Veronique Enos Kaefer:

The following is a recording from Progress on the Path to the Cure, a research roundtable presented by The Michael J. Fox Foundation on Saturday, October 23, 2021. Hosted at Jazz at Lincoln Center in New York City, the intimate event welcomed members of The Michael J. Fox Foundation's leadership and Board of Directors, and dedicated supporters.

Foundation CEO and Co-Founder, Debi Brooks, opened the event with conferral of the annual Robert A. Pritzker Prize for Leadership in Parkinson's Research to Dr. Glenda Halliday from the University of Sydney. Our founder Michael J. Fox shared his outlook on the promising Parkinson's research field before introducing our panel of experts. MJFF's Vice President of Research Partnerships Dr. Katie Kopil moderated a discussion around new programs and findings toward better treatments and deeper understanding of Parkinson's disease.

Following the discussion, stay tuned for a Q&A session featuring questions from the audience.

Debi Brooks:

Good morning everybody. This feels great. I am so excited. This is somewhat of the kickoff, of course, for our weekend, our day of activities. But we also had a board meeting on Thursday and it truly feels like we're getting the band back together. And so I really am grateful for all of you joining us and helping with all our compliance around our requirements. So welcome. This is our 2021 Research Roundtable, and we are really focused on our progress on the path to a cure.

Debi Brooks:

It's really nice to be live in a room, and I hope through that experience, you really start to get a sense of what we see and what we're motivated by in terms of the science. We have a lot to tell you about Parkinson's research and drug development is moving forward at a gallop. And the hardest part of today's program is for us to prioritize what to talk to you about because we have to think of things that can reasonably fit into an hour and a half discussion.

Debi Brooks:

We'll be updating you today on the latest crop of drug trials, where we awaiting results. So you know the things that are already in humans, that we're waiting to see the answers to. We're going to talk about some huge new investments that are linked to how we can better unravel the complexity of Parkinson's biology, and then continue to really support the drug development pipeline to be sure these efforts are moving ahead on the shoulders of giants. And to us, those giants are you. Our community, our global community of patients and families, and researchers are all on the front lines in this pursuit for a cure. So we can't wait to get started. And as always we'll have an extended Q and A, because we can't necessarily get to every single topic doesn't mean it isn't something that we work on or that our panel of experts can't address. So rest assured there'll be time at the end for you to raise any questions that are on your mind and we will share our thoughts.

Debi Brooks:

Before we launch into the panel, it's my pleasure to announce the winner of the 2021 Robert A. Pritzker Prize for excellence in Parkinson's research. Our foundation bestows the Pritzker Prize at this event each year to honor researchers pushing us forward towards our goal of better treatments and a cure, while these awardees are also recognized for their work in mentoring young researchers, so that we can

maintain the growth of the community of scientists who are really dedicating their careers to both eradicating PD and cultivating the next generation of leaders. Our 2021 Pritzker Prize winner is Dr. Glenda Halliday. And she's an internationally renowned leader in the study of neurodegeneration and on the faculty of the University of Sydney in Australia. Her research has directly influenced the clinical practice by providing evidence, the evidence based for understanding the pathologies underlying Parkinson's disease and clarifying its trajectory over time and increasing the understanding of PD's vexing variability.

Debi Brooks:

Dr. Halliday has brought together leaders in clinical neuro imaging, genetic and biological aspects of Parkinson's and developed resources and infrastructure needed to address some fundamental questions of major significance. To facilitate further research discovery, she has made these resources available to Australian and international researchers to further transformative research studies. As many of you may appreciate Australia has recently announced that it will reopen its borders to international travel in November. So for the first time since, she'll get to finally travel in November, but that is unfortunately not soon enough for her to be with us here today. But I am thrilled to share a video of her acceptance remarks today.

Glenda Halliday:

Hello from Sydney. I am extremely sorry that I am not in New York with you all today. Thank you so much Debi for the introduction and for this award. It is truly an honor of my career.

Glenda Halliday:

As you know, Parkinson's is such a complex disease. My research goals and those of my colleagues and students I've worked with have been to understand what happens in brain over time. This work is focused on the genetic molecular and anatomical change of that occur over time, and also to identify surrogate biomarkers for these processes in order to enable disease modifying rather than symptomatic treatments. My hope is that this information will help better understand the disease and lead to new ways to stop it at any time during its course. As the Parkinson's community well knows, that is our greatest need.

Glenda Halliday:

I'm also very proud to be recognized for mentorship as part of this award and proud to be working with many other professors and academics I've trained. We need as many smart minds as we can working together towards cures and better treatments. It is a real joy to mentor the next generation of scientists and a joy and honor to receive an award from The Michael J. Fox Foundation. The Foundation has been instrumental in furthering my own research and that of so many of my colleagues and collaborators. The Michael J. Fox Foundation is truly an unparallel partner and leader in Parkinson's research. Again, thank you for this recognition. A special thank you to Karen Pritzker and the late Michael Vlock for their support for this award and its research grant. Like too many people, we have something in common, a parent with Parkinson's. And thank you so much to Michael J. Fox for all who've done for Parkinson's research to community,

Debi Brooks:

Our congratulations and thanks to Glenda and hopefully next year she will be able to join us in person. So we do actually have Karen Pritzker with us here today. She and her late husband, Michael established

this prize in 2012 in memory of her father, industrialist and management guru, Robert A. Pritzker who lived with PD. We are also fortunate to call Karen a friend of The Foundation. Her generosity, her wisdom, and her continued support of our mission has made substantial impact, not only on today's scientific progress, but also in the breakthroughs for tomorrow. It's my pleasure to now introduce Karen to say a few words about it and get us going.

Glenda Halliday:

Thanks so much, Debi. If I'd known you were to say all those things, I wouldn't have come. But like so many of you who have experienced Parkinson's first hand in a loved one, a dear friend, a parent, it's not an easy road. It's not something you would wish on your worst enemy, let alone someone that you care about. And for many of us who are concerned, I've got two children who have two grandparents with Parkinson's. We have to get moving. We have to get moving, and Michael has been such a visionary in getting us to move quickly to a cure.

Glenda Halliday:

I first met Michael 17 years ago when I was working on...I interviewed him for the My Hero Project. What really struck me was his clear vision of bringing a community together of patients and caregivers and more importantly, the science and getting scientists to be talking to one another in very collaborative ways. Within two short decades, his vision of racing for a cure is happening. And everyone in this room is a part of it.

Glenda Halliday:

Our family is so inspired and grateful to the scientists, the Fox Foundation team, and the patients and the families in this community. Please join me in welcoming the person who has brought us all here together and whose vision we share, Michael.

Michael J. Fox:

[inaudible 00:12:21] I actually use it. I think Jeff.

Michael J. Fox:

Hi, how you doing? Thanks Aaron. Thanks to the warm welcome and okay so warm welcome. Karen is behind the My Hero Project, which seems fitting for someone who has been such a hero of people with Parkinson's. Its 17 years, it's hard to believe. But you've been there every step of the way and you've been someone we can rely on so profoundly and it means a lot. And I...

Michael J. Fox:

Hi everyone. I want to... You guys, Glenda and thank you for your contributions to the incredible PD research happening down under, good on ya [phonetic 00:13:05]. As we'll see you next year, fair income and all that stuff. Australia's been an integral part of what we've been doing internationally. And I've had a few Australians for dinner and talked about or worked towards coming with a cure for PD for everybody.

Michael J. Fox:

What else I say? The gala tonight, for those of you coming into gala tonight, Sting is playing. So that should be good. I don't know if you saw that. And then, Brad Paisley is also playing. So we got everything

and who else? We get comedians that have to do this every year. Comedians, they swear a lot. They say dirty things. They say some imaginably creepy things. But I am an actor and I'm a creative artist and I believe that creative artist should be able to do what they do. And so hopefully it'll be entertaining if you're offended, get over it. No, enjoy it.

Michael J. Fox:

Our panelists tonight are not household names like Sting and Brad Paisley, but they are rock stars of science. And then we're big fans. The round table is at the heart of what we were all about. The party tonight is great and it's great way to celebrate all those that have helped us with the work that we do and all of you, but, it's really about talking about the science that is bringing us closer to a cure. It's a privilege for us to have these academic and industry scientists on Vanguard [phoenetic 00:14:51] of PD research and care.

Michael J. Fox:

Let me see, I had something else to say.

Michael J. Fox:

[inaudible 00:14:59]. So thank you for your attention. Your great questions and your engagement in our mission the year round. Now I have the pleasure of introducing our moderator, The Foundation's Vice President of Research, Parent Partnerships, Katie Kopil.

Michael J. Fox:

Katie.

Katie Kopil:

I'd like to invite... Have the panel come up as well.

Katie Kopil:

It's great.

Katie Kopil:

[inaudible 00:15:49] It's an honor to be here today, presenting and moderating this channel. I'm honored with the privilege of working at The Michael J. Fox Foundation, and as Karen said, it's an organization that has such clear vision and mission. It's really a privilege to get to be a part of sharing that back today with the people that support us.

Katie Kopil:

I'm excited also to be able to share there's a lot of progress happening in Parkinson's disease. Of course, the big flagship story about science and in this current era is COVID, but there's a lot, a lot of progress happening in Parkinson's Disease research highlighted by three new treatments being approved last year, countless major deals that are advancing biopharmaceutical treatments through to clinical trials, with additional capital and resources to get them into the hands of patients. There's a lot that we're starting to understand about the brain, what happens with Parkinson's Disease and these biologic insights are going to continue to fuel innovation in therapeutic development.

Katie Kopil:

And there's a lot of sense of community. And the people that are here with us on stage are all partners in the effort to work urgently towards better treatments. We're excited to talk with you today about three major themes. The first is that better treatments are coming. Better treatments are being developed. The Foundation playing a very active role in directly funding those treatments. And we learn from those experiences. We learn from those clinical trials and get a better sense of what's happening in the underlying biology of Parkinson's Disease. With that, we have a lot of opportunity to collaborate and build tools for the research community, the tools for patients to work with researchers and it creates a very virtuous cycle. We have new therapies, we have better understanding of biology, more collaboration, and that gets us to better therapies. And so those are the three pillars that we're going to be covering in our panel today.

Katie Kopil:

But to set the stage for the conversation, I'm going to pass it back to Debi, but in the way that I've seen her over the past two years, which is on screen and having her explain the challenges of Parkinson's research, why The Foundation is doing what we're doing to speed a cure, and that'll set the stage for a wonderful panel. So I'll pass it back to, to Debi in 2D.

Debi Brooks:

Hi, I'm Debi Brooks, the co-founder of The Michael J. Fox Foundation for Parkinson's research. We launched in 2000, with the goal of delivering better Parkinson's drugs to patients and ultimately finding a cure. We've had a few years to learn just how complex drug development is. Just explaining drug development is a challenge. I often use the alphabet as an analogy, to help make sense of these complicated concepts. The first part of the alphabet, say letters A to F, represents basic research. This is where a scientist, typically an academic, looks at some molecular process in ourselves and asks "What's happening here? Why is it important?". This discovery science is the backbone of drug development worldwide. Next chunk of the alphabet, say letters G to P, represents translational research. Discoveries worked on for years in basic science are now examined in the context of a particular disease.

Debi Brooks:

This work helps us identify ideas that may actually get us closer to new medicine and enable the leap of faith from testing in a Petri dish to testing in a human being. The bad news is that most ideas will fail at this stage. It's the valley of death where breakthroughs go to die. The very few therapies that do make it through the valley of death still have to navigate Q to Z, clinical research where potential new drugs enter human testing. Clinical research is a lengthy multi-phase process. At this stage, it's necessary to design trials, recruit volunteers, collect data from patients, analyze the findings and finally prep for approval from regulators before a drug can become part of a physician's arsenal. Even after getting as far as Q to Z, only one in 12 of those treatment ideas are ultimately proven safe and beneficial to patients.

Debi Brooks:

We are willing to take higher risks that can tilt the odds in favor of success. We are seeing real progress. Our work goes far beyond check writing. We really assess what is needed to get from A to Z and then we bring it. We must be sober about the work that needs to be done. It'll be a great day when we find that last breakthrough, patients have the treatments they need and we can close our doors. Until then, we will keep at it and do whatever it takes. We're problem solvers and we're optimistic.

Katie Kopil:

Great. Thanks virtual Debi, and thanks to our real life panel. Joining us today, on my right, I have Dr. Warren Hurst, who is Senior Director of Neuro Degeneration research unit at Biogen, which is one of the biopharmaceutical partners that is invested heavily in Parkinson's disease research and is leading clinical trials right now, for people living with Parkinson's. Followed by Dr. Ekemini Riley, who's Managing Director of the Alliance Sciences across Parkinson's or ASAP, in case you weren't thinking that people were moving urgently. ASAP is a basic science initiative that's advancing really monumental insights into why Parkinson's happens, what's underlying it and that helps unlock some of the new paths to cure. They're also very committed to collaboration, resource sharing and open science that helps everyone move faster. We're going to hear more about ASAP today and how the Fox Foundation is partnered with them as an implementation facilitator.

Katie Kopil:

We have our warmup act for the comedy, later this evening, with our friend Bryan Roberts. He promised not to say anything offensive this morning, so there's no creative freedom here. He is a member of the Fox Foundation's patient council. He's an associate Dean of Communications at Ithaca college in Ithaca, New York. And he's our experienced expert today. He was diagnosed in 2010, at the age of 30. Followed by Dr. Ken Marek who's President and Senior Scientist of the Institute for Neurodegenerative Disorders in New Haven, Connecticut. He's a special advisor to the Fox Foundation since our inception and has led our landmark study, understanding Parkinson's disease called the Parkinson's Progression Markers Initiative. Then finally, my colleague, Dr. Brian Fisk, who's the Chief Scientific Officer at The Michael J. Fox Foundation. Among many things and many hats that Brian wears, he directs our research strategies and the investments, in ensuring that we are putting our money in the right places to get to promising new treatments faster. We're going to spend the next 40, 45 minutes talking about a range of topics. There's a lot to cover. There's a lot of progress happening. We can't capture it all in this panel, unfortunately, but we will have time also in a Q & A session after the panel. Please take advantage of the question cards that are on the table. Our staff will come around later to collect those, and we'll try to get to as many as we can.

Katie Kopil:

So with that, we'll officially start. We are going to start where we always want to. How close are we to a cure and how close are we to better treatments for people living with Parkinson's today? It's been a very busy time since The Foundation started. There's over 17 new therapies for Parkinson's disease in the last seven years, alone. We're still working, very urgently, towards something that could slow or stop Parkinson's disease. One of the biologic insights that we know from genetics and other research is that alpha-synuclein is something that plays a key role in Parkinson's disease, for almost everyone affected by the disease. Opening us up, I love Dr. Marek. If you could talk to us a little bit about what alpha-synuclein is, why it's important in Parkinson's disease and what treatments are being developed around that target.

Ken Marek:

Sure. Thank you, Katie. First, let me say what a great pleasure it is to be here today and thanks to everybody for coming. It's so nice to have one of these events we've missed them. It's... Hopefully this is just the start. I would say, just in prefacing [inaudible 00:24:38], I would say that it's clear. I think I'm the oldest member of this panel. I've been engaged in trying to find therapies for Parkinson's disease for about 30 years. I think what is remarkable is that in the past five to 10 years, the pace of discovery has

really accelerated so much. I think just as we've all been privy to, with regard to the pandemic, I think science has really driven this. What's happened is our understanding of the underlying pathology of Parkinson's disease has really led us to a whole new range of therapies. Some of which focus on this protein that Katie has already mentioned called, synuclein. I think probably most people in this audience are familiar with that. This is a protein that exists in all of us. But in people with Parkinson's disease, it acts in a way which is abnormal and either is increasing evidence from many different areas, that this is at least one of the key pathologies in Parkinson's disease. What is exciting, is that this has led us to directly to develop therapies that directly address this issue. Those therapies have been developed as you saw from the short video, that it takes a long time for therapies to make their way into the clinical realm. We are now at a stage where there are numerous therapies in the clinical realm, some of which are in clinical trials being tested, some of which are in an earlier stage, backing up those medications that are already in trials.

Ken Marek:

I think it's a very exciting time where we're seeing a number of different ways of reducing the amount of synuclein in the brain, in individuals with Parkinson's, that can actually result in a therapy that can really slow down the disease, perhaps stop the disease and really created an enormous amount of hope. I would mention one other thing. That as these types of the therapies develop, we have already seen some of these drugs have not been successful. I wouldn't be discouraged by this. I think what we end up seeing is that there are... it's a number of shots on goal need to be done. We have to learn from treatment trials. I think we have an enormous number of trials and opportunities in front of us. It's a very exciting time when it comes to synuclein. As I'm sure, Katie's going to follow up, synuclein is not the only target that we have available to us.

Katie Kopil:

That's right. One of the companies that had learned from a failed synuclein trial is Biogen. You're still moving forward with other treatments, as Dr. Marek referenced. There are many other targets that are polled promise for treatment of Parkinson's, in a way that could slower stop the disease. One of those is a protein called LRRK2. Dr. Hirst, I was hoping you could tell us a bit about the role of LRRK2 in Parkinson's and specifically the trials that Biogen is planning around that.

Warren Hirst:

Absolutely. Thank you. Thank you for the kind invitation today, to join you all here. It's wonderful to be here in person. So, LRRK2 is a very interesting protein. It was only relatively recently identified, so less than 20 years ago. It's still amazing to me to think that we've gone from an identification of a protein, not knowing what it does, but that we recognize that it was strongly linked to the disease. For a number of pharmaceutical companies, including ones that I worked at in the past, I was at Pfizer before Biogen, to essentially on the strength of that data, the genetic data, to start entire drug discovery programs. As Katie's mentioned, we are now partnering with Denali, who were also at the forefront of some of this research, back in the days, when some of those key folk worked at Genentech. They've moved forward this, with some small molecules.

Warren Hirst:

What we know about LRRK2, we found a lot of this out along the way, this is a classic example of building the plane as you're flying it. Where we are placing billion dollar bets, this is...epitomizes the risk essentially, that we within the industry are willing to take, and do take on a daily basis. Way back in

2004, when it was first cloned and identified, we, as scientists have recognized that this, of a protein looked like it had specific sort of functional domains. One of these domains is what we refer to as a kinase domain. This acts really like a switch within the cells. By phosphorylating proteins, it changes the way that they interact with other proteins.

Warren Hirst:

Ultimately, we then sort of begun to understand how LRRK2 behaves within the cell. Some key studies were involved in determining what the substrates were and that pointed more towards the underlying biology and then understanding of what's happening and what's going wrong within the disease. We recognize, within the industry, that one of these domains was this kinase domain. We knew from the oncology area that this was a class of enzymes that we could target with small molecules and we could inhibit this. The genetics was also telling us, very informatively, that there was a gain of function. That's the current hypothesis, is that these mutations that are linked to the disease result in an increase in the function. So there, very simplistically, we are testing the hypothesis, that if we inhibit that function, that this may alter and slow the progression essentially of the disease.

Warren Hirst:

We do know this is a large and complex protein and that they could be other things that are going on. At Biogen, we partnered with Ionis and we are generating antisense oligonucleotides. This now targets, not the protein itself, but the messenger RNA. If we reduce that messenger RNA, which is the precursor, this is the instructions for a cell to make the protein, then we have less protein. The hypothesis here, is that there's more and more active protein, within the disease. If we reduce that, then we expect or anticipate, hypothesize, that there may be a beneficial outcome in patients.

Warren Hirst:

Where are we in terms of the clinical trials? Last year we partnered with Denali. They had finished phase one studies. We're working with them and ramping up to start phase two studies, in the very near future, with a small molecule. Then the program that I lead behind that, which is the ASO program, we're in the phase one studies. These are two very different molecules. I'm very proud that Biogen is actually, really, placing some very significant bets on this. We know that this is important. We don't know exactly which is the best way of therapeutically targeting it. We are trying to cover as much as we can, within that space, to move this forward.

Katie Kopil:

You've heard in there, there's a lot to unpack. One of the themes that will continue to come up, is that as these treatments are moving forward. We're learning more about the biology and that unlocks other paths to pursue different types of treatments, that might go after the same target. This one, Dr. Hirst mentioned, is a genetic target. The question that might come up, "Is this only for people that have a mutation here, or is this something that would work for anyone with Parkinson's?". Maybe, Dr. Fisk, you could talk us through that.

Brian Fiske:

Yeah. I think it's really important. Obviously, it's been amazing how genetics is really sort of showing this light on what's happening under the hood, in Parkinson's and helped us understand the types of drugs that we could be making. I often think of it as, genetics are a flag in the ground of biology to help you understand that if you mess up with this particular biological pathway, in this case, through a genetic

mutation, this is one way to get Parkinson's. What we can do with that information, is look at that pathway more broadly and say, "Okay, do we see evidence that this pathway is messed up in other people who don't carry that mutation?".

Brian Fiske:

That, when we start seeing that evidence build, starts pointing to the fact that you don't have to necessarily have that mutation to get that form of Parkinson's. It could be just a signal telling us that there's a larger piece of biology here, that we should be looking at. That's what I think has been really exciting about LRRK2 and synuclein, and some of the other gene targets that we've looked at. They're really just helping paint that biological picture to help us understand what we can go after, therapeutically.

Brian Fiske:

It's been interesting to think about though, a lot of this has been driven by the genetics and largely by genetics in European populations. As we've started to look more broadly and around the globe too, we realize these same genes are probably explaining at least a portion of Parkinson's and other groups as well. Maybe slightly different flavors and versions of it, but it's been really important for us to think about how we can also expand our understanding beyond the original genetics to make sure that we're getting that sort of bigger picture of the underlying causes of Parkinson's disease. That's something we've been seeing a lot more recently too.

Katie Kopil:

This undertone. There's something to go after, if you understand the genetic basis of a disease is really exciting. That LRRK2 story, that something could be discovered and already in clinical trials, within 20 years is amazing. Dr. Ekemini, I know you're a believer in genetics. Can you tell us how the ASAP program is investing in new genetic discoveries?

Ekemini Riley:

Sure. First, let me just say, this is exciting and an honor to be here. Also Virtual Debi, you are on that. Amazing. On genetics, and I'll touch on several aspects of what I'm about to say, much later in the panel. But we are thinking about genetics from two different aspects. One, we are supporting the global Parkinson's genetics programs, as Dr. Fisk mentioned. We're thinking about how we can dramatically expand our knowledge of the genetic architecture of Parkinson's disease, by involving more people from around the world. Right now, about 95% of the genetic data sets that have been produced on Parkinson's disease and several other diseases, are concentrated in people of European descent. We're thinking about, how do we break that open? How do we understand if these are the same genetic targets and people have other ancestries? Are there different targets? How do we expand that? How do we really understand what we're going after? So that as we're developing drugs and getting ourselves towards a cure, we have things that can apply to everyone. So that's one aspect. The other aspect is thinking of ourselves as a future proofer. So we are on the basic science side of things, also funding research into the function that underlies several other genetic targets. So you all have heard about synuclein from Dr. Marek. You've heard about LRRK2 from Warren, and there are several others. So we know now there are just about 30 that scientists consider causal genes and many more genes that increase risk of getting Parkinson's disease or risk of progression of the disease and understanding what exactly those genes do, how they function. This is where our role sits, and I'll get into more of that later on.

Katie Kopil:

So there's a promising pipeline of treatments that are being developed, science that's being explored to figure out how do you slow or stop Parkinson's disease. But I'm sure there's people in this room know there are things that you're living with today that are really bothersome and that are really troublesome. And so Dr. Fiske, can you tell us where the pipeline is today for treatments that could help people live well, even if it's not slowing or stopping the disease?

Brian Fiske:

Yeah. I mean, so obviously we would, of course love treatments that can slow the disease down, but we also just need to deal with the symptoms that everybody lives with today. And so over time, it's been interesting to sort of the watch the evolution of the pipeline and those, I think the early days when The Foundation was just started getting on our feet, a lot of the focus back then was really just on the dopamine problems. So how do you kind of replace the dopamine that's lost in the brains of people with Parkinson's and mostly kind of focused on restoring their motor symptoms. And obviously that's been groundbreaking options for people today to address those symptoms. Over time though, we've seen people really addressing and focusing on some of the other non-motor symptoms too, which has been really important. But also dealing with another aspect of Parkinson's is that Parkinson's progresses.

Brian Fiske:

And so we have to keep that in mind, too, that as the disease progresses, even some of those dopamine replacing treatments sometimes need help later on with different types of approaches, different types of delivery. And that's really what we're starting to see in the pipeline is more that kind of innovation happening. So a lot of the treatments that are in sort of mid to later stage testing right now are looking at different ways. For example, to deliver dopamine. Some are looking at sort of different pump models that you can sort of wear that sort of like sit under the skin that you can sort of deliver different types of dopamine medications. So we're seeing a lot of innovation there. We're also seeing companies that are starting to develop treatments, targeting some, like I said, some of the non-motor symptoms, are there a handful of companies now, they're specifically trying to look at aspects of cognitive impairments, sort of thinking problems and dementia, that can be a problem for later stages of the disease in some individuals we're seeing.

Brian Fiske:

So we're seeing some good innovation there and people really focusing on that problem. A few companies are also focusing on sort of walking problems, gait problems as a company. Takeda, for example, that has a drug, but it's testing right now to explore its impact on gait and walking function in people with Parkinson's. So we're really seeing people thinking about these sort of the diverse picture of what Parkinson's really is, especially at those later stages. And that's been, I think, really good to see as well. We're also seeing a lot of sort of innovation in the use of technologies as well. So there's a project we're funding right now. That's actually looking at a sort of different way of delivering deep brain stimulation, which is the surgical sort of putting the electrodes in the brain to help address the symptoms of Parkinson's.

Brian Fiske:

There's some groups now that are trying to develop small nano electrodes that you can inject. So you don't actually have to put in all this crazy hardware, you can actually inject these electrodes in and use sort of less invasive ways of potentially stimulating the brain. So seeing great innovation in that kind of a

development. And we're also starting to see people use technology in different ways to really assist people with Parkinson's. I think that's sort of a different twist than sort of a giving a drug that might try to go in and sort of change your brain chemistry or something, but devices and technologies that can help. And we're funding a small project with a group, for example, that is working on a speech intelligibility app. So the idea that you can help people with Parkinson's by helping sort of train their ability to speak better through an app-based sort of therapeutic approach versus sort of more traditional approaches. So we're seeing, again, this, I think innovation in the technology too, which has been exciting to see helping address symptoms today.

Katie Kopil:

I love this last point for two reasons, those types of devices don't need to go through FDA approval. If the trial that the Fox Foundation is funding shows that it's beneficial, that could be ready tomorrow. There can be things that are ready for patients really, really soon. And that makes me excited. But the other thing that makes me excited is I think the role The Foundation plays is attracting those innovators to Parkinson's disease. Because there are applied technologies that could work in many, many spaces, and Parkinson's isn't always the most commercially viable ones. And so I think that is a very key role that The Foundation plays in bringing people together and saying, we have resources, please focus here, and we can help get those better treatments to patients faster. So Bryan, based on what you've heard today, and I know you have a peek behind the curtain as part of a patient council, how do you feel about the opportunities on the horizon as someone living with Parkinson's?

Bryan Roberts:

Yeah. Well, first of all, thank you for having me. It's been two years since I've been in New York City. I live upstate and the Knicks are good again. So it's been a long time, so it's nice to be here. And just so everyone's clear, I'm not a medical doctor. I'm happy after this is over to look at your family history and judge you, but I can't help you at all. So just to make that clear. I'm a dean, you don't want just the dean. So I tend to be an optimistic guy, but I'm really optimistic kind of when I look at the different types of treatments and the interesting kind of avenues we're going through in Parkinson's research. I've been diagnosed with Parkinson's 11 years now. Have I changed a little bit from when I first started? Yeah, but I'm also over 40 now.

Bryan Roberts:

So it could be that as well. But the thing that excites me with the Parkinson's research is that we're not just following one thing. We keep looking at different areas, but where does this come from? It comes from a patient's voice and that's really important. It's very important to have the patient point of view to drive the research and research, a patient-centered research is key, and that's what I see coming out of this. And I'm a social scientist. So I can tell you if your research study is good or not, and these are really good studies too. And that's important because this may seem shocking, but neuroscience is some somewhat complicated. It's not like communications, which is really complicated, but it's somewhat complicated. And yeah, I guess that's where my optimism lies is that this is an incredibly complex, hard thing we're going after, but we're smarter than it and we will just do the work. I always say, I have a 10 year old daughter, I say, do the work and we'll do the work. And that's why I'm optimistic.

Katie Kopil:

I love this idea of optimism and taking action. And one of the things that we rely on you, the community for is also helping with policy and advocacy for change. One of the things that we won't have enough

time to talk about today is the environmental risk factors that could precipitate Parkinson's disease. And we see that there are very increasing data that support this idea that there are environmental toxins that could increase someone's risk for Parkinson's disease. And with that in mind, Dr. Fiske, could you tell us what The Foundation is doing on that front from an advocacy perspective?

Brian Fiske:

Yeah. So, I mean, obviously, so there's good reasonable research evidence suggests there might be environmental aspects, contributors to Parkinson's disease. And yes, pesticide exposure seems to be one sort of common theme that's come up over the years in the research studies. And as a relative, and what's interesting about that is unlike maybe more traditional biology, we have to go through all the steps that sort of turn it into a drug and get it approved. That's something we could actually be doing today around environmental toxins and removing some of these toxins from the environment. And even if we don't know for sure, a hundred percent that they, yes, they cause Parkinson's, we can at least try to remove them and reduce that risk. And so some of the work of our policy team and then Ted Thompson is here, who leads our policy team has been trying to advocate more and more of course, for ways that we can remove some of these toxins from the environment.

Brian Fiske:

And one of the more recent things we've done in color, I think the first time we've done this as an organization is we actually joined with other groups and have actually sued the EPA to try to remove Paraquat, which is a pesticide, a weed killer from the list of pesticides that are used in the US. And it's been kind of a long battle. The EPA just went through a long multi-year process and actually this summer sort of reapproved its use. And so what the lawsuit is trying to do is really trying to reverse that decision and hopefully, try to get that pesticide out of the environment. So when we think about the different ways we can actually develop quote unquote "treatments for Parkinson's", this is actually an interesting twist on that, because in this case, we're actually trying to remove a potential cause of Parkinson's from the environment, with the idea that could over time reduce the number of people who ultimately get Parkinson's disease. So yeah, it's a really important work.

Katie Kopil:

And Dr. Fiske alluded to this idea, we don't necessarily know why all of these environmental toxins or pesticides could cause Parkinson's disease. And that brings us back to one of the other pillars that we wanted to talk about today, which is our increased understanding of the biology of Parkinson's. And so Dr. Riley, one of the biggest investments that is driving new understanding of Parkinson's disease is the ASAP initiative. Could you tell us a little bit about that?

Ekemini Riley:

Absolutely. So I'll start off by saying that the ASAP initiative would not be here in the way that it is now without the strides that have been made over the past two decades in the Parkinson's community. There's a lot that we have learned over the past 20 years. But in that, in learning, you always uncover more unknowns. And so we were thinking about how best to contribute to the Parkinson's space. And so I see us in three roles. One, I mentioned before, future-proofing. We don't want to look back a decade from now and say, oh, I wish we studied those pathways starting now so that we know things moving forward. That's one. Two, we also see ourselves as filling gaps in the space. So there's a lot that the Fox Foundation is doing. I won't even be able to get into it all today, but the Fox Foundation, there

are other groups in the Parkinson's space, the government. There's a lot of research going on, but there are still gaps.

Ekemini Riley:

There's a lot we don't know. And so thinking about how best we address those gaps, how best we address controversies in the space and actually bring scale to those problems so that we get concrete answers in a shorter amount of time, that's two. And then the third acting as a scaffold. We want to both bring in people from outside the Parkinson's space, who can bring their knowledge, bring their expertise and kind of bring a fresh take on the Parkinson's space, but then also thinking about how we collaborate with funders in the field, how we bring together scientists and investigators to collaborate and move things forward. So Katie described the ASAP Initiative up top. We are coordinated basic research program, and we're fortunate to be partnering with the Fox foundation. They bring both implementation prowess, their grant-making machine, but also thought leadership and expert scientists on staff.

Ekemini Riley:

I mean, I have the pleasure of working with Brian and Katie all the time, Todd, Cellini, Brett, and several others. So there you have it. But on the biology side of things, there are several things we don't yet know thinking about cell types that are involved. If we think about the immune system, we've highlighted scientific themes over the past two years, that are either really nascent in the field, that are coming out of things that we've learned over the past five to 10 years or highly controversial topics that would benefit from very targeted investigation, get an answer and move forward so that we don't have protracted research around controversies that'll drag on for the next 10, 12 years. Let's find out the answer now, let's understand what we can about deep, controversial issues. Where does the nucleon travel? How does it get there? Because these things all matter for both diagnostics, for targeted treatments down the line.

Ekemini Riley:

So people like Warren and other pharma companies know what to target, but as virtual, Debi said, we are looking at things, at cells, at molecules and saying what's happening here. But also the wonderful thing about science is that it is a continuum. So she's described translational research and clinical research. And out of those research phases, you also get questions that will feed back into the basic research. And so we're sort of building a pipeline to bolster all of that understanding. I'll end with the last thing that we're really excited about. So next week we're going to be announcing our next crop of folks in our research network. And so we're bringing together people who are looking at the functional genomics, as I explained earlier, looking at the interaction between the nervous system and the immune system, and then also bringing people that are working on circuitry. How do all of these molecules and cells ladder up to brain circuits, communication between the brain and your gut or other areas in the peripheral nervous system.

Ekemini Riley:

And I think bringing all of those together under one umbrella requires scale that we're helping to bring to the problem, but then also scientific stewardship that we are getting through The Michael J. Fox Foundation to help all of our investigators really get to those answers quickly.

Katie Kopil:

What you heard about was not invention that's innovation, right? This idea that you don't have to have a great discovery, you want to build a good team, you want to bring the right people together, you want to build on strong science and move that forward quickly. And that is how I think we are really going to get to better treatments faster is through that type of innovation. So these are some of the large biology efforts that are happening in collaboration with MJFF as an implementation partner. Another place that we've partnered with the ASAP is around our Parkinson's Progression Markers Initiative, PPMI study, which is now over 10 years in the making and very exciting progress happening there. Dr. Marek, can you tell us about the study and what we're learning from that?

Ken Marek:

Sure. So the Parkinson's Progression Markers Initiative or PPMI is a project that began about 10 plus years ago. Really, it grew out of the Fox Foundation Scientific Advisory Board, and it was really an enormously innovative project that Fox developed with the idea that it was important to think ahead and think about how we might have the tools we need to understand how to measure change in disease effectively when there were the science and the med and the drugs had sort of caught up with us, so they would be available and to be tested. And indeed, that's exactly what's happened. So over the past 10 years, the information that's been acquired as a result of that project has been used to really accelerate therapies, and that's been great. But what is even better is that now with the support of both Fox and ASAP, we can do so much more.

Ken Marek:

And so we've launched an enormous expansion of that project that is going to help us to really take advantage of these scientific advances that you're hearing about. And as we move ahead, because one of the... Yes, as you saw from Debi's video, I think there's a long path from A to Z. And it isn't always in one direction, it kind of goes back and forth and we need to be able to be prepared to have the tools in hand. These tools are often called biomarkers, but biomarkers are simply just objective measures of disease that will enable us to determine whether drug X or drug Y might have a very important effect in slowing Parkinson's disease or in modifying heart disease in one way or another. And this effort really has now grown over now 10 years, and will continue to grow to this very broad international effort involving hundreds of scientists throughout the world, but more importantly, hundreds of participants.

Ken Marek:

So now, we're hopeful to evaluate up to 4,000 individuals over the next five years. And this is supported by an even grander effort, which is called PPMI Online, which is an online platform, which would enable everyone over the age of 18 to join and support effort and ultimately participate in gathering information that will really help us to find new therapies and partners.

Katie Kopil:

So I've been at the organization about eight years. I've watched us evolve our strategy in funding, and we've supported many exciting things. But, I think perhaps the best thing that we could be investing in is PPMI. And, I know that other people would want to be a part of that. So, before we go on, maybe we could highlight the opportunity, and pull up the slide that shows where people could join PPMI. You'll see here that we are talking about this as a study that could change everything. The Foundation invests in PPMI because we believe that studying people with Parkinson's disease, at risk for Parkinson's is the best way to learn more about it. We fund it and support it because we believe that biomarkers are really critical tools to driving drug development. And, we want to make drug development easier for industry.

Katie Kopil:

This is a hard road. People don't necessarily know how to run the trials. And so, that's what people are learning from PPMI and Dr. Hirst's, Biogen in one of our industry partners on PPMI. I'm hoping you could share a little bit of the perspectives about the value you see in that study and how that's integrated with therapeutic development at Biogen.

Warren Hirst:

Yeah, absolutely. Thank you. So, I mean, we know Parkinson's disease is immensely complex disease. And, we need the partnerships that we are talking about here today to even begin to understand that. And PPMI, in terms of the consortium there, and there's many industry partners that are within that. And, I think this speaks to the open nature of the work that the Fox Foundation are doing. And how we realize that we can't just take this on our own, and we need to do this essentially really, truly in collaboration with everyone else. And so, this has already been reiterated, I mean, we are in a super high risk business, investing a lot of money. And, we need good data sets, like what are coming out of PPMI to help us progress, and make the right decisions, on the drugs and on the treatments.

Warren Hirst:

And, as we've already sort of alluded to, we got genetics that may point us towards certain aspects of the disease. But, expanding that out and understanding how the genetics is informing us on those pathways, and how those pathways may be more affected than just the 1 or 3 people in a 100 that carry LRRK2 mutation, and how that pathway itself could be affected in the next 20 or 30 people out of that a 100 that, that is hugely important. And the PPMI data, encaptures that in the sense of the biomarkers or the biosamples that it collects. And, as it has been said, it's been a very insightful study planning back 10 years. We think and anticipate that there are going to be ways of actually better measuring these things in the future. And that we are now starting to see. And it's an exciting time, now that we actually have access to that. The other aspect, which is really important is it's a longitudinal study. So it goes over years, it follows peer patients from their early stage of diagnosis right the way through to the later stages of the disease. And that's immensely important for us within the industry and the research community to actually understand how things change over time, and how we can start to think about populations of people. Because when we start to think about the therapeutics, I don't think that we are going to unfortunately be in a position of having one therapeutic that's going to be good for everyone. And we're going to have to understand how over time these are changes. And, how these biomarkers are going to inform us on which treatments are going to be better applied at different times. And that may well change during the course of the disease.

Warren Hirst:

And, the exciting part about the new version of PPMI is that we're going even earlier than that. We're going into this what we call refer to as prodromal phase of the disease. I think we now fully understand that things are happening well before that point of clinical diagnosis, but it's really key to get in as early as possible. And, I think I probably state the obvious that at the point that people have clinical diagnosis, these individuals, people with Parkinson's disease, probably recognize that they're worth changes that were happening much, much earlier. But, that never merited that full clinical diagnosis. What if we could treat back at that point, five years before where we are now clinically diagnosing? We stand a much, much better chance to change the progression and output of the disease.

Katie Kopil:

So, this is one opportunity, one perspective on how industry is leveraging the PPMI data. But to give a sense of the impact of what Dr. Marek in collaboration with The Foundation has built. Something like an average of every 4 people are downloading PPMI data globally, around the world, every 40 seconds. So, this is one company's perspective. And, think about people working in Parkinson's research around the world, every 40 seconds downloading these data. And that's part of the philosophy of ASAP, it's part of the philosophy of The Foundation, is making data available. We're not funding one lab for one lab success. We're funding projects that are a rising tide to lift all boats. And, Brian maybe you could talk about the evolution of that. I know it's been a core part of The Foundation's philosophy. But, how collaboration, and open science, building a community, our third pillar, a community of collaborators working on Parkinson's, has become forefront in terms of what The Foundation is doing today.

Brian Fiske:

Yeah. I mean, I think, you can't overstate the importance of that collaborative environment, that ecosystem to really accelerate progress for Parkinson's. I think, when we first started, and when I first came to The Foundation in 2004, we were so really laser focused on raise as much money as we could, and get it out to researcher hands as quick as possible. And, we just, built this well-oiled machine to do that, which we still are today. [inaudible 01:00:02] is as a committee was saying, we really are a grant making machine.

Brian Fiske:

But, I think one thing we realized, after a few years of doing that was that there was something else in the equation that we still needed to be able to address too. And that was, I think, really building this collaborative environment, bringing in people, getting different stakeholders at the table, and really making sure that the money wasn't just going out into the void, that it was actually going into the right hands. And, people were actually then working together to really solve these problems. And probably one of the best examples of that, I was really lucky and fortunate early in The Foundation progress, we started really when in about 2004, 2005, 2006 when first genetic mutations for the gene, LRRK2 came out, that Warren was talking about earlier. Some of the first consortium building we really did was around that target. And, Warren with us back in those early days. And, we started giving grants out to different labs, and research groups, and started bringing in companies. And, suddenly we built this sort of consortium ecosystem around this, in this case, this one particular biology that we thought was so critical.

Brian Fiske:

And that really just helped accelerate, I think, in so many ways the research in that area and bringing those people together. Even to the point where as several companies were getting close to starting their clinical trials for their first LRRK2 inhibitor drugs, we hit a snag in the biology where it looked like some of the drugs might be having some potential safety issues in some of the laboratory models that were being tested. And everybody freaked out. We stopped, we got the companies together, and they all actually agreed to collaborate to try to address this one question. And then, over a series of a couple of studies that we funded they were able to get clarity on what that actually was. And, that it actually wasn't so concerning as what we thought it was going to be. And they were able to then proceed into the clinic to move their drugs forward around LRRK2. And so, that collaborative model, I think just really became core to how we operate. In addition to, of course, raising a lot of money and getting it out the door.

Katie Kopil:

So, in my role in partnership at The Foundation I get the opportunity to talk with other disease organizations that are looking at us as a model to build a successful program. And, one of the questions I get asked the most is how do you work with industry? And usually say very easily. Warren is not a unicorn. There are hundreds of other Warrens. I mean, you are, you're wonderful. But, there is a sense of community and collaboration. Dr. Marek you've been able to build a consortium that has over 30 industry partners supporting PPMI. And, maybe you could talk a little bit about how you see this as a broader trend in Parkinson's disease.

Ken Marek:

Sure. Absolutely, I think, certainly, I think working with industry is a key component of PPMI, because after all, what we are trying to do is develop the tools that industry will need to develop new therapies. So, if we're not developing the right tools or the tools they're going to use, then we should know that. And, it's really important to have industry be a key collaborator with us along the way. And, I mean, honestly, as Katie says, it's very easy. There's a lot of close interactions, a lot of close collaboration. And, I think industry is a group that helps to fund some of the aspects of the project, although it is a Fox project. But more importantly, contributes intellectually to the PPMI project in every way.

Ken Marek:

I also wanted them to just mention the idea of sort of an open-source study, and how valuable that is. And, I just want to make the point, I mean, I think you said that communication is complex. It is complex.

Katie Kopil:

Right.

Ken Marek:

One way it's complex is, how do you communicate the data that you have developed in a clinical study. And, what we have done in PMI is really make that data available as it is being collected. So, just let me say that again, we're making the data available as it's collected. So, investigators in China, and in Europe, and in South America, and everywhere in the world can go onto the PPMI website and download the data. And do whatever their experiments are, use that in whatever way they can to accelerate their research. And, as Katie points out, there have been millions of downloads over the years.

Ken Marek

And I think this is a really novel strategy. And, you can imagine that for some scientists who are doing a lot of work and are spending a lot of their time contributing to a study, they might be a little bit initially reluctant to make all this data available to everyone. They may want to say, wait a second, I need to use these data to advance my career, or to publish papers, and so forth.

Ken Marek:

And so, I think this has really been a shift in everybody's mind. And, I think it's been very effective. And, I think it's one of the ways in which I think PPMI has been able to really lead the way, and accelerate really, research in a very direct way, all around the world.

Katie Kopil:

And, that's a perfect segue, Dr. Riley, to talk about how ASAP is bringing together global cohorts committed to open science. And, can you tell us a little bit more about this global approach, also that you're taking, especially with genetics in the GP2 program?

Ekemini Riley:

Sure. So, I will say that open science, open data, this is key to shortening the time to getting information out and actually integrating it into research. So, we have very progressive open science policies that really try to shift the culture towards generating data and sharing it out immediately. We also partner with... I explained earlier a lot of our basic science work, but a lot of other work that we do is supporting resources and resource generations, so supporting PPMI, supporting GP2. And, what was really important to us is making sure that all of these studies were open. As this valuable data is getting collected it should be in the hands of investigator, it should be in the hands of patients. Anyone who wants to know this information and this data should be able to know it, without a pay wall, when they want to know it. So, that is our philosophy. And that's what we've been supporting through all of these studies.

Ekemini Riley:

So, I mean, I think it's a really valuable opportunity to accelerate research, not just for Parkinson's, but also for neurodegeneration across the board. You know, the big thing that's coming out now is recognizing that a lot of these neurodegenerative diseases have some common aspects. And so, as we're getting discoveries and information out about one disease, it's really valuable to be able to share that across all of the other diseases. Maybe we might be finding shared path pathways. We might be able to glean something from some other space. Another space might be able to glean something from the Parkinson space. So, I think it's just really important to make sure that ecosystem of openness is out there.

Katie Kopil:

And, one of the things that I love that you're invested in also is making sure that all patients are represented in science.

Ekemini Riley:

[crosstalk 01:07:33] Exactly.

Katie Kopil:

And, maybe you want to talk just briefly about the way you're thinking about a global perspective to treat everyone with Parkinson's.

Ekemini Riley:

[crosstalk 01:07:41] Right.

Katie Kopil:

Not just those who have participated in research traditionally.

Ekemini Riley:

Absolutely. So, I think the global approach kind of underlies everything that we do. But, as I mentioned about GP2 early on, under the leadership of Dr. Andy Singleton and Dr. [inaudible 01:07:55] they really had the vision for how we set up the infrastructure to work with people in other countries. And really not just bringing the patients from other countries, but also the physicians, the investigators, how do we involve everyone across the ecosystems? I mean, everything collecting data and biosamples from people of diverse genetic ancestry. But then also, how we engage investigators and physicians in country to be able to be bolstered with the information that we are helping to generate. And then, be able to help patients within their own countries as well. So, I think, we have the full pipeline of things happening to be able to enable discoveries, to benefit more than just one group of people.

Katie Kopil:

That's great. So, to me that sounds like the best science. And, Brian you're going to take us home. When we were talking earlier, you said you want people to be working on the best research. Can you tell us what that means to you?

Brian Fiske:

Well, I look at the field of journalism, we always say a newsroom should reflect the people it serves, right? And Parkinson's research or research in general should reflect the people it serves. And that's a rich mosaic of people. I also think what's really interesting is the open source data. That spurs innovation. I mean, if you think of it, you're a researcher, you're seeing things going through, it may excite you. Something might click, and all of a sudden you have a new idea, new pathway. I mean, I work with a lot of young future researchers, and this is what excites people. You hear great ideas, and you build from that. Even today, here, I heard a great idea. Let's say I have to have an uncomfortable conversation with my daughter, maybe about the birds and the bees, sit her down at the computer, virtual Debbie Brooks comes up, she explains it. I'm not even there anymore. Thank you, Brooks it's done. So, innovation can come from a lot of different places. And I think that's what excites me.

Katie Kopil:

So, I hope everyone here feels excited. You feel optimistic, and that there's progress. There are people working urgently, and not just these five very bright people on the stage with me, but people globally. And, we're excited to invite everybody to bring your questions about the progress that's happening, progress we haven't gotten to today, things that you want to know about in a Q&A session. So, we'll have everyone take a 5 minute break, stretch your legs, grab a drink, and then we'll meet back up here for another 30 minute session. Thanks all.

Brian Fiske:

Thank you.

Veronique Enos Kaefer:

That concludes the panel discussion portion of the event. Now, you'll hear a Q&A where members of the audience submitted questions for our expert panelists.

Katie Kopil:

We good to get started? Great. We're back up on stage and joined by the Fox Foundation's residents, medical communications expert, movement disorder specialist, and the friendly face of Ask the MD, Rachel Dolhun, along with our panel. And we have a nice amount of questions from the audience. If there are others that come up, feel free to drop them off with our colleagues up here at the front table, and we'll try to get to as many as we can. So I think this is something that comes up constantly, Parkinson's affects people differently. You've met one person with Parkinson's, and now you've met Brian Roberts. So you've met the person with Parkinson's. Dr. Hirst touched on the fact that people respond to therapies differently, and that there's a promise of precision medicine. The question is, could there be a number of separate diseases that we call Parkinson's today, each requiring its own therapy? Maybe, Dr. Marek, you could start with that, and let us know what you think.

Ken Marek:

Sure. This is a great question. And of course this is the standard lumper versus splitter problem. But I think that as we have learned more, my own bias is that, yes, there are many different kinds of pathologies that cause Parkinson's disease that may have a final common pathway, that we now kind of view as Parkinson's disease. And clearly we now, because of the information about the genetics of Parkinson's disease as an example, that there are certainly medications that are going to be useful for some people and not others. And that the concept of precision medicine, or targeted medicine, or whatever we want to call it, it's something that we're all looking to develop.

Ken Marek:

And that's really, in a large measure, a key component of this project that we mentioned earlier, PPMI, where we are trying to use this large group of individuals, to try to understand from within that group, who may have different characteristics that may respond differently. Two medications that may enable us to identify new ways in which Parkinson's disease develops and can be treated. And I think that's really the future. Again, I would go back to something I mentioned earlier, that there is an effort now, which has just started, called PPMI Online, which is an effort to identify tens of thousands of individuals who would contribute information. And I think this is going to be very helpful in trying to understand this really important issue, which is, how do we define different subsets of individuals who might benefit from different types of therapies moving forward?

Rachel Dolhun:

And if I could add in on there, because we're talking about precision medicine and therapies that could potentially slow or stop Parkinson's, which I think all of us agree that there's going to be some combination, different therapies for different people, whether you have a genetic mutation or not, those sorts of things. But I think we see this at work already today.

Rachel Dolhun:

So Katie mentioned at the top of the hour that something like 17 new therapies in the last seven years. And again, I probably don't have to tell everybody in this room that the reason we need more of these therapies, and more tools in our toolkit, is because not every drug works for every person. And so I've talked to countless people who say, "This new drug on the market is the best thing since sliced bread, thank God it came along". And other people who say, "I tried it and it didn't work for me, and I just went back to what I was on, because that was working better". So I think we see this at work already with how complex Parkinson's is, how different it is in different people, that we need different therapies for different parts of Parkinson's and for different people with Parkinson's.

Katie Kopil:

And going to this personalized medicine approach, Dr. Hirst, we enjoyed hosting you on a webinar for our researcher audience earlier this year around precision medicine. And some of what you were talking about along with our experts was this idea that it's maybe not just one target that we need to go after, it's not just one medicine that will work. How are you thinking about the future of precision medicine for Parkinson's?

Warren Hirst:

Yeah, thanks Katie. So for sure, I mean, as I said earlier, it's a complex disease, the genetics and our pathological understanding are pointed towards key pathways. And within those pathways we can kind of place where LRRK2, where GBA, sort of sits. But something that I've always sort of thought a lot about is, if the entire pathway is compromised, is down and it's just not functioning as well as it should be, is targeting one of those things going to be sufficient to pull it back up? It may be that we may need some things that are more pleiotropic, that address the pathway as a whole, as opposed to just that one single gene or target.

Warren Hirst:

And I think that's where we are looking and trying and understand, and this is where the data from ASAP and these larger datasets come in, to understand how the complex biology is interplaying, and where are some of these kinds of key hubs. And some of these hubs, maybe, at the level of controlling transcription of multiple different genes, that ultimately then indirectly feed back, essentially, to within these pathways. And that's where I think we're going to have to essentially try and pass out the therapies that are going forward. And as I said earlier, different ones at different times, I think, is likely going to be part of the clinical sort of intervention.

Katie Kopil:

So more pills for everyone, everyone. Question is, does this group believe the research being done at advancing our understanding of Parkinson's will help other movement disorders, like MSA and other brain diseases. And maybe Dr. Riley, you could talk about the team science approach you're supporting. You talked earlier about learning from other disease areas, bringing it to PD and vice versa, how you see work in Parkinson's affecting other diseases, like MSA.

Ekemini Riley:

Absolutely. So for what we know about MSA, there is a different cell type in the brain that is compromised. And so in MSA, we're talking about glial cells having alpha-synuclein issues in Parkinson's. We're talking about neurons having issues with alpha-synuclein. So if we're funding work that is focused on understanding what goes wrong with alpha-synuclein, and on top of that also funding work looking at different cell types that go awry, to me the path looks completely clear that the research should be able to interplay between MSA and Parkinson's disease. It just seems so crystal clear to me.

Ekemini Riley:

I know from the investigators that we have in the network, there are several of them that work across other neurodegenerative diseases, including MSA. So they're also bringing that insight from what they

know in those disease areas, and that is informing the research as well. So I definitely think it's not a linear path. There is going to be interplay across multiple diseases, for sure.

Katie Kopil:

Dr. Marek, we started with synuclein, and talking about this as being an important target for Parkinson's, but of course it's important in other diseases as well. Maybe you could share some light on how you're working with various groups designing clinical trials. When is the right choice for them to move forward with Parkinson's? When did people consider other diseases that could have the same treatment work for them?

Ken Marek:

Yeah [affirmative], I think that's a great example. And synuclein is a pathology that is important, not only in Parkinson's, but in MSA and other disorders as well. And as we have come to understand these types of problems, I think it's probably best to call them synucleinopathy. So these are problems that cut across a variety of illnesses. And the tools we develop, and the therapies that we develop may well be valuable to treat a number of these different problems. Similarly, what we're seeing is that as we look at the ultimate pathology that you can look at as individuals pass away and get autopsies. With Parkinson's, if more commonly than not, there is mixed pathology. So it's not just in the brain. We can detect evidence that of abnormal synuclein or other proteins that are relevant to Parkinson's. But sometimes there are also abnormalities that might occur in other disorders like Alzheimer's disease or other neurodegenerative diseases. And so I think that we should look at neuro degeneration as a broad problem of which Parkinson's disease is one, a very important one. And I think the efforts that we're making in Parkinson's disease are very often applicable to these other disorders. And the reverse is also true. The efforts that are being made in these other disorders like Alzheimer's disease or MSA or Diffuse Lewy body disease, or PSP are often very important and help us to move forward with Parkinson's as well.

Katie Kopil:

This is going in a deeper science direction. So the question, maybe I'll direct this to you, Dr. Fiske, are there any studies in the future involving CRISPR? So maybe first you could explain what is CRISPR? It's not where you store your vegetables and then what's on the horizon.

Brian Fiske:

Yes. Oh, so CRISPR is sort of a fancy technology, genetic technology that allows you to sort of go in precisely and essentially change a little bit of your DNA code. And so it's been used in research for a number of years to do a lot of different things to study, obviously biology. You can use it to create sort of genetic preclinical laboratory models of genetic versions of diseases like Parkinson's. So it's a really, really powerful technique. And, and so it is obviously because of that, there's a lot of interest in the idea of using it to develop therapeutics as well. And so the idea is if you could go in and sort of fix, genetically, what's wrong in individuals, could you use a technology like CRISPR to do that?

Brian Fiske:

And so there's not, I can't say I'm an expert in the technology and others here might be able to comment on how in reality that is being used in any sort of therapeutic programs, specifically today. I don't know. If I'm looking at Warren, he might know a little bit better than me, but it is I think an example of how sort of invention, and we were talking about that earlier, of a technology like this, can then lead to

innovation and how it ultimately gets used in different diseases and not only in research, but also therapeutic development. So I don't know, Warren, I'm trying to think about some good examples.

Warren Hirst:

Yeah. I mean, I think probably, the best examples and where we're going to see it be applied first. It may not necessarily be within the brain or, or within the neurological disorders. And in part it's because there is one of the main challenges is how do you get that reagent? And how do you start to modify that in the cells that you want to target? And what people use right now is essentially viruses to deliver the CRISPR reagents into particular cells. And I think we are lacking a bit behind, around the technology to get enough cells, essentially within the brain transduced in this way. And so I do think that we will likely see it be applied in, in more peripheral applications first and also, focus very much on these very clear, single genetic, monogenetic disorders where you actually have that clear aspect.

Warren Hirst:

With Parkinson's disease, although as we've already heard we do have the strong genetic aspect. It's not a classic monogenic disorder. And we see that people, there are plenty of people that carry some of these mutations that we link to Parkinson's disease who never get Parkinson's disease. And there are complicated aspects of the biology and the genetics, which is essentially compensating or preventing essentially the disease from forming in that case. And that then starts to essentially complicate the development course of a gene therapy, because as I said earlier, the way to do that is to actually get in very, very early. And so you may want to look at something like Huntington's disease. If you're thinking about the CNS where with a certain number of expansion repeats, the probability of you getting that disease can get to be very, very high.

Warren Hirst:

And so something like that to intervene prior to disease, in that way, probably is going to be more attractive in the foreseeable future than for Parkinson's disease. Because someone that carries a G29 nest mutation, or ERE for [lock two 00:15:26] or an N370S mutation for GBA, the chances of them getting the disease are still actually probably quite low to merit this sort of treatment right now. And then the other aspect is, of course, if someone already has the disease? How do we know that going in and correcting something at that level is the right thing to do [crosstalk 00:15:46]. And that is also sort of the uncertainty that we have, but that also applies to other therapeutics, to be honest.

Katie Kopil:

So we don't want to mess with your genes until we are sure that that's the right thing to do. Very good. And, and Dr. Hirst, you were talking about some of the challenges here of things getting into the brain. I have an interesting question here- is PD an autoimmune disease, and what's the role of the immune system in Parkinson's disease? Dr. Riley, do you want to start?

Ekemini Riley:

That is the million dollar question, isn't it? I would say it is one of the key questions.

Speaker 1:

The billions.

Ekemini Riley:

Yes. Yes. You're right. Multiple of those. Yes. So, that is a key question that was a driver to our scientific focus of neuro-immune diseases. There are publications out there that suggest a role for the immune system in either the start of disease or the progression of disease, how exactly that happens, which cell type is involved in that those are all open questions. And that's what we have, teams of investigators, where we've brought together classic immunologists paired with neuroscientists and neurologists to really tackle those questions. So I'd say the jury is out, but there are people working on it.

Brian Fiske:

Maybe just to comment on that too, I think one of the things we've realized, especially when you think about the immune system and its role in in Parkinson's or some of the other cellular pathways is, often, those are hard questions to answer, because we actually don't have good tools to measure them in people. And one of the things that we found in, I think the immune system is a good example of that, is building better tools so that people can actually measure those things in people. And then see if they're actually disrupted in some way, is one of the powerful ways that we could actually help make progress.

Brian Fiske:

And so we've been, over the years, funding a lot of work, for example, and looking at different imaging approaches that could explore the immune system and sort of inflammation in the brain or different types of bioassays we can develop that can sort of tease apart different aspects of this biology, but more as a sort of biological tool, and a measurement tool to help address some of these questions. And I think once we start having more of those toolkits, then hopefully we can also better understand foundationally too. Is it really cause contributor, when in the disease process, is it really sort of show up in the disease. And I think that's a really key part of this too.

Katie Kopil:

So this is hinting at, also this concept, that inflammation is an interesting approach to try to treat Parkinson's disease. What's the pipeline look like for therapeutic programs that are happening or moving towards clinical trials that are targeting inflammation? I'm going to take anyone that wants to jump in.

Ken Marek:

I think there's a very, this has become of tremendous interest because there are these scientific underpinnings that suggest that that inflammation does have a role in either the big start or the progression of Parkinson's. There are many biotech companies that are making their way with lots of very innovative approaches to try to modify the immune system. And again, I would just go back to the previous question that this is no less true for other neurodegenerative diseases. And so this is an example of where this type of strategy, this type of science can benefit Parkinson's disease, but also other related disorders as well.

Warren Hirst:

Yeah. And to build on that a little bit, I mean, we've been looking at MS. Multiple sclerosis. And thinking about how some of those mechanisms could apply back. And so this is an example of taking one disease, thinking about these pathways and processes and seeing what we can think about and learn from another disease. And so, I'm just working right now with a long term collaborator, Jeff Conover on a model that he's generated, which is an MSA model. And now we're taking to [Sarre 00:19:56], which is

one of the Biogen's marketed products for multiple sclerosis. And we're asking the question, which works pretty well in that population, is this going to potentially work in a preclinical MSA model? And these are the sorts of data that we would then look to generate internally to then support, first of all, smaller exploratory type trials and then larger pivotal trials, if it were to work. And I think the concepts can then further be extended from MSA to Parkinson's disease as well. There is also a very appealing aspect from a therapeutic development perspective about what we're talking about, inflammation modulation is, it is accessible. We can take blood samples. We can actually start to try and determine whether there are specific profiles within those, that could be identifying subgroups of people with Parkinson's disease that would most likely benefit essentially from those treatments. So that is a very strong plus from that angle.

Katie Kopil:

Maybe go to Dr. Dolhun. This is a question from someone that's considering DBS and given some of the advancements that are being developed around; not the device necessarily, but the technology. What's happening in that space? How should someone think about waiting to get DBS for new innovation versus getting something today?

Rachel Dolhun:

It's such a great question and I hear it very often. So, to get everybody on the same page. DBS; deep brain stimulation, this is a surgical procedure that aims to treat Parkinson's symptoms. So, just like our medication, it aims to lessen movement symptoms, primarily tremor, slowness, stiffness, some walking problems. It's FDA approved for people who've had Parkinson's for at least four years, who get a good response to medication, but who have complications from medication. So when years into Parkinson's, we start to see off time when medication isn't working as well and symptoms are coming back. Or dyskinesia, those extra involuntary movements that can sometimes come along with medications too. The ups and downs of day to day when you're taking medication and things seem to be going well and then coming back down and doing that fluctuating over and over. Deep brain stimulation, may be an option. So it's not for everybody because it doesn't treat all symptoms of Parkinson's. And it can potentially make some significant thinking or memory changes, speech changes a little bit worse. So doctors carefully evaluate somebody for potential deep brain stimulation.

Rachel Dolhun:

So all that being said, Brian alluded to this earlier, that there has been a lot of work on deep brain stimulation. To innovate. To improve the technology. Make advancements. And over the past couple of years, we have seen a lot of these tweaks and incremental steps to improve the systems themselves. Now, that being said the system itself and the way it works, has remained pretty much the same. So while we see some improvements in the leads that we put into the brain and how they can potentially sense a person's individual brain signals, and we can start to see some patterns and things like that. We're moving forward toward our next step of deep brain stimulation. Which probably, given the trials that are ongoing right now, is what we would call closed loop or adaptive deep brain stimulation.

Rachel Dolhun:

So right now, the way DBS works is we put leads in the brain. We put a programmer under the collar bone and we program electrical settings into there, unique to each person and their Parkinson's. And that delivers a small electrical pulse over and over to treat Parkinson's symptoms. So, the way that we're moving toward, and hoping toward going is that the leads could themselves monitor your brain signals.

Measure those patterns and see, oh, when this signal comes, that means there's tremor. Or when this signal happens, that means somebody's freezing. And now I need to kick in and go on. And so it would be this responsive, personalized system of deep brain stimulation.

Rachel Dolhun:

So that's probably our next step. And then Brian was mentioning some of the other things that are in development. Now, all that being said, to actually answer the question that was posed is, how do I think about this knowing that there are innovations in the pipeline? Is the next thing I'm going to get the surgery and then the next month there's going to be some new, big improvement? We're not quite there yet. So what I always tell people is, don't sacrifice your quality of life right now for the next big thing that might be happening. If and when that big thing happens, we cross that bridge, and it may be that you just need a different programmer that's put in. And it'll still work with the same leads that you have, or it may be that the whole system could be upgraded.

Rachel Dolhun:

But I think again, we're moving toward that. But right now where we are, we've made these incremental improvements. And we're at a good spot that I wouldn't want anybody who's thinking about it to hold on for the next best thing. And the other innovation I just wanted to mention, that happened over the pandemic, which is a great thing. Is that one of the companies now allows doctors to do programming remotely. So you don't even have to go into the doctor's office to get all your programming done. Of course, that's something you'd want to balance the in-person visits with the virtual remote visits. But it's a really neat way of delivering medicine and care remotely.

Katie Kopil:

So, a great segue to the next question, which is highlighted by everyone's favorite accessory, the mask. How has COVID impacted research? Maybe you could start on the clinical trials, what you've seen, the impact there?

Ken Marek:

Sure. COVID of course has affected us all. Fortunately, with regard to clinical research, it has certainly slowed research in some ways. It's of course more challenging for clinical trials to continue of people to get to clinical sites for the trial. But that being said, it has also created an enormous amount of innovation in how we can do clinical studies, in this new world of trying to understand, then evaluate individuals at home. And I'm sure almost everyone in this room has been engaged in some zoom medical activity. And I think they work pretty well. They're not perfect, but it has really generated a whole new area of research. Which I think will grow and ultimately will make clinical trials, I think, more effective, and more able to engage with people for a longer period of time. So, I think maybe it's had a silver lining.

Katie Kopil:

Another COVID related question, of course, for another silver lining, everyone knows what clinical trials are. That people understand that research is not just Bunsen burners and chemical goggles. It's something that you can participate in. So, that's a great way to speed research. What's the current

status of mRNA in Parkinson's disease as a therapeutic tool? This is building on the mRNA vaccines. And maybe we could start with what's the current status of a vaccine approach to treating Parkinson's?

Rachel Dolhun:

Brian, do you want to take that?

Brian Fiske:

Sure, yeah. So, when you think about what a vaccine actually is, you're trying to essentially convince your immune system to create antibodies against something that you're trying to get rid of. And so for Parkinson's, where vaccines have really been... That concept of vaccination has been utilized is mostly around trying to get rid of the protein Alpha-Synuclein in the body. And we talked about that earlier. About why Alpha-Synuclein is so critical for Parkinson's. And so, there's two flavors of this approach that are in the pipeline right now. There's some bleeding approaches that are trying to actually deliver the antibody itself. So it's basically giving you the antibody against Alpha-Synuclein, so you don't have to necessarily make it yourself. But there are a few groups out there that are actually trying to do the more traditional route. So they actually are trying to give you a slightly synthesized version of the bad form of Alpha-Synuclein injected in you. Almost like they would a little component of an actual viral particle. So that your body will then produce those antibodies and actually try to clear out that bad Alpha-Synuclein directly.

Brian Fiske:

And so some of the approaches, and the pipeline that we've talked about earlier in the discussion today are trying to use that vaccine approach. And so that concept that you could use and leverage the immune system to do something it does really well, which is to make antibodies against foreign things. To trick the system to go after pathological proteins that we want to try to get rid of. And that I think is a powerful tool.

Katie Kopil:

Maybe I'll start with you, Bryan Roberts. What can people who care about those with Parkinson's do to help move research forward?

Bryan Roberts:

That's a great question. I think they can do the same thing to help push research forward that patients with Parkinson's can do. Engage in whatever level you feel comfortable. I think it was Dave Iverson who once said, we need people with healthy brains. We need people with brains like Brian's. So it was right. I mean we need everyone. And I think, but not just for Parkinson's research, for everything, right. We need a different range of voices and engage. I think that's one of the things I've been really pleased about is being a somewhat younger person with Parkinson's. When people get over the initial shock of, you know, you're so young, how sad, that sort of thing. It's actually good because then people ask questions, they engage and people want to be involved. People want to know that they're doing something good. I think Parkinson's research advocacy, fundraising. I mean, Team Fox, whatever you can do, whatever you're comfortable with. I think that's how they can help. As a researcher, Parkinson's fascinates me, as a patient it fascinates me, but I think what the thing I really find interesting is people's reactions to it. There's so many good people out there, no matter what your level is, or your engagement with Parkinson's, if you want to engage in research or whatever you're comfortable with, that's a win for all of us.

Katie Kopil:

An easy way to do that, visiting PPMI online's Michaeljfox.org/ppmi. If you're over 18 and you probably are in this room, you can join online with or without Parkinson's and help contribute information that helps us better understand why people get the disease, why others don't. That's an easy... if you consider online surveys easy, relatively painless, no one's going to poke you... a way to participate in research. Another question about PPMI. Ken I... let me pass this to you? What are plans for studying the people that were originally enrolled in PPMI. Sounds like we have some PPMI volunteers in the room that are among those getting poked.

Ken Marek:

Great. No, I think that we are continue... and are continued to be very enthusiastic about having those individuals who were originally involved in PPMI continued to be in PPMI. The expansion of the project has... it does not want to leave those people out in any way. In fact, they are in many respects, the most valuable people, because we have the most information about you already. That has turned out to be just very, very important in understanding the course of Parkinson's disease over time. I think now we have an opportunity to compare what happens to people who've had Parkinson's disease for some time, what happens to people who are just developing Parkinson's and what's happening to people who may be at risk for Parkinson's disease, but have not developed it. We don't know if the same kinds of sort of biomarkers these biologic measures occur in all of those people in the same way. That would be very important. We need to have all of these individuals continue to be engaged in the project to really answer those questions effectively.

Katie Kopil:

Could be getting close to our time here. Maybe the last question. We talked earlier about the role of genetics and maybe precipitating someone getting Parkinson's disease, but what's the role of genetics on someone's presentation on the symptoms that someone has. Is there any connection between genetics and Parkinson's symptoms?

Brian Fiske:

It's actually, a really great question. One we haven't really had the good data yet to answer well, and it's one of the really exciting reasons why I think the ASAP, the global genetics project is going to be so powerful because it's you... with the numbers, you need to kind of make those kinds of analyses to understand the role of genetics as predictors of that sort of progression and things like that. You need large numbers. I think that's one of the things that GP2 is really going to be able to address and understand. You also then of course need deep data. You need to understand what those different clinical features are and how they've progressed over time, so you can match that then with the genetics. I think few years ago, this kind of question, isn't really something we could answer.

Brian Fiske :

I do think we're starting to get to a point now with PPMI providing a lot of the clinical, deep clinical picture GP2 really providing that sort of genetic foundational basis. We can start answering some of these questions better. We do know some genetics that may influence onset of disease. It's not quite the answer of the actual progression, but we are starting to understand potential genetics that might sort of predict whether you get it earlier, a little bit later and things like that. I think that is starting to paint a little bit of that picture, but I think it's a real opportunity for if others want to jump in on that.

Ken Marek:

I'll just jump in. I think this is something which is going to rapidly develop in the next few years, and we're seeing this already, that there are, of course... people have genetic mutations that confer risk, but I think all of us have genetics. Right? I think so the character of one's genetics is... influences how Parkinson's disease affects you. We don't understand that very well yet in most people, but we will understand it. I think with the information that's being collected in GP2 and in PPMI, and we're beginning to see some inklings of this, as recently as two weeks ago. In one of the PPMI investigators uncovered, what might be a gene that is... it makes people more likely to have cognitive problems than other people. I think these are the kinds of findings that we are now able to begin to understand. I think this is rapidly going to develop over time and be very informative.

Katie Kopil:

We're back where we started, biology. New insights that are being shared more rapidly through collaboration and open science, that's driving new therapies. There's a lot of progress that we hope everyone is excited about. We hope you've learned something here today. I'd like to end by thanking this panel. I'd like to thank all of you for your support of The Foundation, your support of the Parkinson's community, and looking forward to being able to share more progress with you a few soon. Thanks all.

Debi Brooks:

It's not quite like sitting down and eating your vegetables. There's so much exciting stuff going on. Just want to thank you all for being here today and to also thank the panel of experts for leading us through this discussion and addressing questions. We hope you feel the momentum and the progress. There's so much that is happening. I hope you also have a keen takeaway about the role that patients and families and just people who don't even know they need to be caring about Parkinson's, can already... the help that they can bring to this challenge and the role they will be playing, going forward. Research participation. I kept hearing it referenced, and I would just want to say very directly how important it is to speeding progress. Often we get asked, what can we do? Of course there are a lot of things that people can do, but probably the most genuine and unique contribution that anyone can make to the effort around research is to actually consider participating in research.

Debi Brooks:

As we think about this expansion of knowledge, and particularly this area being driven by recent data that says we are learning more about who's at high risk. It's a moment for the people in your lives to think about being involved too. This to me is so exciting. Before you leave I ask that you... we'd love to know what you think about this event. There's a piece of paper with a QR code on the table on printouts. If you would scan that with your camera app and do a brief survey, that's how we learn best to address the topics and areas of interest for you. Also, don't forget on your way out to grab a bag. There's some more information on the programs that we've talked about today, and also a little afternoon snack since we weren't able to serve our traditional brunch. If you're attending our event tonight, we will see you there. We're very excited. Thank you all. Thank you for being here today for being intentional and engaged listeners and also partners in the work that we're doing together. Have a great afternoon.