or four approaches, very interesting things which will show us their newest approaches and products. Our idea is that we are going to have 10 minutes talks, or 10 minutes presentation and after the presentation we have time for a few questions. Our first presentation will be hold by Mariya Moosajee, she is coming from the Moorfields Eye Hospital from the University College London, so, are you ready?

(Mariya Moosajee) I am ready.

(Sebastian Klaes) Ok, then.

(Mariya Moosajee) So, good afternoon ladies and gentlemen, I wanted to say thank you for inviting me to speak at this conference. The last two days of the

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scientific meeting have been inspirational and very informative.

I think there is a real push that it is moving towards clinical translation and therapies. Today I am going to talk about clinical trial design for nonsense suppression therapy for USH2A Ushers disease.

So, to start with, I am just going to quickly go over what a nonsense mutation is. Now this is a single change in a letter in your genetic code within an instruction part of the gene that leads to the introduction of an abnormal stop signal. And these are quite common mutations, they can account for up to 70 % of human genetic disease. Now, what happens in your cells normally is, you have protein making machinery, that reads the instruction parts of gene to create protein. When you have a nonsense mutation or an abnormal stop signal, when your protein making machinery hits that stop, it just stops and so you end up with shortened non-functional protein. This is what ultimately leads to the disease process.

What we have done, we have identified a number of small molecule drugs, the one I am going to talk about today is Ataluren which has been commercialized by a company called PTC therapeutics. But when the drug Ataluren binds to the protein making machinery, it weakens its recognition of the abnormal stop signal and can overwrite it, leading to the production of normal full-length protein. And it is able to do that, so it generates around 20 to 25 % of

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normal USH2A or whichever protein that you are missing, and that can be enough in our patients to actually hold or slow the disease progression down.

Ataluren has a large body of evidence for various different conditions, multi systems and including retinitis pigmentosa and genes such as USH2A, USH1C and various others. It has approval for treatment in Europe and in the UK for Duchenne's muscular dystrophy, for patients which have nonsense mutations. And the drug itself is safe and tolerable to be used in children from two years onwards. It's a powder that is, that is dissolved in water and is drunk three times a day.

So far, there have only been minimal side effects, so transient diarrhea or nausea when you first start taking the drug, which subsides after about a week. But there have been no serious adverse effects or any serious ocular events and they have treated nearly over a thousand patients with 5 to 8 years follow-up now.

And currently there is a phase 2 clinical trial for aniridia, a different eye condition where children are born without the colored part of their eyes, their iris, and they develop cataracts, they have glaucoma. They can have wobbly eyes, nystagmus, they are born with poor vision. So, this trial is on the way and we hope to see the results of that in 2020. Now, we want to apply this drug to Ushers and in order to do that in a clinical trial setting we need to know what the outcome measures would be, so we can monitor a response to treatment.

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So, what we started to do was a natural history study of our patients with USH2A. At Moorfields we selected 57 patients that had on average three clinical visits one year apart. So, we have many more patients, but these were ones with good data sets. And of those 57 - they were almost equally divided - a third had nonsense mutations. That is a depiction of a cohort generally in Usher syndrome Type II, USH2A, 30 % are due to nonsense mutations, and then a third were insertions and deletions and 17 were missense mutations.

The average age of that cohort was 40 years and it ranged between patients that were 15 to 66 years of age. The first thing we did is look at their visual acuity, their central visual acuity. And there is a graph behind me on the screens, there is a lot of blue dots and a lot of lines connecting it, but essentially, if you can see there are quite a few horizontal lines which means that over time their vision didn't change very much. So visual acuity isn't the best indicator of a treatment response over a minimal period of time.

We then looked at another parameter, something called optical coherence tomography or OCT, it's a scan that most of you will have each time you go to see your clinician. And it is where we shine infrared light into the back of the eye, we take a cross section. We measured the area where you had intact light sensing cells, your photo receptors, and we measured that area, it is called the ellipse width zone length over a three year period. What we found was that on average across the whole range of pa-

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tients we detected a 7 % reduction in that size of length of the ellipse widths zone, over a one-year period, but a 22 % change over three years.

So, we are detecting a change every year, but the issue that we have is that there is a measurement bias, an error that is introduced by people who are measuring that length. So, to be absolutely accurate, we felt that a one-year time point was on the curve of where you would detect a treatment response. But if you look at the graph as well, you can see that if we looked at patients younger than 30 years of age - The dots indicate a patient and the lines joining them are the change over time.

The younger patients have more steeper lines, showing a steeper decline, whereas the older patients that were 30 plus, their lines are much more gentle. There is not much change going on. So, if were to do a trial, the best cohort to detect the biggest change would be the younger patients.

Another imaging modality we looked at is called Fundus autofluorescence. Again this would be routinely undertaken in your clinic visits, where we shine a very bright flash of light into the eye. And in Usher syndrome we get this characteristic bright ring around your area of central vision. And we can draw a line around that ring. And that ring, the reason that it's bright, is because that supporting layer of your light sensing cells, called the retinal pigment epithelium it has a buildup of metabolite products that cause it to hyperfluores, and this is showing that the

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cells are present, but they are sick. They are not working very well, because they are burdened by this buildup of product, and so they autofluoresce, they shine brightly.



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Now, over time, those cells that were under stress and are sick and are dying off, so that ring is encroaching into your area of central vision and is getting smaller over time. We measured it at one year and at three years, and we found that on average there was an 11 % reduction in that ring size over a one-year period and after three years a 32 % change. So, this is probably a better parameter than all of the others, but if we combine them all we are more likely to be able to gauge an effect.

So, then we come to the clinical trial design. So, we had patient discussion groups at Moorfields and some of the

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members that came to that are actually in the audience here. And one of the biggest things that they said was they didn't feel comfortable with a trial where you were treating a set of patients and giving the other set a placebo and not giving that other set of patients the opportunity to ever have the drug treatment.

So, we decided to have a cross-over trial. One, because this is a rare disease and we need to maximize the number of patients who are on treatment. But we are giving everyone an opportunity to be on the drug, but also it will inform us about what happens after you stopped the drugs. By having a group that is on Ataluren and then having a small wash-out period, - the drug can be washed out of your body system after just a month - and then just following those patients on the placebo, we will be able to see if the change of decline, the rate of ring constriction or loss of light sensing cells remain stable or when they start to decline again. And we felt that we needed a two-year period to be absolutely safe, to be able to gage whether there was a change at all.

So, this is what we decided: Around 20 patients would be on Ataluren and 20 would be on a placebo, and then have a wash-out period. Then the patients that were on the placebo will then be given the drug, to see if that would slow down their degeneration and the other 20 patients would continue on a placebo and we would monitor the effect of the drug. For the outcome measure the trial, this drug has never been tested on a population with retinal disease, so working with the company it was felt that the

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primary outcome measure should be safety to ensure that there were no adverse effects. And as secondary outcome measures we would consider measuring the auto fluorescent ring size, using OCT to look on that ellipsoid zone. But we would also look at visual acuity, because even though those cells which were brightly fluorescing, were sick, they were still alive, and if we could provide protein to them, by mechanism of the drug action, then maybe they would start working better and maybe the vision would improve slightly. So we wanted to include that.

And then there were a number of other tests that we would include as exploratory parameters, like visual fields, color vision, adaptive optics. So, how can you get involved? The first step always is to establish your genetic diagnosis. If you don't know the gene that is causing your condition I urge you to seek out your clinicians to get genetic testing. If you do know the gene, then it is important to find out what type of mutation.

Because if you have a nonsense mutation then this therapy may benefit you in the future. And the fact that this drug works on a mutation, it doesn't matter what gene causes it, or what the name of your disease is, if you have a nonsense mutation, you may benefit from this. And if the trial is successful, we hope to move to a phase three clinical trial, where we involve patients with all different retinal disorders caused by nonsense mutations.

If there is a natural history study on the way, near where you live, please participate in that, especially if you

are unsure about going into treatment trials. Because by allowing clinicians to study your disease, it gives us insides, it helps us to develop therapies and it helps us with the outcome measures with trials. And if any of you have any questions or you would like me to check your genetic mutation, then please feel free to contact me, using my e-mail address which is mariya.moosajee@moorfields.nhs.uk. And if you need that, I am sure that the Usher conference will circulate that. And so with that I would just like to thank my team and special credit to Dr. Adam Dubis, who really lead on the natural history study. Thank you very much. (applause)

(Sebastian Klaes) Thank you very much. We have now time for, I guess, one question. I don't see any hands. So maybe you can also use the opportunity to write Mariya an e-mail, so please feel free. Then we should now go on with our next short presentation by Annamarie Dillon, she is coming from ProQR Therapeutics, it is a small biotechnology company in the Netherlands, and she will tell us something about gene therapy for Usher syndrome type II. So. You are ready? Ok.

(Annamarie Dillon) OK, we are on? Everybody can hear me? Great, first I would like to thank the organizers for the opportunity to come here today to provide you

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with short updates on our QR-421a program that I'll walk you through in a moment.

Just to let you know, that as a publicly traded company this presentation will include some forward-looking statements. So, as it was mentioned, ProQR is a Dutch biotech and we are based in Leiden and our approach and therapeutic strategy within the company is to really try to have a patient centric approach. We are focusing on rare genetic disorders, where there is a med need and currently no treatments available.

It is also important that we understand the cause of the disease for which we hope to develop RNA therapies that we will be able to deliver locally to the target organ, so in this case it would be the eye. I included this slide just to provide a very high-level overview of drug developments, it is a very busy slide, but it's just to highlight the lot of the different steps that have to be taken. From a drug, taking a drug candidate to pre-clinical testing and all the different steps through clinical research.

The studies that will have to be performed to better understand the drug candidate and to make sure that it is safe and that it works and to be able to submit the dossiers to the regular authorities for the approval. And ultimately that physicians will be able to prescribe it for their patients.

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This is just an overview slide of our ophthalmology pipeline. So, we have several programs currently in development at different stages. Our most advanced program - we heard yesterday, for those that were there - is for Leber's congenital amaurosis type 10, and for the compound called QR-110. It is exciting for us that we'll expect our first clinical results of that later this year. The next program moving towards the clinic is our program for RP exon 13 mutations. We have some other work ongoing more in the discovery phase.

So, just a brief introduction to QR-421a, it is a bit of a mouth full, I grant you that. So, we are trying to develop a RNA therapy, it is working on the RNA and not the DNA, to treat the eye symptoms, so the retinitis pigmentosa. I am not sure what went wrong there. The therapy will target mutations in exon 13 of the USH2A gene, so it is a targeted approach. And there is many different mutations within exon 13 and there is a public available data base listing those out. Building on the work - I think the sound is gone? It is back again? Building on the work from Aron van Wijk and his team in Nijmegen we are moving this program forward. This shows a cartoon, here on the left is a healthy photoreceptor, where there is no mutations for, RNA is translated in usherin protein, which is important for the maintenance of the photoreceptor.

In the middle cartoon we have a situation where there is a mutation present in exon 13 whereby the RNA is broken down. This absence of the usherin protein leads to retinal degeneration of the photoreceptors. Can people hear

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me, because I don't hear? Ok. This third picture is just an illustration to try to show what our approach and treatment strategy is to remove exon 13 from the pre-RNA, so that the messenger RNA, that will be produced will be slightly shortened, but we expect to be functional. So in a way to maintain the photoreceptors.

So, with all of the work that has been done to date, we are fast approaching moving this program into clinical trials. The primary objectives of this clinical trial, which we are going to be calling Stellar, will be looking primarily at the safety, tolerability and effectivity. We will be looking to see if it will have some effect of QR-421a in adults with RP and in mutation in exon 13.

So I can only echo what Mariya mentioned earlier about the importance of understanding and knowing what your mutation is because as more clinical trials, not only this clinical trial, but future clinical trials we see more and more clinical trials focusing in on certain mutations. We have on top of doing all of the different safety tests and making sure that this is safe we will also see if it'll have some impacts if we can check that an efficiency with regards to vision. I can't share a nice diagram of the clinical trial design today, we are still interacting with the regulatory authorities so what we can say now at this moment in time, that we hope to finalize this very soon.

It is good to mention, that we envision that QR-421a will be administered through an injection into the eye, called an intravitreal injection. We will also be looking at dif-

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ferent dose levels within the patients, and for this first study we will only include adult patients with mutations in exon 13. We hope, as mentioned earlier in the meeting, to move this program before the end of the year, that we hope to start it and start recruiting participants into this study and we hope to be able to share more information next year. That we will have some data, clinical data, that we will be able to share. And the study as foreseen now will be conducted in North America and Europe.

It is also very heartwarming to mention that we have been working and that we have the support of the Foundation Fighting Blindness, they are supporting us financially with this program, and we are partnering with them moving this program forward. And also it is good to mention that we have been interacting with representatives of the Usher community these past months. Before we even talked about writing a protocol we had an advisory board earlier this year, with representatives both from the international Usher community, but also from several different countries in North America and across Europe.

This was extremely helpful for us, as we started thinking about the design of the study. And any time we have questions, representatives that we reach out to are very gracious with their advice and support to us, so I wanted to say a big thank you for that. If you would like to stay updated on where we are at, and how the program is moving forward, I would encourage you to just periodically check our website as we will keep that updated with the latest information. And once the clinical trial is on clini-

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caltrials.gov, you will be able to see a full list of participating sides as well. With that, I think I am on time. (applause)

(Sebastian Klaes) Thank you for this update. Yes, are there any questions? Ok, then we will go on, we will change a little bit and we left the area of the biomedical approach or product, then we are now more going in the field of the retinal prosthesis and implants. The next presentation will be held by Dorothea Kohlhaas, she has an Argus implantation or prosthesis and she will tell us a little bit about, your Argus system by second sight.

(Dorothea Kohlhaas) So thank you very much for giving me the chance to talk about my experience as a user of a retinal prosthesis system called Argus II.

My name is Dorothea Kohlhaas, I am from Germany. I am totally completely blind because of retinitis pigmentosa. I am not the only user here today from this system, from Argus II. I have brought two colleagues, one is Gabi Gätjens, she does have retinitis pigmentosa, too, is totally blind and is using Argus II. And the second one is Volker Tim, he has got Usher, is using two hearing aids on both sides and is using the Argus II as well.

First of all, I just want to tell you a little bit about the

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technique, I am not an engineer and I am not a doctor, I am a user, so, but I just want to let you know how it works a little bit. So, I have had a surgery about 3 hours in a clinic in Cologne, and I got a little implant on the retina. Then I have been out of the clinic 10 days later. I got a camera, glasses with a tiny little camera on and on these glasses there is a swell on the left side, where my implanted eye is, because only one eye is implanted.

I have a little antenna and there is an induction coil, then I have a little cable, a cable which goes down to a little computer, a VPU, this is to switch on the system, to change filters because I can use three filters with this system. I have one normal filter, I have one to increase the contrast and I have one to make it easier to find a board or something like that.

That's the technical part of this, like I said, I am a user, and I think that is the most important thing why I am here. And I want to tell you what is the benefit out of this system? What am I now able to see. Well, see, to see is a high word. I want to say I can perceive something. Because it is not a natural vision I got back, it is an artificial vision. With this artificial vision I am now able to perceive obstacles for example.

And you may ask, yeah, but what do you see? What exactly do you see? And this is very difficult to explain, because we just have a light flash or a light point some people say, and you have a face field back from about 20 degrees. Many people say, ok, but it is not a natural vision what

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are you going to do with this? And I say, well, for me - my life changed because of the system, because now I have a better orientation and mobilization.

Like I said, I have been totally blind before the surgery and now with this system I am able to be in a room, which I don't know, for example, and I can perceive windows, for example on my right side. Or lights or now I have a lot of flashes in front of me, these are the people sitting in front of me. I can't see if it is a person or whatever, you could be a tree, or just a chair or whatever you want. But hopefully you are people. So, I am talking to nice persons here.

That is the first thing, so, after surgery we have a special rehabilitation where we learn how to use the system. We have 30 lessons in low vision, that means, we will be shown how the system works how to move the head. Because with this system the camera is now my eye and I have to move the head to get any perception, so we have to learn that, but you get so easily used to that, that it is no problem anymore after a while.

Then you learn to you make your first steps, for example, there is a black screen in front of you and on this screen, you find white squares about 3 cm. And you have to find these squares on the screen and you have to touch them with your finger. This test is done before the surgery. When I did this and tried to touch a square on the screen, it was just like the computer voice always said, „no“, „wrong“, „wrong“. And after that when I had switched on the system the first time and I did this test again and the

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computer suddenly said „right!“. „You are right!“ This was amazing for me. It just, yeah - to remember this is still amazing for me.

Then after the low vision you have an O and M training, orientation and mobilization training, you go with a specialist outside to learn to use the system outside. With this Argus II, you have great help, but it is not possible to go out only with the system, you have to take your cane or I have a lovely little dog out to help you as well. But it is a very, very good help, because now outside I can perceive for example the pavement board or the white crossing stripes. I can find that and I can safely cross the street. And can give my dog better orders where she has to go.

Or you find it, when you are away, you always go for example to the bus station. You can make yourself some marks, for example there is a big building, a big tree or a white sign, something like that. You can see, aha, there is now I can perceive something there, this is the white sign or the, the building, now I know where I have to change the street, for example, have to go right or so, that it is easier to be outside. For me this is a great help, because before I was blind, I loved to travel a lot, and then I got totally blind and was really sad, because it was so difficult to do that again on my own. But now I am safer with the system and I can do other things again.

I can perceive stairs if the contrast is quite good. Inside in the house I use it often to do the householding. I use

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it for example when I do the ironing, because it helps me perceive the, that there is maybe a shirt, I can't perceive the shirt, but I can see where it starts or where it ends. And I can see the movement of the iron, so I don't burn myself so often anymore.

Or to distinguish clothes, I can, I have no colors to see, it is just black and white and some shades of grey, but I am able to see if there is dark socks for example or bright socks, so I can distinguish them and I can sort them out better. So, for example things like that, this in a household.

Yeah, and then I have some special highlights, which I really, really love because now I love to see a firework. But I couldn't do it anymore, which was really sad for me and then I have been out to a festival and there was a firework and I switched, I had the glasses on, the Argus II system, and the firework started and I could perceive it. It was so great and amazing for me to do that again.

I can't see, like I said, I have no colors, but I can see a flash, a big flash or there are very nice fireworks who do rain down, so I could perceive that, the raining down from the fireworks. And it was, I cried. I have to say, I really cried. Or, I have been in holidays at the sea and I could perceive the waves again on the sea. That was amazing for me or just my husband is a good help, he always says try this and try this and that. So he is really nice with that, he said, „Why don't you try to find out if you can see the white clouds in a blue sky?“ And I said, „Oh, I don't know

if this is possible“, but it is. So, I stayed and looked in the sky and I could perceive where is the cloud, where is the sky. But you should not do it while you are walking. This is - this is a bit difficult. So, Argus II for me - I am really lucky to get it, that I was able to get it, I have to say for me life changed, and I have a better quality of life, it really changed a lot. Ok. My time is over. Thank you very much.

(applause)

(Sebastian Klaes) Yeah - thank you very much, there is just one more information you have one or two other persons with, the second sight system, so one person with Usher syndrome wears also the second sight system, you can meet them in the break. At the yes - ok. Thank you.

(Dorothea Kohlhaas) You are welcome.

(Sebastian Klaes) Ok, then we are now going on with the next presentation by Alfred Stett from Retina Implant AG, in the morning we have heard the presentation by Eberhart Zrenner. And Eberhart Zrenner founded in the end of the 90s a company called Retina Implant AG, Mr. Stett, are you ready?

(Alfred Stett) Yes, now I am ready.
So, thank you very much to have the opportunity to introduce our system.

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Frau Kohlhaas, it was a very great presentation of your capabilities that you got again with your Argus II implant. So, I am very impressed. The Alpha AMS, you already know



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from the talk Eberhart Zrenner gave in the morning, retina implant developed two systems for people suffering from retinitis pigmentosa. One is the OkuStim therapy, that is intended for people that are not blind, it aims that to shift the curve where the visual field decreases in the future and for blind people we made this Alpha AMS available.

As Eberhart Zrenner mentioned already, it is a subretinal implant in contrast to the Argus II implant, we just heard. It is a small light-sensitive chip that it is implanted in the center of the retina beneath the fovea and with this chip people can have back some kind of vision comparable to

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what we heard already from Mrs. Kohlhaas. This chip contains 40 by 40 pixel and each pixel picks up a part, a small part of the image that is projected to the eye. And each pixel injects a small amount of current into the retina.

This chip is in close contact with the retina and by doing this stimulation so-called phosphenes are evoked in the patient. This system does not contain a camera, so the camera chip is implanted subretinally. Externally components are this handheld device, that contains a battery and some means for control contrast and stimulation strength. So, with this implant this natural path of image projection onto the eye and processing within the eye can be used. So it is hardly noticeable, it doesn't need any external camera, as I mentioned before. So, this enables the patient to use the natural eye movement and micro saccades to localize and fixate and follow objects, which are important for object recognition and for giving the eyes a base resolution.

So, as we heard already in the morning, we did a number of clinical studies to show that the implant is safe and is able to provide useful visual perceptions to blind patients, that you can see in the papers and you saw in the presentation of Eberhart Zrenner in the morning. The studies are mostly concerned with so-called vision function. There the capabilities are measured, spacial acuity and so on. But for daily living it is not important how patients are good in recognizing a Landolt C rings or so on, it is more important to be able to use the implant in daily living situations in order to recognize a cutlery on the desk or

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find a way through openings or find the profiles of buildings and so on.

So, each person has an individual situation where he is most impaired by his blindness. So, we are looking on these situations and we learned that the benefit the patients have from the implant is not similar from patient to patient. So, we also learned and got this feedback from the patients that the daily use and the frequent training is very important to create personal benefit. So let me quote one patient, he said: „The chip is comparable to a relationship. If I am only passive and expect the chip to do wonders and solve all problems, then it does not work. It is about the willingness to deal with it. This creates activity and finally personal benefits.“

This is the way to get familiar with this artificial vision, we already heard from Frau Kohlhaas, so it is not a natural seeing. It is an artificial seeing, and the patients have to do exercises and have to use it frequently to get the most out of the implant. So, we developed an after-care concept. It is a vision rehabilitation concept.

Our patient start training, up to a year, intensive training up to a year in the domestic environment, at the home of the patient in order to optimize the stimulation parameters. Doing training at home for localizing and recognizing objects, identifying grey scales, hand-eye coordination and so on. Also important is doing an outdoor training, where it is trained to identify houses, trees and street signs and to recognize obstacles and moving objects.

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So, we learned also that it is very helpful to not only learn to see but learn to see together with some haptic tools. So we provide the patients some kind of light box and stencil-like objects, so the patient can touch a triangle or square and can correlate what he feels and what he is seeing. So he is learning step by step, what does it mean, what object is it that he is perceiving with the implant. So and then, also very important is to do training outside, and inside, so the ability to train mobility is very important. Here you see two situations, one indoor, where the patient is going through the doorway, we saw him bumping through the door frame. And on the right side you see exercises, he learns what he is seeing, he is able to recognize both road sides together. So it is very natural moving he is learning here.

And the most surprising experience we were reported by a patient, he was able to combine what he is seeing with his memories. So he writes that he was travelling on the North Cape, and he said, „I could walk around on the ship as my device was scanning the light dark contrast with the chip.

It was quite interesting, whenever we were sailing through a fjord I could scan the sky and notice where the rock would begin. This way I could precisely trace the shape of the fjord.“ „And all of a sudden, the contour filled with color - without any eye sight.“ So, to be honest with our implant it is not possible to see colors, but he remembered how the color was when he was there when he was not blind, he learned to combine these impressions evoked

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by the implant with his memories. Taking all together we are sure this electronic device makes a difference, retina implants Alpha AMS makes a difference.

So electronic devices today are available, are CE marked are very helpful aid for blind people suffering from retinitis pigmentosa. I hope you saw that this implant helps to increase independence in daily living, supported by the use of natural eye movement and hand-eye coordination can still be used. So, we have established a rehabilitation program to foster the use of the implant and the integration of daily living situation.

And very important, the treatment in Germany is covered by the health insurance. Let me end my presentation with a quote of another user of the implant, she said, „I was walking down this country lane, I did not have my white stick with me, I did not have my dog with me and suddenly I thought what am I doing here? I am walking along the road on my own.“ And that is what we want to have, that people get back some kind of independence. Thank you very much. (applause)

(Sebastian Klaes) Ok, thank you very much. As I have seen, you have also a stand in the main hall and so if someone have detailed question, you can ask –

(Alfred Stett) You can come around.

(Sebastian Klaes) They can ask at –

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(Alfred Stett) At the counter, yes.

(Sebastian Klaes) Ok, thank you very much, now we are going on, we will change the moderation to Dominique.

(Dominique Sturz) Thank you, Sebastian. ^(applause) Hello, so good afternoon everybody, I hope you are still awake, because we expect two very interesting and inspiring presentations, first, the first presentation is going to be held by Julia Moser presenting us her patient's view on Usher syndrome.

(Julia Moser) So hi, hello, good afternoon, everyone, thanks very much for the invitation, I am very happy to be here and to meet so many of you.

When I was 4 years old, I got my first diagnosis and at the same time I got my first label. Doctors told my parents that I had a severe hearing impairment, I had not really developed any language by then. They also told them that, and that was the label I would not develop any language, it was too late and I would not go to school. So, life options didn't seem all that bright. And at the age of 13, I got my second diagnosis, and again, I also got a label with this. That was the time when I learned that I have Usher syndrome and the doctor who told me this also told me

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at the same time, that I would go blind I would not really have a career option. I would not have many options, family, kids, if I did decide to have kids, they would probably have Usher syndrome, too.

So, these two experiences really did have a huge impact on my life it really impacted on how I viewed myself as a person. My identity was questioned and I think there were two things that really came with it, one was to try even harder, because I did not want this to come true. And the second was, what I learned, I had to hide. I had to hide that I have Usher syndrome, because only then I would I be entitled to a happy life and to the life that I wanted to life. I was lucky, because my parents did not believe those doctors when I was 4 years old.

I got my first set of hearing aids I got speech therapy and when I was 6 years old, I went to primary school, local primary school, small village in the countryside. I was the only kid with a disability, it worked fine. I think that was also down to the fact, that I loved books and I loved reading and this really compensated for a lot. When I didn't understand what was spoken around me, I could always rely on books. I then later moved on to grammar school again, reading was really, really important to me, so I was actually able to get the education that I wanted, I loved going to school. And when around the time I was 12 years old puberty kicked in, I started feeling very self-conscious about my hearing aid. I hated them, only grandmothers have them, but not 12-year-old girls.

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I wanted to be normal, I wanted to be like everyone else. And soon after that, I found out that I was also short sighted, and I got my first set of glasses and I loved them, because glasses, that was something my friends had as well. And I also thought that diverts from the fact that I have hearing aids.

And then about a year later, when I was 13, my mother had noticed I tripped over a lot and at night I didn't really see that well. She took me to the eye doctor, I was with her to hospital, tests were taken, and they told me that I had RP and then they referred me to a geneticist and that was when I first heard the word Usher syndrome. The geneticist told me, he did nice drawings, lines and a little defect gene and not defect gene and how it all worked. And he explained to me why I had Usher syndrome and why no one else in my family had it, that was the time before genetic testing.

But he didn't only diagnose me with Usher syndrome, he also labeled me, because he then said, you will go blind, you should really choose a job that is suitable. I asked him what job that could be, I was 13. He didn't have an answer and instead he told me, that my kids will have Usher syndrome, too. And he had not got the facts wrong, because he had told me about the inheriting pattern, but what he meant was that if I did find I partner he will certainly have Usher syndrome, because I would meet him in a patient organization. ^(laughter) I did not join a patient organization for a very long time. ^(laughter) Well, I went back home, I was shocked, and I am sure my family was sho-

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cked, too. We did not discuss this issue very much, it was there, but it was also a bit of a taboo, it was not something you like talking about I did not have much information. That was the time before the internet.

We had one book at home, a thick book, family health, lots of diseases, there was one tiny paragraph on RP and I kept reading it, reading it, looking for clues about what my life would look like in 10 years, 20 years. I did not have any more information, I did not have any contacts, I didn't want them, yeah? And then I thought okay, this disease progresses very slowly, surely there will be a therapy option by that time, I relied on that. And then I started doubting, what if there was no therapy option in time, what would I do? I do not want to go blind. This was not something I could imagine.

So, I needed an exit strategy and what I decided to do then, was, I was 14, 15 maybe surely it would be better not to live at all than to live with Usher syndrome. This sounds horrible, I know, but, this really helped me, because I did not have to deal with what might happen one day, it really enabled me to focus on the present, on the life that I have now. So, it did help.

So clearly I lived in denial and I lived in denial for a very, very long time. And when I thought about my experiences with Usher syndrome and about my life with Usher syndrome, I recognized a model that describes the stages of grief, people go through when they lose a loved person. My eyes were to me like a very dear friend, my most im-

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portant friend, because my eyes compensated for what I didn't understand. So it really did feel like I had a friend who was very sick and who would die. And the five stages, that were described are denial, anger, bargaining, depression, acceptance. So, I did live in denial for a very long time, I don't think I ever had a clear stage of anger, I don't remember that. what I did certainly have was the stage of bargaining.

I started thinking about whether I could trade in my disease against something else. I grew up in the Austrian alps, I did not like climbing, as opposed to my parents who did that a lot, I hated it. But there was this very distinct mountain that I saw every day, I thought, maybe if I climb this mountain every day, - an exhausting day trip, 9 hours - if I climbed it every day and didn't have Usher syndrome that might be an idea. Then I thought every day, no, maybe once a week. But I never tried. Because I came to the conclusion that maybe a life doing something I don't like at all and not having Usher syndrome might actually be worse than having a life with Usher syndrome and doing things I like.

The problem I had then was, how you can still do the things you like, when you go blind. I didn't have any role models, I did not know that it would be ok to be visual impaired. I didn't know that it was possible to live with an impairment, with a disability, so I went back to denial. I completed grammar school and I then went abroad. I worked a lot because I always felt rushed, I felt like I have to complete my tasks as quickly as possible before it

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was too late. I completed a university degree, and when I came back to Austria, I considered my options again and said ok, and then decided to go for legal studies, because



I thought legal studies could be compatible with Usher syndrome.

And I think looking back, this was one first step of acceptance, because I was looking for alternatives, I was thinking about ok, what can I do to provide for the fact that my vision gets really bad. What I still didn't do was get open about Usher syndrome. I didn't talk about it, I still denied it most of the time, I thought, ok, let's live in the present, who knows what will be in 10 years' time whenever. I then started my career at a lawyer's office and I also started a family. Soon after that. I was not in any patient organization which wasn't too difficult in Austria, because

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there was no patient organization on Usher syndrome.

My kids are now 10 and 7 years old. I think, having kids was actually really important to me, because kids accept people as they are, and they ask questions. And I was forced to give answers. And these really did quite a lot. But what also happened around that time, was, that my vision degenerated quite quickly in a short time frame and I realized that there are a lot of things that I couldn't do any longer as I used to do, and my answer was to withdraw. To stay at home at night, not go out, find excuses.

I didn't tell people why I chose to not participate. I also quit my career at the lawyers' office, because there were some instances that made me realize that it is really difficult, I did not talk to my bosses about my disease, they knew about the hearing impairment, that was ok, but they did not know about my visual impairments. I am quite sure, if I had told them, it would have not been a problem. We would have found a solution, but I wasn't prepared to come out. I had young children anyway who needed all my attention.

So, there was couple of years where I wasn't really that active. I think you could call this my years of depression. But I am also very lucky because I didn't develop a full-blown depression, but it was a time of loneliness, with not knowing how to proceed. And then I decided to get lots of information, it was a lot easier now than it was many, many years ago. There was the internet, I decided to connect to others with Usher syndrome and I met awe-

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some people and I met them and there was this recognition from the beginning, there was this understanding, a level of understanding I haven't known before because I hadn't known anyone with Usher syndrome before. And this was the best step I could take, yeah.

What I did, as well, was to start asking for help. This was something that was very difficult to me. I started a mobility training, at that time I didn't get funding for this, so I only did a very basic training, but it helped me, I started going out more again. I couldn't read books any longer, that was something, you know the saying if you have Usher syndrome or RP, you can't find the bus stop but can read the time table. When I don't find the bus stop, I can't read the timetable either. So, I can't read books any longer, which is a loss for me, but I turn to electronic books. I got software for my computer, so I can still read what is on the screen, I can find items on the screen, I got good lighting. I got assistive technology.

I got a smartphone which really is extremely helpful, because it has a torch, it has voice over, it has navigation, I can read my e-books on that, I get all my information from my smartphone. And I think smartphones are actually key when considering assistive technology for the future. And what we did as well there was this dedicated team of people, of individuals affected by Usher syndrome, family members affected by Usher syndrome. We got together and it was our vision to found a patient organization in Austria and that is what we did. I think that that was a very important step, I am very happy about this.

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Those were all factors that contributed to me accepting myself as a person with Usher syndrome, accepting my identity, not hiding any longer. Hiding just makes matters worse, because as long as I hide I can't get the help I need. And you just really need to get open about it, come out and then this really is the pre-condition for asking for help and help and support really is so important to all of us, so we can lead the life's that we want to lead. And I am also extremely happy that I was able to travel with a deafblind assistant to come here. It is the first time I have done this and it is amazing, it just empowers so much, finally I find the people I want to talk to, because I have got eyes with me, I have got ears with me, who tell me what someone says if I didn't understand it.

I always considered myself quite independent anyway, but it does really make a very big change. So when, I think we all have our unique stories my story is just one story and I think some of you might recognize some of the stages, some things will be completely different. I do think that patterns of coping with a disease like Usher syndrome are similar but also of course very individual.

And I think what important is to find a way of enabling people with Usher syndrome to live the life they want to live. So they feel confident that they are entitled to the life they want to live. I think that is also important, because when I think back to the time when I was diagnosed, I was denied the right to a happy life, really. I was degraded, my life appeared worthless to me, and I think this shouldn't happen. Of course it is a shock and denial will

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always be part of the process and it is a difficult process, but I think what it really needs is that we have professionals from different disciplines, who get together in a network to support individuals. So individuals can turn to them when they need to at the time they need to at their own pace. That is how we can support individuals to cope with their disease and to find a good way to live.

And also, when I look back at my life, I think what really helped me, I had a supportive network from the start, which was very important. I chose to get information about Usher syndrome, I chose to connect to others with Usher syndrome, I chose to get help, and I chose to work actively in a patient organization.

And keeping this in mind, then considering how to provide support for individuals, I think, we really know it needs a multi-professional, multi-disciplinary approach. And that is why I do the work that I do, because I feel privileged. I feel lucky, I had a lot of chances in my life that got me to where I am now. And I think everyone deserves this, that is why I am doing that work. I am extremely happy if we get together to do this, so the vision is that everyone who has Usher syndrome can live an independent life, can become reality for everyone. Thank you. (applause)

(Dominique Sturz) So, thank you Julia for your very interesting personal and also very touching insides you have given us on your story and your personal view of Usher syndrome. We have two minutes, so maybe we, somebody wants to ask a question now? Otherwise we would

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just proceed to the coffee break and if you want to get in touch with Julia directly during the coffee break just connect with her. So, we are going to have the coffee break until 4.30, we come back at 4.30, we start at 4.30, so I ask you to come back at 4.25 at 25 minutes past 4, thank you. Is that correct? It is a long coffee break, but we need to connect and to talk.

(coffee break)

(Dominique Sturz) Hello, good afternoon everybody. May I ask you to proceed to your seats, so we can start more or less on time and make the best of the time we have left, because we have a very interesting talk now, and then we have the round table.

So please proceed to your seats and let us close the door so that we can hear our next speaker. Would somebody please close the door? Thank you. Okay, so when everybody is seated, I'm going to start. May I ask you to take your seats, please? Thank you. Thank you. Okay, so welcome to the last part of our patient symposium today. I want to inform you that Nancy O'Donnell from the Usher Syndrome

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Coalition is here, so as many families and many patients have asked how to connect and how to keep in touch with the community, with what is going on in the future. So I invite you to get in touch with her, she will be there for you, and she will tell you what to do to be in touch, to stay connected and to have all the information you need and to meet all the people you want to see and to meet.

And what is really impressive today is, and this is really very motivating and inspiring and very positive is that we have 250 people attending today's patient symposium, which is really unique, and we also have - and this is for the first time that we have it like this - we also have almost nine people following the livestream. So we have almost 300 people following today's patient symposium, which means that this is the largest meeting of people with Usher syndrome we've ever had. So this is unique and it is for the first time. (applause)

So, we are going to have to celebrate this tonight at the family dinner. Yes, the family dinner: We meet there. That means that you go there individually. Don't forget to bring your money, because this is in your cost, and we are very glad and happy to see you there and to connect there with you once again after the conference.

Well, so, Claes Möller, I don't have to introduce you, because you have dedicated decades of your life to research and to Usher syndrome, so you were involved in the discovery of one of the first genes in Usher syndrome. And the last decade I suppose, yes, it was the last decade you

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have dedicated mainly to an interdisciplinary approach, that means not only medical, but also psychosocial. And you are going to talk about that.



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(Claes Möller) Thank you. Can you hear me? Which is a very stupid question. How can they answer who can't hear me? Good.

You see the interpreters? The Loom systems are working? Okay, no one is objecting. Friends, I'm so proud and I'm so grateful to the organizers of this meeting to be the last speaker, since my longtime friend Bill Kimberling whom you can see there was the first speaker at the symposium.

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What started in Gothenburg and then in Omaha, Valencia and took really a kickoff in Boston is now in Germany. This is so fantastic! We were a couple, a few researchers at the very beginning, and now we have all this interaction with you who have Usher or are families and professionals. My task today is to tell you a little bit about the philosophy of working together for Usher syndrome.

I have worked with Usher syndrome for 31 years now, and I have seen over 500 patients with Usher syndrome, and we have 400 patients in our registry database in Sweden. So I really have had so much fun, and this is the passion of my life. I am an ear, nose and throat doctor by profession.

„I went to the doctor, and he told me that I would go deaf and blind, he does not know why, not when, but it might be in the near future. Then the doctor abruptly left the room. No, not my hearing, not my vision, it is not fair! How could God do this to me? Why wasn't I told until I was grown up? Somebody out there help me!“ You all heard Julia's fantastic presentation, and this is repeated in every patient I meet who gets a late and wrong diagnosis.

And therefore the aim of my speech today is to urge you as patients, as families, to put on demand on your health-care system so that the next generation of children with Usher syndrome will face a little bit better than this. Why is it important to know the cause? Well, to get a correct diagnosis. And if we have that, we can learn from other experiences, from other patients with the same diagnosis,

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from research within this. So this is extremely important. And if we have a cause, we are better in determining the prognosis.

Most of my patients when I meet them the first time have been told by their eye doctors that they will go blind. Which is not true in Usher syndrome. It might be true in other causes of retinitis pigmentosa, but very seldom in Usher syndrome. We can also get correct rehabilitation. And as we have heard during these three days, the treatments that we are hoping for will be extremely specific to the cause of Usher syndrome, the mutation, the gene. And if we get the correct diagnosis as early as possible, we can avoid or justify other tests.

And the most important thing is, the family and the patient need and want a reason for the problem. When I get a cold, I always think: Who gave me the cold? And if you get a serious disorder, as a parent you want to know why. And if you don't get the knowledge you will invent things. And often fantasies are much worse than realities. So this craves an interdisciplinary work with patients and parents, if we are going to succeed as researchers and clinicians.

Now, we have five senses. And men are relying very much on the far senses, which is hearing and vision. We communicate with hearing and vision. Sometimes you could say that we see with the ears and we hear with the eyes, because they are so intermingled, they are working so closely together. Now touch, tactile sensation is also quite good or actually very good in men but is not used so

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often. Smell is good, but we are walking on two legs, we are not going like our friends the dogs down on the carpet or in the ground looking for who was here yesterday. So we are not using the smell that much. And taste is not that good. Now, the eye and the ear resemble each other very much, and it has been very clear during the last decade that the basics of the eye and the ear, the vision and the hearing are very alike, and especially also when we get into the brain. And that has been very clear by Usher research, where we have these two organs. Why just eye and ear? Well, probably because they have exactly the same basic constructions.

We need basic and clinical researchers to find out how the eye and the ear work in normal situations. And what we have known now during the last 20 to 30 years is that by research, for example, by Uwe and others, when it comes to finding the genes and what they do, we also learn how the eye and the ear works normally. It would not have been possible without all of you who have contributed by having a specific disorder. Now we all are going to be doctors.

You see a child here. You know we are talking about Usher syndrome today. What do you see? Do you see anything in this child that makes you suspicious? Hm, this could be Usher? Someone says no. Is there anyone who sees anything in this child that might give you a suspicion? No. It's my grandkid. ^(laughter) Now does this child have a syndrome? What do you see? Well probably nothing. It's a normal guy, except he has Usher type I. You can't see Usher syn-

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drome. You can detect it, if it is a hearing loss or a vision loss, but you have to be clever. Now look at this girl. It's the same girl, but in two situations. Here you can start to see something.

On the left, the girl is not that happy. For those of you who can't see, she closes her eyes, she has some wrinkles on her forehead, but then she puts on eyeglasses and a cap, and suddenly her face is much much better. Of course this girl has Usher syndrome. So if we start with hearing, we all in the Western world at least have neonatal hearing screening. This means that every child with Usher syndrome, even Usher type III, should be detected at birth.

But, all children with Usher syndrome have, when they are detected at neonatal hearing screening, have a false diagnosis. They all have the diagnosis of what we call a ,non-syndromic hearing loss', because it is not until you either genetically or clinically find that it is Usher syndrome that the child will be correctly diagnosed. And therefore we need to be much better in finding Usher syndrome very early.

This is just a slide telling you that today we have no problems. Every clinic with audiology should be able to exactly measure the degree of hearing loss and the location. If it is in the middle ear, the inner ear or in the brain. This can be done in small neonates, and you don't have to put them to sleep, because small children do three things: they sleep, they eat and they poop. So you can do this.

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But you also have to realize that it's not just hearing tests. It is also other things like finding out how is the brain. Is there a malformation in the ear, is there malformation in



the brain, or looking at the heart, the eyes, maybe kidney, brain, thyroid gland, which also can give a syndromal hearing loss, there are more and more important genetic tests.

And as we have found in Sweden and in other countries that a fair proportion of children with hearing loss also have a CMV, cytomegalovirus infection. It's not going to be the topic of this speech. Genetic screening for hearing loss. Sweden has 10 million inhabitants. Assume that we have 100,000 newborns every year. Out of those about 200 will have a hearing loss or profound deafness. 81 will be profound deaf. 120 will then have a moderate to severe

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hearing loss. 30 cases of those will statistically be what we call Connexin26, a hearing loss which we can genetically test, and if we find this, we know it's not a syndrome.

So that is a very good test to do immediately. Ten will have Usher type I. When Bill and I started, it was said that five out of 100,000 will have Usher type I. But Bill found in Iowa and in Nebraska it was double, and that is the same in Sweden, and I suppose it might be a little less in some other countries, because we have a large proportion of type I in Sweden. But anyway, in Sweden ten will be Usher type II. But a positive genetic finding, if one is screening your kid or yourself for Usher syndrome, it is not Usher syndrome just because you have a gene for Usher syndrome. You have to do other things, because you can have a gene, a mutation which only gives a hearing loss.

And that is extremely important for parents to understand, because I'm sorry to say, a lot of clinicians have no clue. At least not in Sweden, maybe it's better in Germany.

So when a child has a hearing loss, you need to have an otolaryngologist, an ENT-doctor, you need an audiologist. You probably - because it's a crisis in the family - might need psychological support, you probably need to do radiology, and maybe if it's profound, you also need a CI-team, a cochlear implant team. You need teachers in the preschool and later in the school who are informed, you need geneticists, and we need parents. Well educated parents that can put pressure on the medical system. And many of you know how you have to hunt and bribe the

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doctors in front of you to get them to understand what it is all about.

So, children with hearing loss: 50 % of children with a severe or profound hearing loss at seven years of age have a visual problem. So half of all children with hearing loss have a visual problem. Might be a small visual problem, but if you have a hearing loss, or if you are deaf, you need your eyes much more to lip read or see signs or whatever it is. A small vision loss in a hearing-impaired child can be a large vision loss. So every child should have not just one checkup, but regular checkup of visual problems. And I will come back to that very soon.

If you have normal hearing, it's 20 %. Five minutes left? Okay. Then I have to speed up. This is a picture of how you measure hearing. You can't detect Usher type I, II or III just by a hearing test. Usher type I is easier, but Usher type II and III can mimic each other depending on which age you are. So identification of children with possible Usher with the vision also craves a lot of different things.

And the main test is electroretinography. You should have that in every child. It's extremely sensitive. And we have seen, it's often said that Usher type II is later, it might be later in symptoms, but we have had children who are only four or five months who have a pathological ERG with Usher type II, although they might not have problems until later. And we have to rely on parents, on preschool, to detect such things as darkness adaptation, contrast problems, light sensitivity.

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There are very few tests that we really can do to see that. This is a picture of how it can look like when you are a teenager, and when you educate others, please try to use different devices to show how a visual field restriction can be. 20 to 40 years some get cataracts, then it gets really problematic. But the positive thing is that most people will up to their 60s or 70s have very small central vision that can be used in good light conditions. This is how the visual acuity goes slowly down in Usher type II and Usher type I.

And those that are 50 to 59 have a visual acuity which will allow them to come to a low vision clinic. Of course they should come much earlier since they have RP also. When a child has a vision loss due to Usher, we have other professionals who do not talk to the otolaryngologist. Ophthalmologists, opticians, teachers, orthoptists, low vision clinics, maybe cataract surgeons, and once again the parents and the family. When it comes to balance we balance with three organs: eye, somatosensory and vestibular. And in balance in Usher type II you might have a problem with the eye, but as a child you can use all three of them.

If you have Usher type I, you don't have vestibular and you have maybe in darkness problems with your eyes, which means that you are very very insecure. And then you have to have an otolaryngologist, a physiotherapist, teachers at the school, you have to be encouraged, to understand why you are clumsy, to be engaged in sports, in physical exercises etc. So the rehabilitation when you get older in Usher type II, hearing loss is discovered early, a

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vision problem is more discrete. I don't know how others see.

Difficulties in school are often blamed on the hearing loss. Contrast, light sensitivity, darkness, late diagnosis, denial. As we heard Julia talk about. Teenagers don't want to be different. This is not what I have planned, and we have all this as Julia explained so well. So, the team work with professionals, parents, patient and family is so essential and is lacking in most places. This is a poster which you can see still outside, where we are talking about psychological health in Usher syndrome type I, II and III.

I'm not going into details, just going to show you that we have found depression, fatigue, sleeping problems, and if you look to your right it says suicide thoughts and suicide attempts. And all three types of Usher have much more problems than when you compare to a normal population. I was really really sad to see these large suicide thoughts, mainly in men with Usher syndrome, and also suicide attempts. So there is a lot to do in psychosocial rehab in Usher syndrome. I'm finishing in 1 1/2 minutes.

This picture is wonderful. This is what we are facing in Sweden. It's Swedish and you can't read it, but every little box of this is someone that you have to deal with as a parent or as a patient with deafblindness. And think when you go from here, how many different authorities and things do I have to deal with every week. Maybe the bank, maybe tax, maybe insurance, maybe etc., but you

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don't have to deal with maybe 10, 15, 20 different people who are going to say to you: „I don't know what Usher is.“ „Interesting, can you tell me?“ How do we get all us pro-



professionals to work together? What do people with Usher syndrome need?

Well, they need medical and functional diagnosis. They need personal knowledge concerning deafblindness, different support depending on age. Knowledge among caregivers, good follow-up of hearing, vision, balance, physical and psychological health. And I urge everyone who is young to try to have regular visual checkups, even if it is depressing.

Because if we are going to have gene treatment, or when we are, for sure those that have regular visual checkups

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will be the best candidates for having this. Not if you haven't been at an ophthalmologist for 10 or 15 years.

Communication: the most essential thing in deafblindness. Activity and participation. Research, treatment, cure. And this craves that all of us who work in different disciplines start to work together. And if in my dream I would, if I had a child with Usher syndrome and a family with Usher syndrome have all these working together. Seeing one once a year or something like that. Having a coordinator that takes responsibility from the parents in finding a time when these people can come together, and in corporation with other professionals, because you can have other disorders also besides Usher.

Future: clinical-genetical diagnosis, good prognosis, early habilitation, treatment and cure. Let me finish with two slides. What is this? This is a special measurement of the largest nerve fibers in the brain going from up front to the back, but also crossing over. The brain works in different parts. Vision, hearing and tactile information work together, and they help each other. We should use all these three things.

And now comes my main message which might disturb someone, but hopefully not too many. My dream is that if I had a child with Usher syndrome I, II or III, the second language should be sign language. Because vision helps the brain to create new things. If they have a cochlear implant, of course the first language is hearing and speaking, but the second would in my dream be sign language.

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And if you are a little bit older and you will start losing your vision, and if cochlear implant doesn't work, - we really don't know in 30 years - then you need sign language learned when you have vision, because it's extremely difficult to have tactile sign language learned. So that was my last dream. Research team in deafblindness in Sweden. Thank you very much. (applause)

(Dominique Sturz) Thank you Claes, and sorry for insisting to speed up, but as I know that you are on the podium now, we have the possibility to ask you some questions there. Thank you.

(Mark Dunning) So, can I ask Emma, and Laura, and Isabelle and Brendan to come on up here? We are going to do a combined family and researcher panel.

And I am going to moderate this panel. And I am going to ask some questions. But if we have time at the end, I will open it up for questions and answers from the audience as well. Okay, so I am going to ask everybody to introduce themselves briefly. Brendan, we have you go last for introduction. As I know, you have a little bit more you want to say, okay? So, I will start with Emma, do you want to introduce yourself?

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(Emma Boswell) Hello everyone, my name is Emma Boswell. I am from the UK. I work for a charity called SENSE. I am also the chair of the DBI Usher Network, and I have also set up a deaf cancer support group. I have Usher I myself, and I am married with children, and I am not sure, if you need me to say anything else? Thank you!

(Mark Dunning) That's perfect. Isabelle?

(Isabelle Audo) I am Isabelle Audo. I am a clinician scientist, working in Paris at the Institute de la Vision and in l' Hôpital des Quinze-Vingts.

(Mark Dunning) Are you married? Do you have kids? Where do you live?

(Isabelle Audo) I do, I have kids. I live in a suburb of Paris.

(Mark Dunning) Claes?

(Claes Möller) My name is still Claes Möller. And I am an ear and nose and throat specialist. And I specialized in audiology. I am trying also to be a vision doctor, but they don't like it. I have 3 kids and 2 grandkids.

(Mark Dunning) Laura?

(Laura Bingenheimer) Hello, my name is... can you hear me? Yeah, okay. Hello? May I use that? Okay, thank you! Hello? My name is Laura, I am from Munich, and I am doing a fundraiser for certain research projects. So, I am actually building a bridge between the researchers and

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donors. So, yeah, that is what I am doing. And I do have Usher myself, Usher 2A. Yeah, that is why I am here.

(Mark Dunning) And Brendan, did you wanna talk? You had a little bit more to say, correct? Or do you just want to introduce yourself?

(Brendan Creemer) Yeah, I will just introduce myself. Hello, everyone! My name is Brendan, I am 19 years old and I have Usher Type 1F. And have taken some action to spreading awareness and fundraising which I will be talking about soon.

(Mark Dunning) One of the nice things about this panel, and the reason we asked for the researchers and some of the families to sit together is: I would like to ask you guys some questions. I really kind of want the audience to see that you guys are really not all that much different. I will ask Claes and Isabelle: If you can answer these questions on a more personal level, as well as related to what you see in your careers? I would be interested in hearing that. So, I start again with Emma. And Emma, my question to you is: What do you worry about on a daily basis?

(Emma Boswell) Well, I worry about not being able to communicate with my children because I have Usher and I am an Usher parent. I believe, that is one of the biggest challenges, I face every day. Oh, don't take me wrong, I try to be positive, but that is probably my biggest worry.

(Mark Dunning) Don't worry I will give you guys an op-

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portunity to be positive. So, Brendan, what do you worry about on a given day?

(Brendan Creemer) Sorry, can you repeat that?

(Mark Dunning) What do you worry about on a normal day?

(Brendan Creemer) I actually try not to worry because I am confident that a cure will be coming out within my life time. I just try to about life every day as if I don't have Usher syndrome. Well, keeping an eye on the research, making sure that it is making progress, like looking out for the cure which will-I know will come some day.
(applause)

(Mark Dunning) So, Laura?

(Laura Bingenheimer) I am totally with you!

(Mark Dunning) You don't worry about anything at any given day. There is nothing that worries you? You are just carefree?

(Laura Bingenheimer) I don't really worry because I think, it is not leading me anywhere. Focusing on the research is great, that it makes progress, but on the other side, I am just living my life, and doing the things that interest me a lot. Because I also have to say that I am not as restricted as some of you are. So, I can communicate and do everything like that. So, I am still very happy actually with that, yeah.

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(Mark Dunning) Great, thank you! So, Claes?

(Claes Möller) I worry about that still a lot of people with Usher syndrome don't get the right treatment and rehabilitation. I worry about that it takes such a long time from research to a clinical practice. And I worry about that I have to retire. *(laughing)*

(Mark Dunning) You don't have to retire.

(Isabelle Audo) So, you mentioned on the personal basis.

(Mark Dunning) Yes.

(Isabelle Audo) So, I try to not worry about anything, but I still do worry. I worry about not being able to do, what I was expected to do on a daily basis. And I have been worried about, you know, missing a diagnosis, or think something that I shouldn't say to a patient or to colleagues that will lead to other worrisome things.

(Mark Dunning) That is a good answer. So, my next question for you guys is: How do you feel, when you meet someone new who has Usher syndrome?

(Brendan Creemer) What?

(Mark Dunning) How do you feel, when you meet someone new who also has Usher syndrome?

(Brendan Creemer) Well, I try to relate to them in some

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ways. But for the most part, I try to motivate them to take action, to follow the research, to keep an eye out for the cure, spread awareness, like what I am doing.



(Mark Dunning) Thank you! Emma, do you want to answer that question?

(Emma Boswell) I was very excited actually to meet new people. Because we are so varied, and I like to see, what other people have achieved in their life, and that actually empowers me.

(Laura Bingenheimer) I don't know really know many people with Usher syndrome actually.

(Mark Dunning) You do, now. *(laughing)*

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(Laura Bingenheimer) I do. But when I meet them, I think it is the same thing as always, when you meet people: you have some things in common and some things you don't. So, that is just one more thing that you have in common.

(Mark Dunning) Excellent, now you guys deal with Usher syndrome all the time.

(Claes Möller) Yes, and when I meet a patient with Usher syndrome and we have cleared out the problems, then I try - because I usually have 3-hour sessions to start with - I usually try to also find all the strength and all the beauty in being a human being, and that people with Usher syndrome are as different as all my other patients. And that is so rewarding.

(Isabelle Audo) So, when I meet a new patient with Usher syndrome, I try also to see the positive things out of all the other things. You know, after the testimony of Julia, I really always keep in mind that maybe this patient has a history of bad news, good news or a deception and so on. So, I try to read with the patient this story. And also to give an example of people who despite everything achieve great things, which I think it is always possible to give some positive input.

(Mark Dunning) Excellent, thank you! So, Emma, I have another question for you: What about Usher syndrome frustrates you the most?

(Emma Boswell) Mhm. What frustrates me, I guess, is: I

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meet a lot of people through my work that don't know anything about their own Usher. They haven't received the right diagnosis, the right information, the right support. They might have met a specialist doctor, like Julia said. And they might have even been misdiagnosed. And it is a missed opportunity. And actually, I come up across that a lot. That is the biggest frustration.

(Mark Dunning) Brendan, what about the disease frustrates you the most?

(Brendan Creemer) I think what frustrates me the most is just the way people treat me. Either good or bad. Just people who worry about me too much. Like, there is some people who think my vision is worse, than it actually is. Like, to be honest which is really, really good right now. It is not supposed to get bad. Only much later hopefully, after the cure comes out. And, people who assume that my vision is worse than it is, try to grab me by the arm and guide me. But I don't like that. Like I just think, in my eyes it is rude for someone to grab me by the arm without notifying me beforehand.

I see myself as a sighted person and people who treat me as if I am blind is just rude. Treating me like someone I am not. Yeah, and overall, whenever people worry about me in general, like ask me, if I need help to get anywhere, or if I need them to read something for me, or something like that. That really frustrates me. I really want to be independent, that's what it is.

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(Laura Bingenheimer) I think, I see it more from an inner part. What frustrates me, would be that this is a progress, and that you have always this back information that you might go blind. And, so, you actually... I try to not live my life with this background information. But to live it just independently without thinking of it. That is something that is frustrating when I am thinking of it, yeah.

(Claes Möller) I wouldn't say like Brendan and Emma, the environment, the others frustrate me most. And in Sweden, it frustrates me a lot, that we have authorities that have no clue and don't work together. In most of the countries we come from, we definitely have resources. But we haven't planned them together to make life easier and to include all people into the society. And since speech and vision, hearing and vision is so important for our social life we should make it much, much easier to participate.

(Isabelle Audo) So, I am going to repeat a lot. So, one thing that also really frustrates me is, how ignorant some of my ophthalmology colleagues are. Sometimes you receive patients and patients are depressed because they were told that they - or parents from children - that they were told that they should register to a special school and learn Braille, and so on. So, which is not needed in the first place in Usher syndrome. So, it is always frustrating me to hear how ignorant and adamant some are, like: you should do this and that. Like some of my ophthalmology colleagues are towards Usher syndrome. I am also like Brendan, and what you mentioned, is that: any young

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children or adults need to be independent. And I do believe that patients with Usher syndrome can be autonomous, and independent, and very happy. And sometimes the surrounding is anxious about that and anxiety just precludes people to move forward.

(Mark Dunning) Good now, Kimberley mentioned before, that we need to be both: balance the positive and negative. So, when I ask you a question that you probably find strange, but: what about Usher syndrome makes you happiest? I will start with you Emma.

(Emma Boswell) Mhm, what makes me happy about my Usher? I think, the fact that I have managed to achieve so much, and that I have just got on with things. I have backpacked on my own. I have done-done operation Raleigh. I did Camp America. I have managed to get a degree and I have achieved so much. And that does make me happy, despite my Usher, I guess.

(Mark Dunning) Brendan, so, what makes you happiest about having Usher syndrome?

(Brendan Creemer) Makes me happy? ^(laughter)

(Mark Dunning) No one said, this was gonna be easy.

(Brendan Creemer) Uuh - this is a difficult question. Shh! Shh. Is it possible, you could come back to me?

(Mark Dunning) Yeah, of course.

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(Brendan Creemer) Thank you.

(Laura Bingenheimer) I find it very difficult, too. Of course I am trying to have a good view on it. But, yeah. It is not so easy to find something that would be making me happy. But I think, for example, at night my friends already stand there at the door and hold their arm, so that I can just grab it. And it is just a next to it thing. So, I am really happy to see that these people just see it as something that is just a part of me. But it is not a topic to talk about. And that makes me happy, that there are people out there who can do it this way, friends, yeah.

(Claes Möller) Without you guys with Usher syndrome I would still be a local ear, nose and throat doctor ^(laughter) - in Sweden. You have made me so happy, because I can travel around the world. I have met over probably 1,000 families with Usher syndrome, I work with researchers, clinicians, I can travel here without paying too much, it's fantastic! ^(laughter) ^(applause)

(Isabelle Audo) I would say like Laura, about what makes me happy about Usher syndrome is to realize, how some patients achieve so much. One of my patients is, - I think - he is Usher Type I, but he doesn't have Usher 1B, but another type of Usher. And he has - I think, he has four gold medals in judo at the Paralympics and I am so proud of him.

(Mark Dunning) That is great, Brendan, have you come up with anything that makes you happy?

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(Brendan Creemer) Yeah, yeah. I have got an answer. I know this might not be what you expect to hear from me. But, I really don't think there is anything about Usher syndrome that has made me happy so far. It has had only a negative impact on my life. I view it as a personal arch nemesis, maybe. I guess maybe that is a good thing to take out all of my anger on. So I end up not harming others. But I really don't think, there is anything about it that makes me happy. I am sorry to say that.

(Mark Dunning) That is not a surprise. That was intended to not be an easy question. I know, I have tried to ask you guys all the same questions. (man from the audience) Excuse me? Mark?

(man from the audience) Mark? Right here. Sorry, I just wanted to comment on that also, if I may?

(Mark Dunning) Sure.

(man from the audience) I don't have Usher, but I am a father of someone who has Usher and this question that you asked: I would say, it is not Usher in particular, that would make you happy. But it's a challenge, like many other challenges that you can have in life. And it does - I am fighting a little bit with my voice, as you can hear. But it does show that there are people around you, that there is good in this world. We have met so many friendly people after we got the diagnosis. And that - I think, many people especially nowadays, when you see, how bad things are going in the world. I that is what shows that there is

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a lot of good in the world, too. That people really fight for you, stand up for you and want to be good to you and help you. So, I think, that is beside - I mean - independent from Usher or other medical or other challenges, that is what was a benefit for us that Usher came into our family.

(applause)

(Mark Dunning) You can't see it, Bernd, but people are taking out the tissues here. Thank you, Bernd, that was a great, great answer. So, I'm gonna ask slightly different questions of you guys. But they relate to the same sort of thing. So, for Claes and Isabelle: What is the most important thing that patients or families with Usher syndrome can do to support your research, outside of raising money?

(Claes Möller) I would say, that the most important thing you can do, is to organize yourself in different organizations, such as Usher Syndrome Coalition or other organizations. Because deafblindness and Usher syndrome in the scientific world are very small and you are quite few, when you are alone. Which means that the funding for research can't compete with cancer, diabetes or whatever it is. So, if you go together, it will help the research tremendously. Without you, there will not be any research. And this meeting is a perfect example of this, where we actually have gathered probably all the main researchers in Usher syndrome in the world. And we were 152 people. That is the content of researches and then we have some clinicians, of course. But that is the main thing you can do for us.

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(Isabelle Audo) I totally agree. And also, I think, you know, being involved in Usher, you can also bring a lot to nearly diagnosed Usher patients and families. Because, when we see them in a busy clinic, we try to take time and this is - I always imagine that it is like a cold shower and unfortunately busy clinics are like that. So, we can't review patients like the next day or the day after to answer questions and so on. And I think the families who also went through this type of things, you can really help, when we can't continue to support the patients.

(Mark Dunning) Thank you! So, now for my non-researchers I have two questions: We are reaching the point from a research perspective, where we are going to need to start doing clinical trials. So, my question for each of you, first, is: Would you be willing to participate in a clinical trial? I know this is a short answer.

(Laura Bingenheimer) Would I give money to-?

(Claes Möller) No, would you like to participate or would you participate in a clinical trial?

(Laura Bingenheimer) Mhm, that seems so far away, so I didn't really think about it so far. But I think that it depends. Because, I need to have trust in the project, and in the trial. And, I would also want to know the risks that I'm taking. But if it's promising, then I wouldn't see a reason why I shouldn't do it.

(Mark Dunning) Brendan, would you be willing to partici-

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pate in a clinical trial?

(Brendan Creemer) Good question: I might wanna wait until I am older and until the research has progressed further. But I think, if the trial sounds like it will work and I feel like I could only benefit from it, if there aren't any nasty side effects, I would be happy to participate in a clinical trial.

(Mark Dunning) And Emma?

(Emma Boswell) That would be a very, very big decision to make. And I guess, the same as everybody else has said: You would have to weigh out the risks. Because at the moment, my vision isn't too bad, and: Would I be willing to risk affecting it or changing it in some way? So, I guess, I can't give you a definitive answer. I would have to wait all up and then give my answer.

(Mark Dunning) I want to make a comment and I am gonna ask you a follow-up question. So Laura had mentioned earlier about that she would have to trust that she knew what is happening and trust the people that were involved. And that is a big reason, why we do these types of events. And that is, why we asked Claes and Isabelle to be here with the patients. Because we want you to know the researchers, we want you to know that you can trust the researchers. The only way, you gonna do that is, if you meet them. And that you see them as human beings and know that they care about you as an individual. And that is not always gonna be the case with every researcher.

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So, it is important that you have the opportunity to meet them and know them personally and hopefully know them for a lot of years. I have known these guys for probably 10 years now. And I completely trust them, because I have known them for 10 years. It takes time to develop that sort of relationship where you have that trust. Which is why we try and do these types of events. Because that leads me to my follow-up question for you guys: The first phase of clinical trials is a safety trial. And in most cases, the intention of a safety trial is not to improve your condition. It is to test and see if it is dangerous. So this is my follow-up question to you: Would you be willing to participate in a clinical trial, if you knew, there wouldn't likely be no benefit for you, but that it could benefit the community in the future?

(Laura Bingenheimer) Are you asking me? Do you already have an answer? I don't, I doubt it.

(Mark Dunning) Would you like to hear my answer? As I might make it a little bit more comfortable to you guys. I probably wouldn't. I would not be willing to be involved in the work and the pain that could potentially go along with the clinical trial, if it wasn't going to help me. But there are going to have to be people out here that do that, if we want to find treatments. And so, if the answer is ,no', that is perfectly fine because that is going to be most people's answer.

(Laura Bingenheimer) I think my answer would be ,no' because you know, you already have this disease and

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you have already had so many difficulties that you had to manage. And if you knew there would only be more difficulties probably, and I wouldn't have any benefit from it, then I would probably say ,no', because of that. Because I am already having to struggle with it and I don't want have more struggles just, so, yeah. (Mark Dunning) Brendan, what do you think?

(Brendan Creemer) Uh, well, for me: I am more concerned about efficacy than safety. Like, safety is - obviously is relevant. But in the long run for me it is partially irrelevant. If I want to do a clinical trial, I want to at least wait until the safety part has been cleared before moving into efficacy. So, I probably would not want to do one of those safety trials.

(Mark Dunning) Emma, what do you think?

(Emma Boswell) Well, I guess, I feel the same as everybody else. I don't know, if I would take the risk of actually damaging the vision I do have. And it would be a family decision, as well because, you know, I have young children and on the back of that, I think, I would be reluctant.

(Mark Dunning) Okay, thank you! Uh, yes, I asked that question because I want you to realize that it is great, we are reaching this point, where we are going to make it to clinical trials. It is going to be hard for all of us. There will be some difficult decisions for people to make to get there. And some people will have to, you know, sacrifice and be willing to do something that I don't think I would be

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willing to do. And I think, it is important for us as a community to realize that people that do that are real heroes to us. Because they are willing to do something to help



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the community, that won't help them directly. So, we have a couple more minutes. I was wondering, if you guys have any questions, that they would like to ask anybody on the panel, or the panel in general? Any hands? No? Oh, we have a hand over here.

(women from the audience) Hello! Is there an international patient register existing where you can register yourself and your mutation you have, because there is one in Germany, but, maybe it is also interesting for the whole world?

(Mark Dunning) That is an easy answer, Nancy, would you

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like to stand up? So that is Nancy O'Donnell over there, and she runs the Usher syndrome coalition international registry for people with Usher syndrome. If you go and find Nancy after the symposium, she will be happy to get you registered and it is actually, there is actually, a German page on the registry. You want to add anything, Nancy?

(Nancy O'Donnell) That's perfect, come on over. I have my laptop.

(Mark Dunning) Anybody else have any questions that they would like to ask?

(women from the audience) Hi, I am Anne Schuer, I am parent of 4 kids, two with type 1b, as a mom I am wondering if the people on the panel who are patients could speak about things that their parents did, that they found supportive and maybe things that were not helpful, so that I can replicate or not replicate. And if the researchers could maybe talk about effective parenting that they have seen with their patients and families. You know, even talking to our young children about this diagnosis and teaching them a healthy way to cope with whatever feelings they might have as things change. I think that for me is my greatest need, watching my children go through this, is, how do I be a support and not hover too much. And you know, I don't know, make sure, that they can become the people that they are intended to be and to not let this diagnosis be something that completely defines them.

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(Mark Dunning) Good question, Emma would you like to answer that first?

(Emma Boswell) My mom and dad are divorced, but I have a set of step parents. My mom knew I had Usher at 7 but didn't actually tell me until I was 18. It was when I was going to operation Raleigh and I started scuba diving and I realized that my balance was very bad, and I asked my mom about this. And said, what is wrong with my vision? What is wrong with my balance? That is when she sat me down. My older sister also has Usher, my brother doesn't. She sat all of us down and told us, that me and my sister had Usher.

But after that point, I know it was rather late, my mom actually encouraged me and my sister to be very independent. My dad on the other hand was very, very different. He didn't want me to go travelling. To Camp America, he didn't want me to do the things I wanted to do. I actually think that was because I don't communicate that well with him. I lived with my mom, grew up with her and I communicate with her amazingly.

Actually the one thing I do wish, is that both of my parents could sign, because I don't know what my vision is going to be like in the future. I might need to use hands-on signing, that is why I've taught both of my children to sign, because I want to be able to communicate with them for the rest of my life. That is probably the biggest thing, I wish my mom and dad had learned sign language. I am very open with my children as well, so I would say that is

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definitely a bonus, a plus.

(Mark Dunning) Brendan, do you want to answer the question?

(Brendan Creemer) Sorry, what was the question?

(Mark Dunning) The question was, what things have your parents done, that have worked well and what have they done that has not done well and your dad will cover his ears!

(Brendan Creemer) Sorry, what was that?

(Mark Dunning) Do you have an advice for parents as to what to do to make it easier with kids with Usher syndrome.

(Brendan Creemer) Definitely being positive from the start like saying: Having Usher syndrome won't stop you from all the things you like doing right now. That obviously helped me. As soon as they are old enough to understand what is going on will all this research, maybe you can tell them about it, and be positive about it. Say like: we are working towards a cure and we hope to have it out in the next few decades. Just being positive, telling them regardless how bad this seems, they can still live out their normal lives and be happy.

(Laura Bingenheimer) I agree with you. And I think it is very important to be honest. For example my mom, she

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told me directly what I have. She was not very enthusiastic about it, of course, but she just told me like, „You have this disease called Usher syndrome“. I was like, ok, and then that was it. We were very honest about it, that was very important. But in the end I think it is important that the parents listen to the child, when it says something, but don't really do something more when it doesn't say something, because I think that is - I would find it restricting if my parents would contact me and be like, „Yeah, what is it like for you?“ and things like that. This would make me feel being different and, I would have a problem with that. So, what my parents did right was not doing too much.

(Claes Möller) My experience is that the - I have seen now over a hundred children who now are grown up, they constantly say to me, that those who come out the best, are those, where, - as you said - where the parents told them very early about the problems that they might face. Also especially when you are young, very young kid, tell them about if you have Usher type I, that yes, you are a little bit more clumsy, you can't do everything. But that is just because you are deaf in your balance organs. So that they don't hear that from others. Then educate all the other caregivers in the pre-school etc. Because many children will get very stupid comments from ignorant people.

(Mark Dunning) Anything to add, Isabelle?

(Isabelle Audo) Yes, I can only speak also from my experience. First, I think as parents you need to trust your

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children - any children, not only your children with Usher 1b - that they will be going to be fine. And second, I must admit, - except of course when you do any RG on the 6



months year old - but when I see patients, children with Usher syndrome, I tend to see them with their parents. And I try to explain in a simple way why they came, because, you know, performing RG is not something easy. And, and try to explain them, you know, you don't see very well, maybe at night, and so to explain them why they don't see very well.

And that very simply, because, maybe I am wrong, but I do think that maybe not saying things can create false anxiety and just saying: We understand why you don't see well at night, you are going to have a flashlight and everything will be ok. So, I do think being honest and rationalizing

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things help a lot, rather than hiding things. Because the kids, they know. They understand quite a lot, I think.

(Laura Bingenheimer) Can I add something? I think the diagnosis effects - this is the first time you actually have to do something with the disease. I think it is very important to think about how you tell your child. I think it is very important to just say it without any emotions, so that the child can like put it in the right order. Because I think if you would already tell the child with a crying face, then it is probably, not the best thing for the child. Because it thinks, „Oh, my life is over and this is probably going to restrict me so much“ and thinking bad about it. I think that would be bad. Yeah.

(Mark Dunning) Great, thank you guys, so, we have gone over our time. But I know, Brendan, wanted to say a few words, do you have...

(Brendan Creemer) I had a speech that I wanted to give.

(Mark Dunning) Sure, do you have to time to give it? Do you have it with you? Are you ready to go?

(Brendan Creemer) Yeah.

(Mark Dunning) Hit it, kid.

(Brendan Creemer) Alright, you heard a fair amount about me earlier when I was answering those questions, but I think it is time to tell you my story, to really inspire

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people to take action. So, once again, you know my name is Brendan Creemer, I am 19 years old and currently in college. I go to the Lewis and Clark in Portland, I am from Palo Alto, California. And over these past few years I have taken some action to raising awareness for Usher syndrome in my community, so I am gonna speak about that. So, with that, here I go. Dear fellow community members, Usher families and researchers, imagine for a moment that you are a child who has recently been diagnosed - no, that your child was recently diagnosed with Usher syndrome.

You are probably between 9 and 15 years of age, living a pretty normal life so far. You go to school, hang out with friends, play with toys and have fun. You are simply cruising through life, nothing will go wrong, right? Then one day, completely out of the blue, your parents tell you, that you have Usher syndrome and that your eyes do not work as well as you believe they do. In that moment you feel like your whole life was a lie, you are devastated, you isolate yourself from your friends. You give up all of your big life goals feeling like there is no way out of the dark future that looms ahead.

Well, I will tell you this, I am NOT that kind of person. Instead I am a person who upon realization does not see Usher syndrome as a thread. I am a kind of person who takes action! A person, who reaches out, who is motivated, who is resilient, who knows that there is some solution out there, regardless of how awful this situation seems. Let me tell you a story, a story of how I found out

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that I had Usher syndrome, stayed motivated and eventually won several victories in the war against this dreadful disease. I was diagnosed when I was very little, but my parents withheld the truth from me until I was 10. For the next 4,5 years I dismissed it, not denied, dismissed. Thinking it was not going to be an issue at all, because I was pretty happy with the way things were going for me at the time.

In the middle of 9th grade, however, I became more aware. I was upset with the intense accommodations I was receiving in school at the time, because I had grown out of many of them. At the same time, I learned about biotechnology in my biology class and had just learned about genetic mutations. It was in that moment, when I realized that all of my current problems could be traced back to a single mutation in my DNA. Immediately after that I decided to pursue biotechnology as a career, while swearing a personal oath to cure Usher syndrome before I lost too much vision. In the meantime, I would raise money for the research that was currently going on in order to give as much support as I could.

During my sophomore year, I began my own personal war against Usher syndrome working together with this organization called the ,BrankstreetGarage Fund', now renamed ,Think Fund', an organization in Palo Alto, California, where I am from that helps teens run programs. I got together a group of people and planned an open mic talent show event where all the proceeds went to Usher syndrome research. I raised over 700 dollars for Edwin Stone's

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research at the university of Iowa. Additionally, I was able to spread awareness to the community. We named our group ,science for sight' and continued to build more fundraisers the following year when I was 16. Unfortunately, I had to shut down the club at the end of the year, because we weren't having as much as success as before and the rest of my group lost interest in the project, but I did NOT give up hope.

During that time I was getting more and more involved in another organization in my Jewish youth group, BBYO, I don't know if any of you heard of it, it is pretty popular, a great organization. Anyways I got pretty involved in it at the time and saw another opportunity. At the start of each semester, the chapter, the division of my youth group that I was part of would choose a new standup cause, that is a Jewish organization we would spend the entire term raising money for.

Since Usher syndrome Type I, the kind I have, is very common in Ashkenazi Jews, I decided that would be a perfect idea for a standup cause. Together with my chapters of the vice president of Judaism and community service, we made Usher syndrome our standup cause. The guys in my chapter, which, I would like to acknowledge, my chapter was called ,Simon Wiesenthal, AZA 2524' of the region center. Region west number 45 of the BBYO, great organization that.

Parents, if you have a kid who have Usher syndrome and if your guys are Jewish, please try to get that kid into

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BBYO, that would be a great way for them to raise money and awareness. The guys in my chapter worked tirelessly throughout the winter 2017 term, the second half of my senior year, to raise money for the cause. We created a GoFundMe page and after hosting a marathon towards the end of the term raised almost about 2,000 Dollars for Usher syndrome. My senior prom graduation occurred soon afterwards, so it felt like a real victory to me.

Right around that time, I heard that the mouse model for type 1F have finally been produced, which only further strengthened that victorious feeling. Nowadays I am in college, simply working my way towards a degree in biotechnology where I can tackle this disease head on, but I can't do it alone. I will need your help, with that I have one final message for all of you.

To the people close in age to me with Usher syndrome, high school kids, college students, young adults, teenagers: YOU have the power to change things! YOU have the ability to reach out to your community to spread awareness and to raise money! YOU have that choice to either give up and assume everything is helpless or to choose to take action and not only help yourself but others around you as well.

You have that potential inside you to become a game changer. One who motivates and inspires those around them in ways never seen before. YOU have that potential to do amazing things. To the families, especially those of very young children. You may not see this, but your child

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has the potential to do great things. Your children have the potential to become famous, almost as if they were the next Albert Einstein or John F. Kennedy, if they are older. NOW is the time to start encouraging them. If they too young, simply encourage them when they are older, also if they are Jewish, encourage them to join BBYO, if they are not Jewish encourage them to join community service groups at school or in their community to take action. Spread the message of how I took action instead of giving up in order to help others as well as myself. Inspire them to make their own impact on the world. Motivate them to be game changers, to join me in my quest to cure Usher syndrome.

To the researchers, thank you for your, all of your hard work you have done so far, and I wish you the best of luck continuing the study. To the families, thank you for supporting your children, as much as you have, and I hope you continue to support them further. To those with Usher: DO NOT GIVE UP! YOU have that power to change things, use that to your advantage. Community members, families and researchers: Lets eradicate this disease. Thank you. (applause)

(Mark Dunning) Thank you Brendan, a good note to end on. So, this is the end of our conference today and the end of three days for all of you researchers. I really want to thank all of the researchers who stayed around for today, not only to give speeches, but there have been a number of researchers who have attended this conference and have been available for people to talk to. We

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really appreciate that. I know we didn't have a ton of time to ask questions at the panel, but we are all going to be together at the family dinner hopefully, and that is a great opportunity to ask questions there. Irmgard, is there anything else I need to say? There is? Or no? Do I need to say anything else? You are getting a microphone.

(Irmgard Reichstein) Yes, I would like to thank the technical team, I think they did a very, very great job. And even the interpreters! (applause) To be honest I never saw so good interpreters like we have had today. Because they have been images, they have been so fast, especially now at the end. Thank you very much to the interpreters!

(applause)

(Margaret Kenna) Just on behalf of the organizing team, we knew how hard this is, and there is one person. I don't know if she is here, with a 6 months year old baby, Krista Vasi, who works for the coalition, and who remembers not only everything we remember, she remembers everything that we don't remember. Thank you! (applause)

(Mark Dunning) Uwe, would you like to wrap this up?

(Uwe Wolfrum) I guess I would like to thank you for coming to Mainz. It was a pleasure to us, the organizing committee, Sebastian, Kerstin, my wife, and all the co-organizers from the US, from Austria, all over the world, more or less, what we did here. I guess you, I hope you enjoyed maybe also the boat cruise yesterday. We all - we organized also the weather. This was also something,

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when we can do such kind of research, I guess we really, really can forward a treatment for all of you. Yeah. Thanks for coming. Yeah. And I hope, that we will do our best in research. We are researchers at the university of Mainz and we hope that we can help you. And I like to thank Krista, is she around? She was organizing with us with, I guess, most of the time on the phone and the phone conferences. I don't know, maybe she counted this, maybe around 50 conferences we had to organize this here. Maybe I can hand to you, Sebastian, who was in charge, more or less, for the patient day to maybe give some words.

(Sebastian Klaes) I don't think that I need to say quite much more. I have enjoyed this symposium and, yes, I hope we will have a good talk tonight and maybe, yes, I hope to see you or most of you in the next symposium, I don't know where.

(Uwe Wolfrum) I would like to thank the sponsors as well, you always saw these slides and of course it wouldn't have been possible without the support from the sponsors to get, this meeting together. Thanks a lot for coming and we will see you. ^(applause)

For the patient dinner we will meet downtown Mainz and it is quite easy to get to the place. You will find the address in your booklet and you can go by public transportation or by taxi, you have to indicate where to go. This restaurant will be very close to the theatre. And there you may get also around. The restaurant is called 'Haus des Deutschen Weines', it is the 'house of German wine'. And

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maybe we can have a wine together this evening. Yeah.
And for those, who are leaving today, have a safe trip
back home.

(Irmgard Reichstein) Please don't forget to give us back
the receivers. Thank you very much!

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