Mark Dunning: So hi, thank you everybody for coming here today. My name is Mark Dunning, I am the Chairman of the Usher Syndrome Coalition. We are a 501c3 nonprofit that is dedicated to accelerating research into the most common cause of combined deafness and blindness. We bring together a community of prominent researchers from around the world and families in an urgent movement to find a cure. We are very honored here today to have Congressman David Young from Iowa. Congressman would you like to come up to say a few words?

Congressman David Young: Good afternoon. How you doing. Let's liven the place up a little. Congress doesn't have to be so dull you know. Good afternoon to you and all those who are used to being on the hill and work on the hill and those who are from out of town and have just come in and are visiting us. We are going to get an important briefing today on the state of Usher syndrome research. Before we get started I want to thank the Usher Syndrome Coalition for organizing this event today and the Stephen A. Wynn Institute for Vision Research at the University of Iowa, my home state, for sponsoring this event. I was just telling our featured speaker here that these issues affect everyone. Sometimes it's your family, friends, relatives, new friends that you'll be meeting. My father has had glaucoma for a long time. He is starting to lose his hearing. I don't know if that is because of age or what. He has had 12 surgeries in his eyes up at Mayo Clinic. His eyes look like rag dolls sometimes, they are really kind of scarred but we keep looking. We keep fighting, we keep trying to find what we need to make sure that we can alleviate a lot of this for the ones that we love. Your presence in this room is encouraging. For those unfamiliar with the disease, Usher syndrome is the most common cause of combined deafness and blindness in the world. Nearly 50,000 Americans have lost their hearing and are losing their vision to this devastating disorder. Those with Usher syndrome and their families demonstrate courage every single day and you know this. And they face so many challenges. It's not just hearing and vision loss. There can be balance issues as well as an overwhelming social burden. Consider this: our country spends an estimated $140 billion annually in direct and indirect costs for people with vision loss and eye disorders. That sum does not even include the hearing loss aspect. So consider this: 82%. The deaf blind community as a whole has an 82% unemployment rate. People with Usher syndrome have a suicide rate that is 2.5 times greater than the general population. These stats are disheartening. But we got to use these

as a challenge to do better. We are here today because the Usher Syndrome Coalition has done just that and given everyone reason to be optimistic. Due to the efforts of the Usher Syndrome Coalition, this rare disease has been added as a new category in the NIH categorical spending list for research conditions and disease categories. That is a big step folks. This gives Usher greater visibility in total dollars spent including specific grants that need funded. A lot more needs to be done. A great investment in Usher syndrome research is still a major hurdle but it's a great start. We know there is no cure right now for Usher syndrome but we need to make sure that that changes. I am very proud now of the research that has been done at the University of Iowa, Iowa Hawkeyes, under the direction of our featured speaker, Dr. Ed Stone at the Stephen A. Wynn Institute for Vision Research. They are making breakthroughs every day. I thank you and I look forward to hearing what you are going to say here and share with us. They are on the cutting edge and like you I am fascinated to learn more. I hope you will join me in welcoming Dr. Stone.

Mark Dunning: So we are going to increase the anticipation for meeting Dr. Stone. Earlier I mentioned the urgency of our need to find treatments. To demonstrate that urgency, I'm going to invite my daughter, Bella Dunning, to come up here and say a few words. So come on up, Bella.

Bella Dunning: I'm Bella Dunning. I am a sophomore in high school and I have Usher Syndrome. I was born profoundly deaf and I got my first implant at 20 months. Now I have two and I can hear fine. My speech is good and I'm great. My vision, however, is slowly getting narrower and narrower and I can't see this podium as I talk to you right now. And my balance, you probably saw me wobble up here, not great, I can't balance on my foot for more than 20 seconds. But that doesn't mean I am not capable. I am a straight A student in the public high school. I love animals. I ride horses as you can see in the picture here. That's my horse Apollo. If my equestrian team does well next week in zones, I am going to be able to go to nationals in Florida. I plan to go to college. I wanted to be a vet but I don't think my vision is going to be good enough but I will be ok because Dr. Stone is working very hard on treatments but he just needs more resources so it would be great if you could help. Thank you.

Mark Dunning: Thanks Belle. I would also like to, this was one end of the spectrum with Bella who is young and still has some usable vision. Sorry Moira, I didn't mean young. I would also like to invite up our Vice-Chair,

who is not old at all, to - yeah, Bella's just younger – yeah, I know, I'm trying to back out of it, give me a second – I'd like to invite up our Vice Chair, Moira Shea, to give you an idea of what it is like to live through the different stages of the disease and to be old.

Moira Shea: Hello, it's a pleasure to be here and as usual Mark forgot to introduce my guide dog. His name is Finnegan. He is more than a guide dog. He is my American Express card because I can't leave home without him. He is accepted everywhere. Speaking of being accepted everywhere, almost 20 years ago I was working up here in the Senate and I couldn't get my dog onto the Senate floor and it made national news in terms of standing up for my civil rights. When you have the combination of deaf blindness you also are faced often times with discrimination. I just wanted to put a face to what one goes through and basically, the science is great but the impact, the toll on individuals is enormous. Someone mentioned it is 82% unemployment. I am so lucky that I was able to work and to retire. For some reason I find myself very resilient. So many individuals including myself are faced with anxiety, stress, depression and social isolation. We need to move forward on that. Bella did not have the same experience. I don't think she had the same experience as my parents did when you learn that you have Ushers you are told to go to school and learn braille. Today we don't say that anymore. We say there is hope and an excellent chance for a treatment and the only thing that is holding us all back like everything else is money. I hope you will support us in appropriations and I hope you will after Dr. Stone's speech see that we are so close but we need to move quicker. I had the pleasure of going to Dr. Stone's Institute about eight or nine months ago. I was very impressed with his facility. What I was overwhelmed by was after 30 years of doing fundraising for retinitis pigmentosa, ushers, that when I visited his office I had skin cells taken from my arm which are being converted into stem cells and that will develop a new retina. That is amazing and I am just so thrilled by that. I have met so many researchers over the years but I have never been more impressed than I am by Dr. Stone. Without further ado, I introduce you to Dr. Edwin Stone.

Ed Stone: Thank you very much Moira and thanks to all of you very much for coming today. It is a terrific pleasure for me to be here and speak on behalf on the patients and their families who are faced with Usher syndrome. I'm going to tell you a little bit about it today but the majority of the talk I really want to give you a glimpse into what we think the path out

of the woods is, what the path to the cure is. I'm a professor in the medical school at the University of Iowa so I teach medical students and I tell them you really only need to know one thing about being a doctor and everything else is window dressing on top of that. That is you go into the room and you assess the situation in the room and you ask yourself knowing what I know about this thing and about this situation, what would I do if this were me? If this were my child? Who would I call? What would I read? What would I do tonight, tomorrow? What would I do and do that. Nothing more than that. Nothing less than that. Just do that. That's what you need to do to be a doctor. So the first few minutes I want to just do that. Imagine you just had your first child and the child is going to grow into the beautiful young lady that you just met. You are so excited and a pilot newborn hearing screening thing has just gotten started in your hospital. It used to be that the deaf kids would get by you for awhile. So they got this new pilot thing. They come and tell you that your child failed this pilot screening program and you think yeah, whatever. They probably didn't have the batteries in it just so. It's a new thing. Finally you have the definitive second test six weeks later and you are confronted by the reality that your daughter is profoundly deaf. She doesn't hear at all. What this means is if you don't take some sort of action, your child is never going to develop speech. Fortunately these days there is this technology called cochlear implantation and when Bella was just being diagnosed with her profound deafness this was far enough along to be essentially a routine thing. But routine like what? Look at this thing. It is mounted to the side of your head. They drill a hole down through the skull and kind of wind your way through the middle ear and into the cochlea and thread this little thing in there. And if you go home and get to reading about that you find out how it might not go well. You might have infection. You realize you have to do it and you do it and it goes well and your daughter starts developing normal speech miraculously. These children now speak basically normally and communicate and interact normally. Now we're back, we got our daughter back. We are settling in and things are going good. Then you are about 8 years old and you say you know what we ought to do is get this second implant. There is some evidence that having two of them improves your communication ability and your sense of where you are in the room. You go into be evaluated for that and while you are in there it slips out that you are having a little trouble navigating in dim light and the person who is interacting with you for the second cochlear implant goes uh-oh, are you going to tell me more about that? So before you know it you are talking about this. One minute you are sitting there and you think you have dealt

with this terrible attack on your daughter and you have survived it and you are now up at age 8 and everything is ok and the next minute you are in there again talking about another rare thing. You are being told that there are these genes that affect the sensory neurons of the ear and the eye. There are analogous functions in these two organs. Now the retina is going to slowly be lost over time. Usher syndrome. So what do you do? You start asking around about it and find out it is this autosomal recessive condition. There are 12 genes that are known. As was already said it's the most common cause of combined deafness and blindness. That doesn't sound so good when you are reading that. There are 20,000 people in the US. Bella touched on this. She is already standing up here interacting with you perfectly normally, she is riding her horse, she is competitive, she is great in school but when she was standing her looking at her notes she could not see the rest of the podium. So her field of vision is already constricted and it is constricting more. Moira used to work up here in this building and she used lip reading to augment her reduced hearing. Then she lost the remainder of her central vision and she can't see any view now and she can't lip read and so she couldn't do the job that she had done before because she lost that. She touched on it. When you are faced with that impending loss of vision you think about that every single hour of every single day of your life. So, you read more about Usher syndrome. You read more about these things Moira talked about communication barriers, educational difficulties, social isolation. All these things are real. We were out there today on the street with the guide dog. Cabs are driving by us. They don't want to fool with the guide dog. Try to get into this building if you have a cochlear implant. You can't go through the machine. You have to wait for them to go find some woman in an adjacent building to come over pat your daughter down. On and on and on. You read these things. You go I don't want these things to affect my daughter. It was mentioned most patients with Usher syndrome are on social security disability or on medicare. 82% unemployment. The bright spot in all of this is they met Moira. Here is a woman who graduated from the Kennedy School of government at Harvard. She worked in this building for senators and congressman. A very accomplished, driven person. That is a bright spot because you go ok life is not over. We can conquer this disease. But truth be told we really just don't want the guide dog thing. You know what? Moira doesn't want the guide dog thing either. She wants to get her vision back. Back to this being a doctor thing. What would you want? You go in that room and this diagnosis is now you or your daughter. You want treatment. Above all you want to protect any vision you have and you want

to get back any that you have lost. You want improved diagnosis and prognosis. How fast is this going to change? Can I tell if one of my other children is going to be affected? Can I tell if other family members are going to be affected? You want treatment, diagnosis and prognosis but above all you want it right now. All through this conversation we are going to have today you are going to hear this strain of urgency. This is not some theoretical thing; this is something that is affecting real people right now. You want it now. If you facing all that yourself or your family came to congress, what would you ask for? If you were going to walk in and knock on someone's door and go look up some folks from your state. I think what you would ask for is this. You'd say we want increased NIH funding for projects that will lead to safe and effective therapy for this disease. That's what we spent this morning doing, trooping all around asking people for that. That's what our 'ask' is. That's what our purpose is of being here. So what do we want this money for? What do we want money to do? The goal is actually sort of distractingly simple. We want to treat everybody with Usher syndrome. We want to be able to treat them regardless of the state of their disease. We want to treat them for $15-$50 thousand a piece. That's a stunning number. The reason I put it up there is if you troop around to corporate entities who are also working on this disease. God love them. I hope they succeed. They are talking about $1million a patient. Multiply 20,000 patients by $1M and see what number you come up with. When we trooped round the halls of power today we did not see that number lying around. I don't know exactly where the solution is going to come in but it is going to something less than $1M per patient between now and the time we treat everybody with Usher syndrome. One of the strategies is to appeal to philanthropists. This guy on the right up here is Steve Wynn standing next to his longtime colleague Steve Dezii. One of the weigh points on our journey to curing Usher syndrome is having available to us our own GMP facility. What a GMP facility is is a specialized laboratory that allows you to make gene therapy vectors and stem cell reagents in a fashion that are compatible with the Food and Drug Administration allowing you to put them back into a person. They are pretty expensive facilities to create and are expensive to maintain and it was one of the barriers to us being able to operate in the space of super rare diseases. I'll show you how rare in just a minute. Mr. Wynn built a GMP facility for us and we now have the opportunity to make our own gene therapy and stem cell reagents at the University of Iowa inexpensively and that's where that $15-$50K number comes from. So let's be clear. If a corporate entity can have a business model that will

make a safe and effective therapy for Usher syndrome and if third party payers will pay for it, that is fabulous. Let's go do that. But if there is one of the other types that doesn't fall within the commercial viability spectrum then we have to do that some other way and I think that other way is going to be philanthropically assisted academic laboratories at universities. We have this big sign, we actually have a whole series of these in the laboratory and the big banner across the bottom says Leave No One Behind and that is our way of sort of taking that idea. It doesn't matter whether you are Moira Shea and you don't have any photoreceptors left or you are Bella Dunning and you can still see fine. Everybody in there wants some sort of treatment and we want something for all of them. This slide is to sort of illustrate the notion that we have touched on several times here that depending on where you are in the course of the disease, different interventions would be applicable to you. Notice down at the bottom, maybe you just failed the newborn hearing screening; you don't have anything wrong with you. There is a thing that says prevention. What does that mean? Your family is at 25% risk of having another affected child the next child that you have. You go up the ladder and you see things like gene therapy and stem cell therapy. If you don't have any vision we are talking about Google cars and text to speech and guide dogs and stuff like that. All of these things are good. All of these things need to be developed and fostered so that we can keep all of these people functioning in society as valuable members of our society. A central thing in all these treatments is genetic testing. The reason for that is that there are a bunch of different subtypes of Usher syndrome and frankly there are a bunch of other inherited eye diseases that look sort of like Usher syndrome. Many of the treatments that we want to offer our patients depend upon knowing exactly what the person has because the treatment is very mechanistically driven. I just want to update you on where the state of play is for genetic testing of Usher syndrome nowadays. If you got on the web and looked around and called people you would find genetic tests for Usher syndrome ranging from about $450 to more than $7000. If you do everything that you know how to do in 2015, you will find a disease-causing mutation in about 79% of people who have the clinical features of Usher syndrome. Part of that is because there are still some more rare genes to be found and part of that is deafness is common so you can just have deafness and retinitis pigmentosa together accidentally every once in awhile. Things like that. So that number is never going to become 100% but I find it stunning that it is almost 80% because when I started in this business almost 30 years ago that number was zero. We could not molecularly diagnose a single

person. But, there is this sort of curve of how much it costs to find what. There is an important number I think there that you can find the genotypes of 53% of Usher patients for $575. That is where the state of play is in 2015. I'll explain that a little more in just a minute. The numbers I am referring to, these statistics I'll show you in the next couple of slides, comes from this study of a very large cohort of patients, 2200 patients with Usher syndrome gathered over the last 30 years by all the people that you see up on the slide there. These are all our collaborators that have shared samples with us over the last 30 years. I want to specifically note the first one on the list, Bill Kimberling. Bill Kimberling is known to most people in the Usher world. They know him personally. He has probably been in their living room talking to them about their kid or about the research program. Bill is a faculty member at Boystown National Research Hospital in Omaha, Nebraska and we had the great good fortune to have him work in our lab sort of on an extended sabbatical for three or four years where he shared his large collection of DNA samples with us and a lot of these statistics I am telling you about came from the study of his samples. We just had a donor give us a big gift to create what is going to be known as The William Kimberling Usher Research Laboratory at the University of Iowa to permanently acknowledge and sort of memorialize Bill's terrific contributions to the Usher community and one of the things we are going to be able to do is study the 35 years worth of clinical data that Bill collected to understand the genotype/phenotype relationships of Usher syndrome and the other thing is we are going to be able to offer genetic tests for patients who can't afford genetic testing otherwise. There are different strategies for doing this and just like I said with the corporate thing, let's just get people tested. Let's get everybody tested by whatever means possible. One possibility and we did this for another disease, Leber congenital amaurosis, a few years ago where we had philanthropists contribute money to support people who couldn't afford the testing themselves and that is what we are doing in the Kimberling Laboratory now. So what are the data? I mentioned this. We screened these 1765 people and 53% of them were positive at the $575 rate and then the other people needed a more sophisticated test for larger genes and more in depth sequencing. On the whole the testing cost is probably a little bit under $1500 if you did the whole thing averaged across the whole cohort. This is way the genes break down. You see they are very different. USH2A is far and away the most common cause of Usher syndrome. Because this is about 1000 and so findings you can just look at those numbers as sort of like percent's so 60% of the people have USH2A.

24.9% of the people have Myocin 7A and at the bottom USH1G, one patient affected with USH1G out of more than 1000 people. I saw a family not long ago who had a disease as rare as USH1G and they said so how common is this thing? I said not very common. She said well like how rare is it? I said I think there are probably less than 40 people in the US with what you've got. So your daughter is 7. There is not another 7 year old. So the mom asked me who is going to work on it then? What's the answer to that? Who is going to work on it? Yeah we are. The way we are in this philanthropically funded nonprofit setting is we are going to re-use parts. We are going to re-use the vectors we use for one gene for another gene. We are going make these gene therapies in the basement with philanthropic money and the costs of these clinical trials are going to be ridiculously low compared to a corporate model. Again if someone can make it work on the corporate side, go do that because there are more than 100 genes that cause human photoreceptor disease and we need to treat all of them. So just to show you this business about the tiered testing one last time. Let's say you have $57,500 burning a hole in your pocket and you put it in this account. If you use it for the $575 tiered test you find 53 peoples genotypes that way. If you say no I don't want to do that I want the more expensive test I want to do the more expensive thing in everybody. That's fine. But with $57,500 you can only do that in a much smaller number of people and so the total number you end up finding that way is 23 people. So again if what we want to do is fan out across the country and find everybody, find all 20,000 people and get them tested. If money is no object, let's spend $2000 and get them all tested. If money is an object, let's spend $575 a person and get everyone up to that 53% level. But in my view you shouldn't spend more than $2,200 for Usher testing regardless of who is paying for it in 2015. Back to our leave no one behind slide. The rest of the talk I'm going to give you an overview of treatment. The treatment ideas that we have for Usher syndrome in 2015. So what about this prevention thing? This isn't for every family. But a derivative of in vitro fertilization that has been around since the 60's is that after you do the in vitro fertilization and end up with a handful of embryos in the dish you can actually test those and see if any of them carry the genotype that is in your family. So this little movie that was shared with me from my friend, Mark Hughes in Detroit. This is a living human embryo held in position with a pipette on the right; the other pipette is coming in to remove one cell from this human embryo. You will see it just being vacuumed off with that little pipette. You can take this one cell off the embryo and do a test on it and see whether the family's disease-causing

mutations are present there or not. We and others have used this dozens of times to allow families to have their own biological children while dodging the disease that is in their families. Again it's not for every family. Some families would say no there is a 75% chance they are not going to be affected and I hope they are not. Science is coming along. We are hoping they are going to be okay. Some people would adopt children. Some people wouldn't have other children. Lots of different choices that someone can make but this is one that exists in 2015 if you know your genotype. The remainder of the time I am going to talk to you today is these two things that we talked about gene therapy and cell therapy. That is really where the action is these days. This is sort of an overview schematic of how we are doing it these days. Every patient that comes in gets a blood sample and a skin biopsy. The blood sample we use to go off and genotype the person to try to find their gene. We then establish patient derived cell lines from their skin. So what do we use these cell lines for? One thing we use them for is we can actually make retinal tissue, actual living retina and I'm going to show you that in just a minute out of a patient's skin cells. It used to be that if we found a very unusual set of mutations in a patient's sample, something we had never seen before, we would wonder does this thing really harm the retina or not. Sometimes you just couldn't be sure. Now we can actually study the living retina of a patient with an unusual mutation and convince ourselves whether it causes disease or not. Another cool thing we can do, as I mentioned that we are going to be making these gene therapy things in our own laboratory. How do we know they work? How do we know that they are effective in restoring the protein function to the cell? How do we know they are not harmful to the cell? In the old days this would be an animal model for every one of those things and sometimes the animal models don't accurately reproduce the disease so a whole field will just be stymied for a decade ringing its hands because the mouse doesn't recapitulate the human phenotype. But now we actually have the cells from the affected individuals growing in the laboratory and we can put the proposed gene therapy into the actual human cells and show that we restore the existence of the protein and sometimes the function. On the other side for people like Moira who have lost their photoreceptor cells, we can actually differentiate these cells into retinal precursor cells just like are present in the developing human retina and transplant these into the retina to restore function and I'll show you that in just a minute. Putting all this stuff together on one arm of this schematic you have people like Moira who have lost their photoreceptors and need them back, that's the stem

cell transplantation side and on the other side we need to make gene therapies for every one of these subtypes of disease as rapidly as possible so that we can arrest the disease with gene therapy. There will be some people in between who may need both things. They may need some gene therapy to stop the disease they have now but have already lost enough that when this gets really far enough along we want to give them some cells back. Here's our gene therapy poster child for the day one more time and for those of you who haven't seen human gene therapy before, this is my partner, Steve Russell at the University of Iowa. This is a historical photo on the day of the first gene therapy at the University of Iowa. This is RPE65. Here you see a 41-gauge cannula injecting a gene therapy construct under the retina of a four-year-old child just to show you what that looks like. Every fellowship trained vitreoretinal surgeon in the country could do this type of surgery. If you have the stuff available, you could really do this very widely once it was going. The other poster child, Moira you and Finnegan are back on the screen here, here's our lady who needs her stem cells back. I'm going to show you the concept behind this. On the right side of the screen you see a normal human retina and a little schematic down below showing that there are three neurons between a photon hitting the retina and the brain. The photoreceptor is on the bottom, they talk to bipolar cells, they talk to ganglion cells, and the ganglion cells talk to the brain. In retinitis pigmentosa, that bottom layer, the photoreceptor cells are the cells that are lost. The inner two layers, the ones that talk to the brain, they persist for decades even after someone is completely blind. The idea is to put new photoreceptor cells back in to talk to those remaining retinal elements. These are keratinocytes, skin cells from a 62 year old of mine. If you treat these skin cells with a series of four cancer genes transiently, the expression of these four genes erases the memory of the skin cells so they now think that they are embryonic cells. These two photographs are taken at the same scale. These are tiny tiny little embryonic cells now called induced pluripotent stem cells. You start on this little scheme I'm going to show you and change the medium that is in these cells every two days changing growth factors to mimic what these cells would ordinarily see during the development of the retina. When you do that at about 45 days you see a clump of dark pigment appearing and that is the retinal pigment epithelium forming. The retinal pigment epithelium starts releasing its own factors in the dish and at 70 days on one side and only one side of this clump clear cells start forming. Over time these cells grow around in a c shape, that's if they are attached to the dish, if they are not

attached to the dish they will actually form a 3 dimensional sphere. I will show you this thing up close. There is the little c shaped thing. What is that thing I am showing you? It looks like an eye because it is an eye. It is a little human eye forming in tissue culture because we got stem cells and we put growth factors on it in the right order to make the cells think they were growing in a person. It is retina on the inside, retinal pigment epithelium on the outside. If you take a little strip of that and stain in with antibodies that recognize things like Recoverin and Rhodopsin, which are normally present in photoreceptor cells, you see that all the components of photoreceptor cells are in there. You can disassociate cells like this. In this case we have just put a marker in there that is green whenever the cell thinks it is a photoreceptor cell. Two weeks after disassociating it from this structure the cells have retained their photoreceptor lineage. This is a four-day-old mouse. He is asleep. He is packed in ice, which is keeping him asleep. You see a dime in the same field. That is to show you the size that a four day-old mouse's eye is about the size of Roosevelt on a dime. That little needle coming in from the side of the field is my partner, Arlene Drack, with a 41-gauge cannula injecting it reliably into the subretinal space of a four day-old mouse. She can do that all day long. Then you put a warm glove full of water over the mouse and he wakes back up again. Two weeks later if you sacrifice the mouse and look, everything that is red in that field is human. All of those photoreceptor cells in that mouse retina are derived from a 62 year-old person's skin. This is the reason that we are really excited about this technology. We and other people have put iPSC-derived photoreceptors into mice and actually shown a restoration of the electroretinogram and some scientists have shown a restoration of actual visual function. Where do we go from here? Now that we can make photoreceptor cells, we have shown we can put them in via needle in a so-called bolus injection, is that all we need to do? Can we just squirt them into the subretinal space of a human and make them work that way? What we know is that if you … the way when I am talking to patients about this, being that we are in Iowa and sort of rural and everything I say if you are a chicken farmer and you have 10,000 eggs and you want to get them to market, one way you could do it is by getting a snow shovel and just throwing the eggs into the back of your pickup truck with the snow shovel and then driving over 20 miles of bumpy road and you might get to market with an egg or two. That is kind of what the problem you face if you are going to transplant photoreceptor precursor cells by shooting it at warp factor nine down a 41-gauge cannula in the subretinal space. The cells don't really like it that much and most of them die. If you can find a way to

support these cells with a biocompatible, biodegradable polymer, there is a 50-fold increase in the survival of the cells and the cells tend to integrate up into the retina better that if you don't support them with a polymer. Just to give you another reason for this, what I am showing you here is the very center of a normal retina and I have a circle labeled the macula and a smaller circle right in the center labeled the fovea. That tiny little foveal area is what you use for your 20/20 vision. If you took a laser and destroyed that little circle, you would have no better than 20/200 vision. It's just that little circle that you need for 20/20 vision. This is a human specimen from my partner, Rob Mullins, showing you what this looks like under a microscope. You see that little quarter of a millimeter diameter spot that corresponds to that 20/20 vision, there are only 9000 cells in there. 9000 cells. We would put millions of cells into the retina when we do a transplant. I remind everybody all the time, you don't have to put 130 million cells back in the retina which is the number we were born with in order to get useful vision. If we get 50,000 cells living in the retina, that would be a big deal. What kind of biopolymer? One of the most abundant polymers on the surface of the earth is what crustrations and some insects use to make their exoskeleton. It's called chiton. It's the thing insects have. If you treat that in such a way to break the chiton down into its monomer, you can add a photo polymerizing agent on the edge of the monomers. The purpose of that, just think about these monomers being like Lego blocks and how you could build something out of Lego blocks. If you put this photo polymerizable moiety onto the building blocks, then anywhere that a light beam is bright enough, the building blocks will stick to each other. What that allows is the use of a 3D printer to make structures out of this biocompatible, biodegradable polymer. This is one such device. Its based on what is called two photon technology in which you have a couple of lasers going into a clear bath and wherever the laser beams cross, the light is bright enough that it will exceed threshold and cause the polymer to be polymerized there. This next thing is the picture that shows you the kind of structure that you can build with one of these 3D printers. The interspace in between the little bars of this tinker toy device are the size of individual human cells. The idea is to make biocompatible frameworks and then put the human cells into that to support them for transplantation. Then over time that polymer will dissolve and be replaced by the normal extracellular matrix. Just to show you a little bit further evolution of this idea, on the left side of the slide to you, you would have the photoreceptor precursors and you are going to make a retina-like layer with the photoreceptors in it and then on the other side

you would make a support layer, the retinal pigment epithelium and then put these two things together to make a multi-layer living transplant. Again this would be made from the cells of the patient you intend to treat so that they would be a perfect immunologic match and so the patient's immune system would think the cells belong to them. This next thing is sort of an artist's rendition. This is just me drawing with Photoshop and not a real thing. This is real – this is a patient with retinitis pigmentosa but this is to just to sort of give you the idea that if you made these two little semicircular discs of living retinal tissue made from the person, you could sort of roll them up and put them through a small retinotomy in the retina and unroll them under the retina and then basically cover the entire macula with living photoreceptor cells or you could make long strips of living tissue and put them in from retinotomies at the periphery and guide them in towards the center with the retina detached and then do an air fluid exchange to put the retina back on. The next steps in our mind are to go ahead and put some of these cells into people. Of course the people we are going to put them in are completely blind. Why do we want to put cells into completely blind people? Two reasons. Do no harm. We don't want to endanger any vision that someone has now with an unproven technology. Secondly, it will be easier to tell whether you've got any sort of response if you don't have any light perception at all and you get restoration of light perception. Initially we will just put the bolus injections under the retina just like we did in the mice just to show that the cells are safe and tolerated by the body and then proceed with devising the polymer strips that I told you about.

In summary, I've shown you now that in 2015 we can find the genes for almost 80% of people walking in the door. I think we should fan out across the US and find all these people. Reverse that negative message that Moira said, there are a bunch of people out there that were told to go home and go blind. Go home, there is nothing we can do. They are out there still. They don't even know they have these diseases. Nobody is talking to them about any of this stuff. We need to go find all of them and genotype them. Then we need to get going with viral mediated gene therapy for the early disease and cell mediated therapy for the late disease. Not wanting to leave you without putting the ask up one more time, for anybody in this room that knows anybody who knows anybody who knows anybody who could help us bust some money loose for this effort, we would really really appreciate it. Thank you guys for coming.