Accelerating Treatments for IRDs: 2020 March Progress Report

3/27/2020

Transcript

Jason Menzo:

Good afternoon, everyone. I wanted to thank you for joining us. My name is Jason, I'm the chief operating officer for the Foundation Fighting Blindness.

I want to thank everyone for taking some time out this afternoon to join us. We have a very special presentation led by our CEO, Ben Yerxa, and he will review the clinical programs. We have a very special guest, the chairman of the Board – Mr. David Brint is on the call. He will say a few words after Ben's presentation. We will have a question and answer session and will give the instructions on how to ask your questions at that time.

And, I did want to let everyone know that in line with our desire to be best in class with regards to accessibility, this call is being closed captioned, and a replay and fully accessible transcript of the call will be available on our website in the weeks ahead.

If you have any feedback related to accessibility or other suggestions for the Foundation, please feel free to reach out to us at info@fightingblindness.org.

I would like to turn the call over to Ben.

Ben Yerxa, PhD:

Thank you, Jason, I hope everyone can hear me well.

Today, we wanted to really find an opportunity to give you a kind of broad update on the stuff going on at the Foundation in regards to the progress moving our mission forward for treating IRDs.

So, first I want to thank our sponsors. These are some of the original sponsors for the Investing in Cures Summit we weren't able to do face-to-face, but we are deeply thankful for.

Blueprint Genetics and AbFero Pharmaceuticals. Also, Wilson Sonsini legal services, who is our pro bono counsel supporting the Foundation Fighting Blindness and our RD Fund. You are a great partner to work with on our journey.

So, jumping into it, it's always good to start with the mission. I know this is familiar to everyone. The urgent mission of the Foundation Fighting Blindness is to drive the research that will provide preventions, treatments and cures for people affected by retinitis pigmentosa, age-related macular degeneration, Usher Syndrome and the entire spectrum of retinal degenerative diseases Today, the Foundation Fighting Blindness is the world's leading private funder of retinal disease research.

This is our north star what we look to to keep us on track daily. Before I get into the full material of presentation, I want to encourage the current situation, the impact of COVID-19, and this is a crazy time.

But first and foremost, we want to make sure that you and all of our researchers are safe. We care about your well-being. So please, everyone make sure you take care of yourselves and families during this time.

We're having frequent interactions with the grantees and funded companies. We are staying in close contact with them. Essentially, some labs are working in shifts, but a lot are temporarily shut down, including clinical trials.

So, essentially everyone is experiencing some kind of interruptions, some you know, and we expect some

delays. We'll get through it.

But we want you to know we're on top of it, we're looking forward to helping you. We are discussing possible grant extensions, milestone extensions if needed. And we were even considering, some grant application deadline extensions but, looks like so far, it's not needed. So, it is good to know that everyone, is staying on track with the upcoming grant application deadlines. And so, we'll keep you in the loop of major decisions we make, including rescheduled dinners and walks and possible changes to the VISIONS2020 conference. Stay tuned on that.

Let's talk about history. So, you know I've been with the Foundation a little over 2 and a half years now. I'm not qualified to be a historian here, but I think we all know that you know our beginnings, began with two families that, really, did a lot of the heavy lifting. The Gunds and Bermans were indebted to the tenacity and financial support and the push to do something, because something was desperately needed during that time.

They got together, and one of the first things they did is they got behind Elio Berson and funded the first retinal degenerative research lab at Harvard for the study of retinal degeneration. They started funding young promising researchers including people like Paul Sieving who got his first grant ever from the Foundation. He went onto lead the National Eye Institute for a very long time, really the largest funder in eye research and the world.

Other important things that, our founders did were working with John Dowling to establish the center grants, and Alan Laties, the chair of the Scientific Advisory Board, really raised our game and prepared us for the future so deeply indebted to all of the Foundational work. We think about the time when the Foundation Fighting Blindness was founded in 1971, very little was known about retinal degenerative diseases. Very little research was being done, and no clinical trials for potential treatments that were ongoing.

I can't go further without talking about Lulie. I know that all of you have heard by now that she passed away on March 15th of this year and, just, to read to you what is on the slide here.

"She was a philanthropist, role model. Really known for her infectious smile and love of life and through all of her endeavors. She was also known for her magnetic personality and smile, sense of humor, and she used to bring people together. She made caring look like fun that to me is great." That was said by a close friend.

She passed away at the age of 79, but she lived an extraordinary and generous life. It is worth celebrating one who left a tremendous legacy for generations to come and the impact on the Foundation, it is just phenomenal. With that, let me pause for a second and then we'll move onto the rest of the presentation.

Let's talk a little first how we've been moving this field forward. Again, few historical notes here I like to talk about – genetic testing and the technology around that, because it had a tremendous influence on a progress we have made.

You probably all heard the human genome project. That started in 1990 with $3 billion to complete at draft sequence in 15 years. About ten years we got a rough draft, and it was completed 3 years later with a complete draft published. And that's a lot of money and a lot of time.

And there's a graph on the slide that shows the increase in the output of genetic sequencing in terms of kilobase pairs. I know many heard of Moore's Law, which is in the microchip industry basically the speed of a chip will double that about every other year.

From this case the advancement of the Solexa/Illumina sequencer between 2004 and 2005, two years, 04-

05 it went up ten billion-fold in speed, in the span of two years.

So, that blows it out of the water this is just an astronomical increase in speed and capability in genetic testing. Now, an individual can walk into an office, get a full genetic sequence completed for a couple of weeks for a $1,000, it's actually a little faster and cheaper than that. Those advances had a tremendous impact on the IRD field.

This slide talks about that impact. If you look at the time spent between 1980 and 2018, you know, in the early 80s really again was nothing known about the genetics of IRDs. It wasn't until 1990 that Rhodopsin was identified as the gene causing RP. So now, think about this, it is almost 20 years in, to the work of the Foundation. And, the first caused of gene identified 20 years later. That's a lot of very patient work going in, trying to figure out what is going on.

But since that time, you know we're now up to 272 genes counting identified in over 300 that are matched. It's a very been a very steep knowledge curve in terms of the genetics behind IRDs and that's really fueled tremendous amount of progress. Even though over the last few years I think you'll see in the slides to come.

The epidemiology of IRD is pretty well-known at this point. If you take them altogether it is 200,000 patients in the United States. When you break them down to individual diseases like retinitis pigmentosa it’s 100,000. Anything less than 200,000 individuals in the United States is considered an orphan category, so all of the IRDs individually, qualify as orphan diseases. Stargardt is about 30,000, and Usher is about 10,000.

Then when you look outside of the U.S. you combine the numbers for U.S. and Europe combined about 670,000 individuals and worldwide it's almost 4.5 million. These are pretty big numbers and when we fully describe these slides. Later with the transcripts we can talk about this pie chart with some of the individual pieces of the pie with X linked and different kinds of RP, LCA, usher syndrome, Stargardt, and all of the different components of the entire field.

I want to acknowledge Steve Daiger, he has done a tremendous amount of work in the field trying to understand the epidemiology. A lot of the data comes from RetNet, which is an important component of the work he has done.

The Foundation has been funding an open access genetic testing. You've heard of My Retina Tracker. Blueprint Genetics is the testing partner, Informed DNA is the genetic counseling partner. Then we also work with Ocular Genomic Institute in Harvard, for some deeper dive in the genetics. Essentially, the My Retina Tracker provides open access, comprehensive, no cost genetic testing to anyone who has been diagnosed with an IRD. The way we're doing it now is much more streamlined and faster turnaround so that you can get the results quickly. And then during the time of the genetic counseling session, you're asked whether you want to opt in the registry and contribute your data, so that, it can live on for research. Also I think as you'll see that it's important to know about your genetic driver of your IRD, because many clinical trials are coming online, and if you want to be informed about those opportunities, the best way to do that is to be in the registry.

Speaking of the registry, current numbers – we're at about 26,300 members, over 15,000 with full profiles. Fifteen hundred of those are outside of the United States, but importantly we've got over 7,500 with a full

genetic panel.

That's really phenomenal – allows us to really, get a sense of what is going on and in fact, the pie chart of those who are in the registry, actually recapitulate the epidemiology from the previous chart. I don't mean to go into the specific slices, but it is fascinating to see the real-world data, not just the predicted numbers from epidemiology. Great progress with the growth of the registry and, our goal is to get over 20,000 or more with genetic tests, so this can really aid in the enrollment of the clinical trial in the future.

So, we've also been busy working on the clinical consortium. What we've been working with top clinical centers around the world, and the consortium now is up to 38 participants. This is shared by Jackie Duncan, our chair of the Scientific Advisory Board. We have got U.S. and Europe covered. We have Brazil as well. These sites are all trained all in the tricky end points in the IRD space. There is a central reading center for these things they're all in the program when a new protocol comes along we're sort of, I hate the term plug and play, but it's pretty simple to get a new protocol up and running everyone is fully on board with all of the processes and it is a great, really exciting group to have together.

Some of the early work was done under the Clinical Research Institute. That was chaired for many years by Dr. Goldberg at Wilmer at Hopkins, and we thank him for his leadership there. We did a big study called **ProgStar**, which is the largest national history study done on Stargardt. This was chaired by Hendrik Scholl who has received awards from the Foundation. He chaired an enormous study, a big list, for $6 million dollars study that followed 460 eyes over 24 months. He looked at many important end points you know fundus autofluorescence, microperimetry, segmented OCT, and things like that. Well over dozen publications have come from that. Many people who are working in the field of Stargardt are looking at this data as a very informative for the design of their trials.

In terms of current and new natural history studies, we've got two ongoing. Under the Consortium, Jacque Duncan is chairing the RUSH2A study for Usher. This is a four-year study of 105 subjects, and 104 have completed the first year, and 13 completed the last two years with only one drop out which is great. The study is going really well.

Numerous publications are already in the works including the baseline data, which is in preparation and you'll find that this is some landmark work in the field of the Usher's research and we're really excited about even just the baseline data. It's fascinating, so that should be submitted for publication here shortly. The most recent study we started is called **pro-EYS**, and this is chaired by Dr. Mark Pennesi. Similarly structured, four-year study of 100 patients. It is going to characterize progression, with respect to functional and structural measures and patient reported outcomes. This is just getting started, we have 30 sites identified, recruitment is started, and we have two in it so far, we're off to a good start there.

I wanted to talk about some novel end point, and this is an important one called **EZ area**.

And for many of you following the Foundation for years you know that we did fund a therapeutic trial. Although that trial did not show efficacy for the acid, and it sort of served as actually the largest controlled natural history study done in RP. When the data was looked at by members of our Scientific Advisory Board, David Birch did a lot of incredible work in this area. We found out that we could use OCT which is sort of like ultrasound for the eye that can quantify photoreceptors in the retina and found that we could actually measure exclusively the loss of photoreceptors over time using this technique. That allowed us to validate this end point with other visual end points like visual acuity and so on. We got this information from the FDA, and the National Eye Institute did a workshop, even co-published with them on these results. It is now considered to be a well validated end point for clinical trials in RP. The point here is that with this end point, people can now do, say a neural protective trial in retinitis pigmentosa

with an objective anatomical read out in two years, instead of 5-7 years. That is a huge change in the field that makes these trials much more feasible and trackable to do.

Quick word on the FDA – many of you probably have heard of Dr. Wiley Chambers. He runs the ophthalmology division of the FDA. We did a little advocacy work. Thanks to Jerry for helping us with this, we wrote a letter along with other organizations like the American Academy of Ophthalmology. Jerry's words were that the ophthalmology needs to have a direct reporting line to the office of the new drug, and not be grouped in with anti-microbial products. The division of ophthalmology is already combined with transplants. It is under the division of anti-microbial products. We were pleased to see that in January of 2018, and it was a mini reorg that allowed Dr. Chambers to report directly to the head of new drugs. We think that's positive development to give ophthalmology more priority within the structure and the bureaucracy of the FDA.

I'm sure many of you have already heard about LUXTURNA – the first gene therapy approved for an inherited disease in the United States. This happened in December 2017. Around the time I was onboarding for the job at the Foundation. I got to go to the advisory committee meeting at the FDA, and I saw Ashley and Cole Carper during the open mic session. Other people from the Foundation family from San Francisco and other parts of the country, including Christine Kay who came up from Florida and let the panel know how meaningful this treatment was to their family. I know the data speaks for itself, and this team has developed a totally end point called MLMT test. It is a way to essentially challenge vision under lower light levels, and it was a way to really measure efficacy of the gene therapy in LCA – childhood form of RP. The results were incredible, a 30-patient trial. Immediately those on treatment, had two levels of increase in their ability to navigate the test. It's still on control, they stayed at the same level for a year. Once they went over into active treatment, they bumped right where the others were. The statisticians at the panel said this the strongest data they have ever seen. No surprise that Spark was very, very popular. So popular they were acquired by Roche for $4.3 billion, and that closed in December 2019. Before that deal was done, they had done a partnering deal with Novartis to commercialize this novel gene therapy outside of the United States.

That's worth mentioning because now you've got a big pharma that will basically teach the world how to do subretinal injections to treat gene therapy. That takes a big muscle to do that. It's worth noting that the Foundation contributed about $10 million in research dollars to the labs that made this happen.

That's the impact of the Foundation long haul, patient money, keep funding gene therapy, even when there were tough times on gene therapy and kids even died in trials, so we kept at it got it over the finish line.

A little about the ophthalmology market. you know for those of you have been following ophthalmology for a while. Twenty years ago, when I got into the field, the biggest specialty by far was glaucoma. if you were a company in ophthalmology, it was all about glaucoma. Now, in 2019 the global ophthalmology market is $29 billion and 13 billion of that is retina. The retina is the largest segment, more than 2 and a half times the size of glaucoma. It is projected to be even bigger in five years with 42 billion total market, and $22.4 billion will be for the retina. It is just important to know that the retina has become the biggest segment.

Part of the reason for that is because they have been able to develop the drugs for wet AMD delivered by intravitreal injection. This is basically a full-length injection in the middle of the eye which you know 15 years ago it was a pretty rare procedure. It was done with little bit of fear not that many people knew how to do. There's a chart on the right here that shows the growth of intravitreal injections from 2008 to 2019 in the U.S. alone it was maybe 2 million or so. In 2008 it was up to you probably 6.9 million, and in 2019

but globally number is 24.4 million intravitreal injections per year. That's incredible, this opened up a way to dose the eye in a very consistent safe and reliable way that is very beneficial for future therapeutic knowing you can at least get the drug there. This is actually the number one procedure now, and it outruns cataracts many years ago. There's another way of coming, so gene therapy is happening, and the first one approved is subretinal delivery. Many of the ones in development are also being tested subretinally which requires more invasive procedure called vitrectomy. You take out the jelly part of the eye, put Saline to create a fluid in there you put the gene therapy under that. And it it's a pretty delicate procedure, but you know what - people are starting to perfect this, they're using OCT to guide that. You can do it very precisely or even, robotic versions of this to be super precise and careful. So, the field is really taking off, there are even new devices in development that can deliver drugs to different compartments of the eye that could be relevant.

Orbit Biomedical, which was acquired by Gyroscope, has a new way to do the subretinal delivery in development. Clearside Biomedical has a device for supra-choroidal delivery which is delivering in the backside of the retina. Stay tuned to this base as more and more therapies are developed, and a new different delivery options become paramount.

So now we're getting talk about the programs in development. We'll go fairly quickly because there are a lot of programs here. I want to start with some caveats, so as I was putting this together I realized that you know this is really, it's a selection of programs in preclinical or clinical development these programs with significant results or resources for moving ahead, it is not everything. It is not all inclusive. I'm doing it alphabetically, but sort of sued alphabetical, the common name not the gene. I'm going to highlight key scientists done at my discretion and somewhat randomly perhaps, so don't punish me for leaving someone out, I left lots of people out. I've done my best to cover the highlights here.

Programs are presented where they're funded by the Foundation or not. And, also as a reminder Dry AMD is in the mix, but only very few limited programs that's a big field. In our view, advances in the dry AMD can help research in IRD and vice versa.

The top is achromatopsia, and these are the genes CNGA3/CNGB3. The first program on the left is two programs from AGTC. The work that came out of Bill Hauswirth's lab, these programs have data through six months, 3 dose levels 2-5 subjects per group. And they're showing some signs of efficacy. They have a light discomfort test, it's a new ground they're hitting with the end point. There's some pretty interesting patient reported improvements, and they have already moved to some higher dose groups, and the adult pediatric patients. They have looked at announcing new data around the second half of 2020, we'll have to wait for the second half of the year for the data on the two programs. Another set of programs is MEIRA GTX, which is a partner with Janssen, Johnson & Johnson company. CNGA3 trials enrolling children 3-5 years old, 23 in total. Dose escalation in progress, and the trial is initiated in third quarter of 2019. The Beta 3 trial is the CNGB3 trial has completed the dosing in 23 subjects, 11 adults and then 12 children, and pediatric expansion.

Here's one slide, this is four phase two programs on one slide for those keeping track.

The next slide is the dry MD program from AbFero called Iron Chelator. This new research is showing that you can decrease some of the oxidative damage, which is known to cause damage in the retina and dry AMD, which can be used in the - IRDs.

They're working on the pre-IND work for this compound, and hopefully it will be in the clinic in the next

12-18 months. This work is primarily coming out of Josh Dunaief's lab at Penn.

A few more on AMD. These are complement programs. These are major programs, the first one on the left is from IVERIC Bio, and his is Phase two results they recently released this year.

There were 286 subjects in the trial, this is one of the dose levels. 2-milligrams of Zimura versus Sham. This is a drug that inhibits the C5 complement protein. Essentially, what you see here is a geographic atrophy. They're looking at the size of the lesion, like an image analysis, essentially an area so it is millimeters. What they saw over 12-month period of time is there was about a 27 percent less increase in the area of Atrophy compared to Sham, and it was highly statistically significant (p 0.0072).

Those are really strong results and they announced they will go into a second pivotal, but they're holding off because of the virus situation.

The next one is Apellis, Phase 2 trial called FILLY, with 246 patients. This is the C3 inhabitation complement, pretty similar effect. They have gotten a 29 percent difference in lesion growth, which are similar numbers to the Iveric Bio graph. They have already launched two Phase 3 trials with 600 subjects each. These are really major programs and hopefully they will read out positive in the future.

Some interesting gene therapy approaches to dry AMD. One of them coming out of MacLaren's lab licensed by Gyroscope. It started in 2019 in the U.K. Retinal injection, open label, but basically, it's the first gene therapy trial to start for AMD that we know of.

There's also a company in Boston called Gemini, a lot of work that came out of this lab. This is a company working on both factor H complement and complement factor I. They have started the phase one study with the common protein just a couple of months ago. What is interesting about Gemini is that their approach is to start with the protein, and if it works, then pivot that to a long-term gene therapy trial so they don't have to keep reinjecting protein in the eye. So, we're keeping an eye on that one.
Then Greg Hageman, a leader in the field for years, has a startup called Voyant Bio Therapeutics in Utah. Being secretive about their progress but they have been well-founded for years, and clearly an expert in this field.

In terms of cell therapies in dry AMD, Astellas has been working on it for a while, and they have a cell-based trial that's 150 participants. It's a sort of a multi-phased trial, got 3 stages, last stage is long term extension. Also using cell-based therapy in a small study for Stargardt, and we're awaiting the results on the read out of that.

Important effort coming out of Dennis Clegg's and Mark Humayun's labs, funded through an agency in California. They're in a fairly large Phase 2 trial in geographic atrophy, and they made the cover of the Science Translational Medicine recently. You can see the outline of the implanted patch that almost looks like a wine bottle in the front of this photograph. But they have got a very clever device for getting it there, and we're awaiting longer term and larger results on that gene.

A couple of other programs for cell therapy: Lineage Cell Therapeutics which is a new name. I forget the former name of the effort, but they have a recent announcement, and they are enrolling in a Phase 1/2 trial in U.S. and Israel. The data update in February announced that all five patients in Cohort 4 had increases in best corrective visual acuity. I have not seen the data myself but waiting for peer reviewed data. They're using the Gyroscope for the subretinal delivery. It is funded by the Israel Innovation Authority, about$14 million worth.

Another major program coming of the National Eye Institute, Kapil Bharti's work, and many other people from the institute. This is Autologous iPSC-RPE epithelial patch. And for those who have been following this work, it's been a long hall they have got an interesting PLGA. You see the picture here showing the RPE cells growing on the matrix, sort of hair like projections of the RPE. But the idea is clear, and they expect to be enrolling as soon as they can get it off the ground. The IND is clear this, and this will be entering, so we're excited about that.

One more program – this is one called the "London Project." This is work from Peter Coffey and Lyndon da Cruz at UCL and funded by Pfizer. They published some of their Phase 1 results, small numbers, but I think a pretty serious effort here. We're also glad to see a non-profit group willing to fund projects like this, when they're in that risky startup phase. So look for more from this group in the future.

Switching gears now to Best disease – this is the Best 1 gene. Iveric Bio picked up a program out of Penn, primarily coming out of Karina Guziewicz and William Beltran's work at the school at Penn, and we supported that work. Basically, when they published this work on the dog model Best 1, it got picked up by the industry. We're glad to see it by the industry, and we thought it was a really extraordinary result, and if this stays on track, it will be in the clinic in the first half of 2021.

Choroideremia, this is the REP1 gene. Three programs here, there's work done by Biogen, it came by the acquisition of Nightstar. Robert MacLaren's work, and they're basically in Phase 3. The STAR trial in choroideremia, this is initiated in the first quarter of 2018. I have not heard their projected timeline on the data release, but I would expect that to be in the next maybe year or so. That will be an exciting time. Really nice paper on their early data.

Spark has a program here that only started a small Phase 1/2 trial subretinal injection of 15 subjects, and company indicated it is in long term follow-up currently.

Another company called 4DMT partnered with Roche on the program. This is an intravitreal approach, and they anticipate first human testing in the second half of 2020. Hopefully that will stay on track, we wish them. That is with the 3 programs there.

A new one is just coming up, this one is called Enhanced S-Cone Syndrome (Nr2E3). Coming out of Neena Haider's lab at Harvard. This is picked by a company called Ocugen, and is really showing nice results in slowing down, even some rescue of the disease caused by variance in the gene NR2E3 gene. They will bring this to the clinic hopefully in the next two years or less. They have signed a deal with the manufacturer CanSinoBIO from China which is a huge, multibillion dollar vaccine manufacturer. They're a good partner for this company to cost effectively manufacture gene therapies. The company is also looking at potential other applications of the therapy for or IRDs based upon the mechanism of action.

Next one is Gyrate Atrophy – this is variations in the OAT gene which is amino transferase. I have had the pleasure of attending a workshop organized by a group of families. They got together called concurring Gyrate Atrophy.

Some of the work done at Johns Hopkins including ground-breaking work by David Valle, showed in this particular disease there's a chronic buildup of circulating ornithine which can be toxic to the retina. If you put patients on a protein restrictive diet, and add back all the amino acids, except for arginine, or arginine in a tiny amount, you can actually stop the progression of the disease. It's a pretty interesting way to validate that approach. Very difficult diet to adhere, because you cannot eat any protein.

So, it's pretty onerous but it showed that if you can bring those levels down, you can actually stem the

disease. There is a presentation by someone from the University of Tasmania who got the award for longest distance traveled for workshop. It showed early preclinical work was kind of interesting showing if you had a designer probiotic it would actually chew up and convert it, it could be potentially a treatment for this condition. So, stay tuned for that.

Let's go into LCA, so starting with LCA1 it's the GUCY2D gene. Some very important work coming out of Shannon Boye's lab clinically working with Sam Jacobson at Penn. This work was licensed by Sanofi and being brought into a Phase 1/2 trial and started enrolling in November 2019. We are anxious to see what those results look like, we do understand Sanofi is getting out of the Ophthalmology field. We're looking for someone in the industry to pick up the program from Sanofi.

LCA2, RPE65 – we already talked about Spark and Luxturna, this is approved in U.S., Europe and other countries at this point. But many key players here, again this slide may you know, raise some hairs because this program touched many people. I think it's worth knowing how Cathy High played an extraordinary role here. And not just Jean Bennett, but her husband, Al McGuire taught the world how to do this safely during the first injections doing it very well, which is really important in the field. Sam Jacobsen did a great work on the clinical course of the disease and overall worked in the space. Will Hauswirth did work on vectors, which is really important for this work. And of course, Gustavo's work on the dog model has been instrumental in having confidence in the program going forward.

Don't beat me for missing some other key players, there are many people worked on this program, but these are some of the celebrated people we wanted to highlight.

This one is LCA4 (AIPL1) gene. Working with Robin Ali's lab in London. It's interesting how MeiraGTx has made this program available in the U.K. called a special license. It's exceedingly rare IRD that effects children at a very young age, and they basically said if you find someone that meets the criteria, we'll make this available right now. Anyone hears of anyone with AIPL1 variant IRD, they should get in touch with the company to see if they can have this looked at.

Next one is LCA5 (lebercilin) and this is the coming out of Jean Bennett's lab at Penn. She showed she could restore structure and function of model LCA5, so not surprising this is picked up by industry called Limelight Bio, who is an investor. This has been licensed and it is in pre-IND development, so we look forward to progress on that particular program.

Next one is LCA6 (RPGRIP1) - many people have worked on this program. I wanted to highlight a couple of people. Luk Vandenberghe at Harvard for his work in the AKD vector that was eventually used to produce the therapy that was licensed first by Odylia, which Eric Pierce is the founding member. This is a really novel non-profit pharmaceutical company moving the ball forward for rare retinal diseases. They were able to bring in and license this technology to PTC Therapeutics to take in the clinic. I think that's a good validation of the business model, and we appreciate all their work on this.

Next one is LCA8 – the CRB1 gene. For those who have been following the science here it's really fascinating. You know CRB1 is extremely complex. There are different forms CRB1 and CRB2.

Jan Wijnholds has been working on this for very long time and really wrote a great review, using the trail of crumbs, being a very difficult one to navigate. Significant work done by Jan's lab supported by the Foundation.

Recently, Jean Bennett has been jumping into the mix, and has been publishing on clinical work on CRB1 in terms of natural history. Jeremy Kay showed up on ARVO last year and stunned everyone with

essentially identifying a new isoform for CRB1. Everyone has been talking about it since.

Jeremy is at Duke, and we've been talking to him as he is a grantee of the Foundation. I think that this space is heating up with new biology and learning, so we're excited with progress here on LCA (CRB1).

Next one is LCA10 (CEP290). This is one of the most active areas in LCA. What is fascinating that there are multiple different approaches to go after the same kind of problem. Rob Collin's significant work on the Oligonucleotide's is licensed by ProQR, and it is in Phase 3. In the middle we have Feng Zhang, who is a major guy in the CRISPR-Cas9 gene editing field. A lot of people have been in this field I cited this one paper I think has been heavily referenced by many people. Company called Editas picked up this technology to bring gene editing into the clinic. They did a deal with Allergan for Ophthalmology program. Many of you have seen the press release on March 4th of this year the first patient was dosed in the Phase 2 trial, so the first patient dose to gene editing was delivered inside of the human body - this is in the eye. Again, ophthalmology and IRDs are blazing a trail in the field of modern medicine.

The third program is Iveric Bio, licensed and preclinical by Hemant Khanna at UMass that has a cool technology on the mini gene CEP290. Take a big gene. Try to find a way to make it smaller so it can fit into a regular package like AAB. This has been licensed by Iveric Bio to bring that into the clinic we're excited about that.

This slide is talking about some of the data from ProQR and CEP290. The companies released 12-month data in the Phase 2 trial, and the teams have been an investigator on the trial and delivering great talks about the data. I think without going into every detail on the graph, that take home message here is that when you have a trial where there's data where the data all hangs together going in the right direction, you've got improvements and best corrected visual acuity compared to control. You've got more sensitive retina measured by FST compared to control, and you've got better performance on mobility test compared to control. You start to get pretty confident this is really doing something.

This is 12 months out, and I think it's really pretty encouraging. They're enrolling a Phase 3 trial called Illuminate, and we wish them well on that on that second trial and Phase 3. Hopefully, it will be reproductive and reproduced to see the results on a larger scale. So far so good on this.

LCA13 – this is the RDH12 gene. This is an example where we work with a patient group to hold a workshop in 2019 where the patient group did a lot of heavy lifting by preparing a briefing document and helping them pull things together. We invited some of the key researchers like Debra Thompson. She recently published, and Jean Bennett also published in the area. A couple companies showed interest – MeiraGTx and Limelight Bio. No commitments from them but showing interest and being there to help and talk about end points, and even the FDA was there. Dr. Chambers we talked about earlier, came to the workshop stayed with us for the entire day, and gave us some great, regulatory insight and wisdom that are very specific. We're happy to do these on a periodic basis when programs are short of that next stage, and they need a little extra pop the wisdom of the key group to move them forward. So really good progress on RDH12.

This one is LCA, a lot of numbers (NPHP5/IQCB1). A couple of programs here - recent publications on preclinical work and in a knockout by Wolfgang Baehr at Utah. Gustavo Aguirre also with some significant work that was recently submitted for IP production, with some of the usual suspects like Jacobsen and Cidecyian. We look forward to some progress on this rare LCA.

The slide here is briefly talking about the optic neuropathy of the ND4 gene. Normally we don't talk about optic neuropathy at the Foundation, but sometimes important work can lead on in our field because

it's very closely related.

Important work coming out of Jose-Alain Sahel's lab and company called GenSight with promising Phase 3 results. Despite some design issues with the contra-lateral controls instead of separate control groups, they did show that in this both eyes are predicted to go downhill in terms of loss of vision. Pretty reliably they showed that after treatment they could not only sort of slow the design and showed improvement in vision. The problem was they had improvement in both eyes. That's led them to do some investigative work in nonhuman primates. There could be some cross over effect with unilateral gene therapy dosing. More to do there, we would like the field to try debunking this to try to figure it out. Interesting results here.

I want to acknowledge, John Guy at Bascom Palmer doing some significant work, and he started his own trial at the university.

Next one is LRAT/RPE65. This is work done initially by Krzysztof Palczewksi who discovered the compound and developed by the ophthalmologist Dr. David Saperstein. This is the synthetic retinoid which was initially developed by QLT at Retinagenix. It's been kicked around for a while, but it did get picked up recently in December and January time frame by Bridge Bio. They are taking it into a Phase 2 study and hopefully do the right study to get an answer to see if this compound could have an effect in this important category.

Next one is RP2 gene for RP. Important work coming out of Anand Swaroop's work at the National Eye Institute and U Mass. Really nice publication of long-term rescue of cones – a model of RP2. This is one that is available for someone to pick up, we're anxious to see who in the industry will take this on and develop it into the clinic.

Another one, PDE6 Beta form of RP. This is being developed by Horama in France, and they have licensed the work done by Philippe Moullier and Fabienne Rolling in France. Currently enrolling in a Phase 1/2 dose escalation trial and based upon the initial work they did on P6 Beta dogs. Pretty impressive work there. We understand this data may have an read out in the second half of the year, and we'll see if there are any delays due to the virus, but hopefully if they stay on track they will be able to release data in the second half of the year.

Another program in RP is the RLBP1 gene. This is an example of a home grown IRD program in big pharma at Novartis. Big pharma is interested in this, and Novartis researchers Terri McGee and Chad Bigelow have designed and developed this in their own lab. They started trial in Stockholm, Sweden, and we await the results. Stay tuned, great to see a big pharma doing the work here.

Let's talk about retinal progenitor cells, and this applies to RP. retinal degeneration. Important work coming out of Dr. Klassen's lab at UC Irvine and a company called jCyte. This is an intravitreal injection of these cells. It is an ongoing trial in Phase 2B, fully enrolled, 84 subjects, and it is a very well controlled trial design. We were expecting data release at ARVO. Unfortunately, this conference is not happening due to the virus. We have to wait and see what their plan is for data release. They have also received major funding from Cirum.

Other important work coming out of Michael Young at Harvard, licensed by a company called ReNeuron. Similar approach like the retinal progenitor cells. There are given subretinally, so different location for the therapy. It is an open labeled dose escalation of 3 dose levels with 21 subjects. They have been releasing some data on the fly. There have been some adverse events with a couple of patient's surgery related vision loss. There are some patients that had some improvement in the vision

compared to untreated eye. I think that any time you see improvement in vision of these patient populations that it's worth paying attention. These are small numbers and early results but, worth paying attention to overtime as more data is released.

Also, there are some pharmacological photoreceptor regeneration. Some work done by Tom Reh at University of Washington. These are small molecule Nr2e3 modulators to help to protect and revive the cones in RP. Those are preclinical developed and licensed by Nayan Therapeutics in Boston. Tom Reh is a recipient for this program.

Matthias Steger is a researcher at Roche who went on his own he got so excited about the potential for molecules to stimulate the native stem cells in the retina, and to regenerate photoreceptors. He started a whole company called Endogena. We got to know him and his approach and found out that he has a compound in preclinical development. This could be in the clinic in less than two years. So, again watch this space, a lot going on.

The Holy Grail is the photoreceptor cell replacement. If you've been following the field, I'm sure you heard of David Gamm who is a leader in the space. He has a startup called Opsis Therapeutics, and it is a spin out of Fuji Film in cellular dynamics, and it got a built-in manufacturer. This is promising and it could be scaled up in manufacture quite well. This is a way forward on Gamm's work to extend into combination work where you've got lay down the carpet if you will, of the RPE cells, and then add photoreceptors on the top of that, get into the retina, and see if it can continue to grow and gain some function. Still a lot to do here, this kind of work, but it’s worth pursuing. This is sort of the Holy Grail for vision restoration and regenerative medicine.

Michael young I mentioned earlier who is working on the Reneuron stuff also has an effort in this area, startup called NRP. That's all I can say, so watch this space.

Next one is RP – this is RdCVF which stands for rod derived cone viability factor. This is coming out of Sahel's lab and Thierry Levelliard at the Institute Vision in Paris. Although it's a gene therapy, it's a way to provide neuro protection in RP regardless of the gene defect. So, it's important one for the Foundation. We supported this company's spin out in 2016. They are poised to be in the clinic in 2021, and we're excited about the progress there. Again, very innovative approach but it is a long hall to get these things in the clinic coming directly out of academia.

The next one for RP is RHO – this is an effort that is now being led by ProQR. Essentially licensed program from IONIS, it's for P23H autosomal dominant RP. Once they licensed it, it went straight into a Phase 1/2 trial in late 2019. We are impressed with the efforts to ProQR to take on multiple programs and glad to see them jump straight into a patient trial in 2019. So stay tuned potential results from this program.

Another innovative approach in RP and Usher syndrome with an antioxidant approach is a company called Nacuity Pharmaceuticals. This came out of Peter Campochiaro's lab at Hopkins. He has been working with Cysteine, issued proof of concept work in 2019. They are developing a compound called NACA which is 3 times more bio available than the Cysteine. They are doing work in Australia because it is a little more cost effective and faster to do there. Getting ready to start a phase 2A study in RP associated with Usher syndrome in Australia. Also have a cleared US IND, and again, we're excited about this effort it could be applicable to a wide variety of IRDs.

There's another approach by a company called Allegro, which is using compound that inhibits integrin targets. They have been using this intravitreally for indication for diabetic macular edema and dry AMD.

In fact, they have got over 1,500 exposures in 370 patients with safety data to show it's very well tolerated, but just starting to work in RP. So, stay tuned here, you know I think it is nice when you have a compound that is already been safely injected in hundreds of eyes. That if there's a mechanism that could apply to RP that they could safely jump into a therapeutic trial quickly, so stay tuned there.

Another approach we've been supporting in RP is based on a metabolic approach. This is a mitochondrial target that has been developed by MitoChem Therapeutics. This came out of the work of Barb Rohrer and Craig Beeson's lab. We're sad to hear of Craig passing away, but two of them have worked closely together to bring this compound MC16 into preclinical development. It's been a bit of a holding pattern, but there's some recent interest from some strategists and also some funders to take this on. They have a new CEO so we're excited about the potential to move this forward, potentially into a clinic. It's a very interesting and novel approach to treating IRDs.

Another interesting approach was developed by consortium called Drugs FORD. It is a European consortium, multiple universities, led by Francois Paquet-Durand. A new spin out company called Mireca is developing a compound working on a conversion pathway related to cyclic GMP build up. If they can modulate that to make it so that is not a toxic signal that it may be neuro-protective in a wide variety of IRDs. They're awaiting financing to move this forward, through the rest of the into clinical development.

Let's talk about optogenetics. This applies to RP and AMD. I think one of the first major effort is Dr. Pan in Michigan, and really a paper in 2006. It showed that if you took a microbial rhodopsin and did a gene therapy into eyes that don't have any functioning photoreceptors, you could restore some level of functional vision. That led to a spin out company called Retrcen, took it into the clinic, and saw that a couple of patients had some improvement in vision, they were acquired by Allergan. It was a decisive move, but since they acquired the company, they have been very quiet, we don't have any new data. It is still in Phase 2 development.

Another effort is by GenSight and Sahel's – it is an optogenetics program here that requires some signal amplification of goggles. They have been enrolling a small trial since 2018, and we await to see the data from that program.

A couple of other programs worth noting – AGTC has some technology out of Sheila Nirenberg's lab in collaboration with Bionic Sight. This requires the device for processing, this is a way to do gene therapy towards the optic nerve cell. There is a phase 1/2 trial that is recruiting now.

The other program is called Vedere, which the RD fund is an investor in. This is coming out of John Flannery and Isacoff's lab at Berkley. They have optimizing the technology initially published in the last couple of years, and company formed in 2019. Stay tuned there for next generation optogenetics.

I hope your hanging with me, we're getting to the home stretch here. Let's talk about Stargardt – this is the ABCA4 gene discovered by Rando Allikmets at Columbia. We supported his work. Early gene therapy developed by Oxford BioMedica, and licensed by Sanofi, StarGen program. Open label phase 1/2A study for pretty long time. You can see that they it initiated in June 2011. Sanofi has decided to get out of ophthalmology, so they actually terminated the trial are looking for licensing for the program. They did enroll 27 patients and it's got some long-term follow-up for the patients enrolled look forward to having someone pick up that program.

Meanwhile Spark has a program more in the discovery phase, but presumably a dual AAV approach. They have been pretty quiet about that.

Biogen also picked up a program from their acquisition of Nightstar, and we don't have any updates, but they're worth noting the significant efforts.

Stargardt visual cycle modulators is another active area. Acucela has a compound called Emixustat, it is compound inhibitor designed for RPE65. Clinical trial is in Phase 3, with 160 patients as of February 2020, about 65 % enrolled, and it is a two-year trial. One of the concerns here is when we slow the visual cycle you can have some changes in dark adaptation or night vision, but we'll see what the results look like at the end of the day.

Another really interesting approach coming out of Columbia and Dr. Washington's lab and licensed by a company called Alkeus. It's a deuterated vitamin A, and this really a visual cycle modulator, so is unfair to have it in the category but it's essentially a small modification to the natural compound vitamin A that prevents the dimerization into a toxic compound called A2E which is in the back of the eye in Stargardt. They have a Phase 2 trial with 50 patients, and two years of treatment. Single dose level again randomized double mass, placebo and controlled. We're waiting the results from that program.

Another approach in Stargardt is visual cycle modulators – Anti-RBP4. These are compound that shows lower circulating vitamin A level from the eye. There is a significant effort by BeLite Bio which is in phase 1/2. They're starting the regular Phase 2 soon. Showing some interim PK results from the biomarker. The new entrance from Stargazer Pharmaceutical and then the got an oral compound that is in Phase 1 in Australia. They plan to start Phase 2 trial for Stargardt patients later in 2020.

And just wanted to point out one of the fathers of the field who is Konstantin Petruhkin. He has developed a first-generation compound, and he is our scholar and an excellent chemist. We thank him for his contribution.

Stargardt – C5 Inhibition. It is the same program that Iveric Bio is developing for dry AMD geographic Atrophy, and this is Zimura. It's a complement size, complements after five. Basically, it's a large trial. It's a 2-arm trial, 4-milligrams Zimura versus Sham, and 75 subjects, this is the largest trial in Stargardt done to date. It’s got a primary end point of the EZ area. It’s the end point I pointed out earlier today in the talk is their primary end point. And they expect to release results in the second half of 2020. So, again, you know almost 100 patient trial of the major data read out later this year.

Moving onto Usher syndrome 2A, Exon13 variant of that. This is work we're co-funding with our partner ProQR. They are in a single phase 1/2 trial, and it is really only a single dose. Four sites in the U.S., and two sites in the Europe. And, the interim results are due any week now. The company said the first quarter of 2020. This is really coming up soon, and we await the results on that. This is just early data, small numbers, but it is an important approach, to Usher syndrome 2A. We have natural history data coming right behind it. We are anxious to see those results.

Usher 1B – this is a MYO7A gene. This is a large gene, so it requires a different kind of approach than regular AAV. Lentiviral approach developed by Oxford BioMedica and coming out of David William as lab at UCAL. Licensed by Sanofi, and they created the UshStat program a few years ago. Not a lot of progress, only 9 patients enrolled before they terminated the trial. Again, this program is up for licensing for anyone that wants to pick it up. We hope someone will pick it up quickly and move it ahead.

Another couple approaches are for Usher 1b (Myo7A) – dual AAV vector approach. You have a gene that is too big for AAV virus you can split it in half and deliver both tabs in a way that they can combine and form the full link sequence within the cell and deliver the target protein. It's pretty complicated stuff, but really interesting coming out of Shannon Boye’s lab in Florida. She also who got a scholar award from

the Foundation to prove of concept, so this is pretty important.

Also, some well-funded work coming out of Italy from Alberto Auricchio's lab. The cellular approach, a little bit of competition, but it is great to have shots on an open goal for this important gene.

XLRP (RPGR) – X-linked RP. Significant results coming out of two programs. AGTC got Phase 2 data, they released six months data. Again, we appreciate the contributions by Cideciyan and Beltran getting these programs into the industry. They have got two higher groups enrolled, and they released some interim data showing increases in sensitivity that they seem to think were meaningful. There will be some more data released in second half of this year, and if that data is positive, it will go into a pivotal trial in second half of 2020. So, we're excited to see those results

Another major program from MacLaren's lab and Biogen and Nightstar. They recently published the results of Phase 1/2 portion of the adaptive trial. Just published in March, everyone is talking about this paper, because this is an adaptive trial that is actually a phase 1/2/3 trial. The phase 2/3 portion is ongoing, with 63 patients anticipated. The overall trial started in 2017, so in the next year or so there will be significant results coming out. The 2/3 portion of this trial as well.

Other work on RPGR – MeiraGTx and Janssen also ha programs. This is in Phase 1/2, 10 adults and 3 children, in the pediatric expansion cohort. Randomized extension study is ongoing. Meira als has an ongoing natural history study of 100 subjects.

4DMT Therapeutics coming out of David Schaffer's. Gene therapy and intravitreal dosing, and that's their goal at 4D is to have vectors that can be delivered intravitreally instead of subretinally. First human in mid-2020, but there could be delays due to the virus.

XLRS (RS1) gene – AGTC partnered with Biogen for a program winding down after some disappointing early results with the intravitreal dosing. Paul Sieving, before he left the National Eye Institute, got a program off the ground internally there, enrolling up to 24 patients in open label intravitreal trial. We have heard on the street they're making good progress there, so we await for that trial to be enrolled and hopefully some data coming out in the next year or so.

Other companies that we just really did not have time to talk about, obviously a lot more going on that what I presented. Abeona – they have a pretty robust platform for gene therapy. Acucela has optogenetics program.

Eloxx has some read through drugs. Generation Bio - theentire platform to go after large genes, except CEP290 and ABCA4.

Hubble Therapeutics has done work for LCA16. MeiraGTx is also in the RPE65 program. I don't know if they will go forward.

Oxford Biomedica has two other lengthy programs - RP1 and CEP290. Australian company called PYC got antisense oligonucleotides. Dr. Zacks at Johns Hopkins has been working with Bayer on multi-kinase inhibitors. There's even more than this. So just pretty incredible.

If you look at the field and look at this kind of the movement, this is the slide called Exits, M and A deals and Pivots.

Again, just to kind of tell you about, kind of what is happening in the field, we talked about Spark and acquisition by Roche and deal with Novartis that is a big one. Janssen basically acquired most of the pop line from MeiraGTX, that's a move from Johnson and Johnson to move back into the field. They're doing it by the way of IRDs, which is great.

Biogen, a company that's been really focused on neuroscience, acquired NightStar Therapeutics to really jump into ophthalmology, that's fantastic. PTC Therapeutics acquired Agilis, turned around and licensed some programs from Avillia. On the manufacturing front, you've got ThermoFisher acquiring Brammer for a huge number, Catalen, acquiring Paragon Bioservices. So again, the big manufacturing outfits want to get into the gene therapy field, and they are making some bold moves. On a device side, Gyroscope acquired Orbit Biomedical, of course they are funded by the venture arm of the welcome trust that's interesting of itself.

And clear side biomedical doing REGENXBIO, for wet AMD delivery in the space. Few more to mention, Blueprint Genetics was acquired recently by Quest Diagnostics for an undisclosed amount, we're happy to hear one of the drivers of that was because Quest wants to get into rare disease. We're grateful to have Blueprint as a strong partner for investors at the Foundation.

ProQR, you look at the vision statement and they talk about vision 2023, and they're a fully integrated, inherited retinal disease company by 2023. For those in the field for a while, know the term FIPCO, fully integrated pharmaceutical company. This is, you heard it here first, it's FIRDCO, a fully integrated retinal disease company. I think that's incredible. Public companies saying that they're going to be 100 percent dedicated to IRDs and want to be fully integrated from research to commercial. Iveric Bio is another one that pivoted, this is formally Octotech, and they transformed their brand, their image to become much more biotech. They filled up a pipeline of gene therapy and IRDs. We're excited to see them make that transformation.

LimeLight Bio made a splash when they financed it, usually that's five or ten million dollars, they are a 75 million-dollar start up financing from apple tree. They made the front page of BioCentury.

Then Astella, acquiring universal cells they have manufacturing abilities. Audentes, they have more gene therapy and building a manufacturing plant in North Carolina, all significant moves. Then Sanofi more on the negative side, saying they're getting out of ophthalmology, but then again, that creates opportunity for people to pick up those programs so a lot going on here in the space.

This slide is just a collage of all the logos, I probably forgot half a dozen, just reminder about how much is going on and really, it is that kind of activity that really led us to creating our own venture fund: the RD Fund, to be innovative here. So, we've got a first of a kind fund focused only on IRDs. It is internally managed, its dedicated only to our space. We have independent board of directors and we launched over $70 million under the management. It includes the three previous investments we made under the Clinical Research Institute and we made a few investments since then.

Remember all the returns come back to the Foundation that supports the mission and generally we invest in things that can be ready for clinical testing about 18-24 months and we're actively raising funds for potentially funding too, because we've been so active in this space. If you want to know more, you can go to the RDFund.org website for more information.

Just one more note on the RD Fund, current investments are six we can follow-up with any of you that are interested in this, we invest in Nacuity Pharmaceuticals, SparingVision, ProQR, LimeLight Bio, Nayan Therapeutics and Vedere – six investments we made with the RD fund are very active with the deal flow.

So, I promise I'm getting to an end here. Big thank you. Your support has allowed us to explicitly understand the genetic basis of IRDs. Has allowed us to offer free genetic testing and counseling and provided funding that led to the first ever gene therapy in the United States and it has led to a deep understanding of the natural history of IRDs and discovered new powerful clinical end-points. It has led to gene specific and gene agnostic therapeutic approaches in development. It's helped develop the entire scientific field over 80 programs in development. And, really it allows us to continue to blaze a trail. I like to say, "Onward!" Thank you for all your support and I'm happy to say some questions.

Jason Menzo:

Awesome. Thank you so much, Ben. That was fantastic and extremely comprehensive. I know on the phone and Zoom, it is a big difference from what the update like this may have been just a couple of years ago. I know everyone learned a lot and appreciates the comprehensive review. We are going to take about 20 minutes of questions – so we'll extend the time, and – encourage everyone to stay on as long as they're available. At this time, I'll ask Chris to review for our audience how to ask questions using dial in or Zoom.

Chris Adams:

Thanks, Jason. Good afternoon everyone. This is Chris Adams, VP of marketing and communications. There are three methods to ask questions today.

First, if you are using the interface, with Zoom you may access the Q&A feature on the bottom of the control bar to type in your questions. Second, you may ask questions verbally and to do so, select the hand raising function on the menu bar at the bottom of the interface, and we will provide instructions on unmuting your line. And third, if you have joined us by telephone only, and don't have the Zoom app, please submit your questions, via email, to info@fightingblindness.org. I'll pass it back over to Jason.

>> Awesome. Thank you, Chris. While we're waiting for questions to compile. We got a question early on and I'm trying to remember, exactly what point of the presentation this was in reference to, but the question was about language, so what is a workshop? So, Ben this may be something you mentioned early on with regards to the regulatory path, but you can address that.

>> Sure. Yeah. I mean it's a made-up name but basically if there's an opportunity to do some convening with.

>> So, workshops, is a loose term for convening. When there's a patient group that wants to get together and talk about moving the field forward could be working with researchers and commissions, regulators that's appropriate. Any key stakeholders that can kind of advance the problem, and you know we can't do it for all 272 genes but sometimes there's a moment where the research has taken a turn and it's ready for next substantial step. We're happy to help provide structure. We cannot do the whole thing, but we are happy to work with the patient groups to do something really focused in order to make some progress. Happy to talk about those offline.

>> Okay.

>> We have a question, that came in, on Q&A, let me review this really quick.

Okay. So, this is probably, actually a very common question, that most folks on the phone, may be wondering about either themselves or their loved ones. This particular question is about an individual

who has a daughter, who is 16 with Stargardt. They live Michigan and they're curious where they can find what trials she may be able to participate in. So maybe we can talk more broadly not just about for Stargardt specifically but for patients that are interested, or individuals that are interested in learning about trials for their particular situation – where they can go to find out what trials are happening and how to connect with companies that may be doing those trials?

>> Yeah.

I think there's a couple ways to do it, one is in a broad sense go to ClinicalTrials.gov you can see everything going on, that lists everything, and it's not a curated list. So, it is best, one is to really talk to your doctor and make sure that your doctor is thinking about what is available for you given your stage of the disease et cetera.

But also, you can go to our website where we list out current programs, and you can just reach to us directly we can talk about the programs that we know about the most and are happy to just talk about it basically.

> Yep. Yep that's exactly right. So, we have, individuals on staff that their primary role is to work with individuals that have questions about clinical trials. We're very well connected with the physicians that are along with the clinical trials, so the generic email address to reach out to us, and we can triage to get the right people to follow-up is info@fightingblindness.org, and we're obviously here to help.

The next question is, actually about the inner play between clinical trials and my retina tracker the question is, can you find out about clinical trials through My Retina Tracker?

>> Yes. So, you have a certain gene variant, and a trial that is getting started in your area, then what we do, is we usually notify people through My Retina Tracker, about that trial starting up. So, we proactively do that. Sometimes we get that request to do that proactively on their behalf, and we can do that in the de-identified way. And then there are maybe some updates through the registries that generally inform people about what trials are going on, as you can see from the presentation it's pretty fluid, there's a rot happening right now.

Um, so we try to stay up to date on that as much as possible.

>> Great. Terrific question. Chris are there any questions on the phone lines.

>> I'll look right now.

And again, if you have any questions on the phone and you are using the Zoom interphase you can raise your hand. And we will then unmute your line.

I'm not seeing any questions right now.

>> Okay. Ben, I know another question that has come up from time to time, is sort of the broad question as to when we refer to preclinical transitional phase 1/2/3 FDA approval. If you can speak to a high level what those various terms mean and what the path from a program that is in the lab to being eventually approved by the FDA, what some of those milestones are.

>> Sure, yeah. That's a good question because there are some gray areas. Preclinical is the broad term for any work that's being done in animal models, and that's a wide range. Sometimes you talk about pre-

clinical and sometimes you talk about pre-IND.

If you're in preclinical development you're at least working in animal models understanding safety and efficacy, does it work and is it safe. Pre-IND means you're doing structured toxicology studies according to the guidelines, to create study reports, you submit to the FDA to justify human dosing.

And once you file that IND or investigative new drug application, and the FDA if they don't stop you within 30 days you can start your trial, typically that's a phase one, which is just safety.

And so, you're not looking for any efficacy, just trying to understand safety. In our space it's called a phase 1/2 where you don't go into normal healthy volunteers, you go to straight into subjects who are affected. Especially if it's a gene therapy, it would be unethical to give a gene therapy to someone who is not affected. You go into a phase 1/2. They call it a phase 1/2A, because it's the early safety and dosing in patients. Then after a 1/2 you do what is called a phase 2B, which is a little bit larger, less number of doses, confirmed safety and efficacy, and if that is successful you go into phase 3, which is a pivotal trial, the definitive safety and efficacy trial. In our space, an orphan disease where the patient numbers are very low, often a well-controlled phase two trial, even if it's 10-20 patients, can be considered one of two pivotal trials. You do your final pivotal trial to replicate the early results, that's kind of how it works. I hope I answered the question.

>> I know we have two questions that have been chatted in and then, we have someone on the line, Chris, we'll ask the individual on the phone to ask the question

>> Absolutely. Debra Mink you should be able to unmute yourself.

>> All right. Hello. So, my question is, Dr. Burson diagnosed my husband over 30 years ago, with retinal degeneration. Is there any hope in some reversal of vision, presently he cannot see colors and faces, he cannot read.

>> That's a good question for a physician. Which I'm not.

But I think, in general it is does depend upon the specific variation and that's sort of, overall disease trajectory.

Someone who is very advanced and whether gene therapy will work or not I don't know. I'm not qualified to answer that. But, potentially, optogenetics and regenerative therapies may be appropriate. It's not my call, but if you want to talk to a different physician, we would be happy to connect you with someone if needed.

>> Okay.

>> Thank you, thank you for that question, and thank you for that answer Ben. We have a couple of questions have been chatted in. One is a question about a term we use, pretty regularly, which is the SAB, which stands for the Scientific Advisory Board and the question is, how we use them and what their role is, in working with the foundation in these aspects.

>> The Scientific Advisory Board, known as the SAB, is a really incredible asset of the Foundation. It's a group that has been cultivated for decades over time. This is a group that is, I'm going to get this wrong, it's at least 40-50 people at this point, from all around the world. These are the experts in all the different aspects of biology and clinical science.

We use this group, to essentially review grant applications, at an NIH style level. We have a super rigorous progress for vetting the science before we fund them.

They also help us with strategic direction on science. And the Foundation is really an R&D organization if you think about it. We rely on the SAB's deep sector knowledge to advise us strategically, where to place our dollars and then how to vet the specific proposal.

We also use them to help with due diligence for investments on the corporate side, on fund side.

>> Great thank you.

We have a couple of questions, that thinking are somewhat interrelated, I guess, about various strategies to approach IRD, one is just about stem cell therapies and another more specific one is can you discuss the differences in advances in stem cell research between HPRC, IPSC and stem cells needed to the retina that may be dormant and potentially reactivated.

>> I probably cannot do that realistically, on the spot. But I think that you know there's a lot going to observe in the cell therapy space and the general buckets, the way I see them, you can get embryonic stem cells which are obviously from embryos but that's a source of material, you can get them from your own self so that is induced stem cell, pick a biopsy from your own body, grow them, transform them into a retinal cells, that's another way. Then there's the stuff in between, whether there's sort of immature cells, which have the ability to not only transform themselves into other cells but release certain kinds of growth factors, and factors that make the retina feel young again in a sense.

So, I'm totally butchering all the nomenclature here, it's something we need to do a webinar on, we should add a list, to do a lunch and learn on self-therapy nomenclature so everyone understands the differences.

>> That's great. Thank you. Keeping an eye on the clock as well, we'll maybe take five or seven minutes of Q&A. We have a question about the strategies with regards to IRDs, and this is sticking to the promise of AON for the IRDs particularly, as it relates to Stargardt. We talk about these quite frequently this question is maybe if you could expand upon what you talked about early in the presentation.

>> Yeah. So, one of the good explanations I think Ben Shaberman said, if you have a break in the strain of DNA or a defect in the strain of DNA, it's sort of like laying tape over it, so it looks normal and reads normal.

And, the cool thing about this technology, it's not a virus, it's not something that, permanently changes your genetic material.

So, it has to be, given chronically over time. But the remarkable the thing we're seeing about the class of drugs they have a very long duration it looks like twice a year dosing, maybe even longer intervals are quite possible.

So, right now, earliest results in SEP290 are encouraging we have a few data reads out to see from ProQR, a lot of companies are looking at this as a very viable way to go for gene therapy.

>> Excellent.

>> One other thing I might add is that, we have to remember, in gene therapy that, once you receive a dose of a gene therapy, you're really not eligible for another dose for the rest of your life. You have to

think about that if you volunteer for a trial or something. With this, you can redose and over your lifetime, there's no immune reaction or immune adaptation to that drug.

>> Okay.

That's great. We've got maybe time for one or two more questions.

There's a couple of questions that have come in, are similar spirit I think behind the questions. Different individuals that have different specific known gene mutations or variants that are curious, actually about how to identify, find patients with a similar experience. I know many of you on the phone have that similar question as well, in addition to the handful have chatted that in.

We at the Foundation look at ourselves as a terrific resource in connecting people with others in our community.

And so, not only do we have our national footprint of chapters and all the various community-based activities that we do across the country, we also have sort of that firsthand qualitative relationship with many folks in the local communities. So, I would defer back to, at this moment the best thing to do would be to reach out to us at info@fightingblindness.org. If we know folks in a different community or a different geography that has a similar condition, we could potentially bring up, and we do that quite regularly actually. The last question was similar to the questions about stem cells and optogenetics, we hear that often and someone was asking if you could in laymen's terms explain what that means?

>> Optogenetics is a way to address retinal degeneration if you have an eye where the photo receptors are not there. You have the underlying architecture sends the signal to the optic nerve in the brain. These are Ganglion cells and other neurons in place and have not degenerated. If you can transform those cells into becoming light sensitive by use of a gene therapy to have those cells produce light sensing proteins, then they can become like photoreceptors they can send the signal in the same way they normally would. That is hopefully the laymen's terms enough, but it’s basically the way to transform existing neurons in the eye to become like photoreceptors and to function like one.

>> Great thank you. It is 2:40 here on the East coast I think we will close up the Q&A portion. What I want to say, is for the questions we could not answer, we have a number of them have been chatted in, we will follow-up individually with each of you over email within the next week.

For some closing remarks, I'll turn it over to David to say a few final words to close us out.

>> Thank you, Jason and Ben and on behalf of all of us on Foundation, we can't thank you both enough for your dedication, for moving the field, and for the professionalism with which you operate. I know this was a lengthy presentation. I hope the next time you do it, its twice as long because that will mean there's twice as many studies going on in the clinic. In my wildest dreams I could never have thought, that we would be sitting here, and you would have to, summarize in one line the number of clinical trials going on, because we just didn't have enough time. So, really spectacular work. Thank you and your staff and Brian and Amy and everyone on the science staff and I would be remiss if I did not thank John Steinberg for his leadership on the Board, to help direct the science program and for Warren for his leadership for directing the RD Fund and the work that we do there. Also, you were modest in many ways I would say, most of the science that you presented in one way or another, we have touched either by sponsoring the researchers when they were young or sponsoring the research or funding, some of these companies so something to really be proud of.

To those of you on the phone, thank you for taking the time to listen, to be part of the world that you're dedicated to, you're our family is what it amounts to, and we really appreciate your efforts in these trying times. Maybe this was good you were holed up in our homes. We had to chance to teach and talk and understand the field moving forward. We need you, we need you to stay close to us and stay involved.

We’re making it happen, and you can see it.

I think you can see it in this presentation, your continued support is critical, stay involved, ask questions, feel free and, at any time, to reach out to any of us for practically anything.

And, we'll be there for you until the fight is done.

Thank you very much.

Stay safe.

Stay away from the coronavirus. Hopefully, everything will be back to normal pretty soon.

>> Thank you.

>> Thank you, everyone. We'll sign off now. I hope everyone has a great rest of the afternoon and great weekend. Thank you for participating.

(session concluded)