Jamie Eberling, PhD: 00:04

Hello and welcome to The Michael J. Fox Foundation Third Thursdays Webinar. I'm Jamie Eberling. I'm one of the scientists on staff at The Michael J. Fox Foundation. I'm joined today by Dr. Todd Sherer, CEO of The Michael J. Fox Foundation and Dr. Ken Marek, President and Senior Scientist at the Institute for Neurodegenerative Disorders and Principal Investigator of the Parkinson's Progression Markers Initiative, PPMI.

The topic of today's webinar is new treatments for slowing or stopping Parkinson's disease. We'll talk about the ongoing clinical trials for different therapeutic targets and the types of patients these approaches could work for. Before we get started, I have just a few housekeeping items. You're able to submit questions throughout the hour. You should see a Q&A box near the middle of your screen. You can type your questions there, and we'll do our best to get to as many as we can.

Also, we're providing the slides from today's webinar for download. You should see a box called resource list on your screen. So you click on the link there, and the document will open a new browser window and you can either save or print from there.

Finally, I just want to point out that today we're talking about trials to slow or stop Parkinson's, but the Foundation has a full library of webinars on other topics that you can watch any time. Some of the topics that were recently discussed include medical marijuana, memory and thinking problems, and STEM cell treatments. The full library is linked in the resource list on your screen.

The trials we'll be discussing include trials for genetic targets; and these include α-Synuclein, LRRK2 and GBA; repurpose therapies, these are therapies that were developed for a different disease that are being tested for Parkinson's disease; and therapies against other pathways, including inflammation and oxidative stress.

First, it's worth noting that the clinical pipeline for Parkinson's disease is pretty full. There are at least 51 therapies that are in clinical trials for disease modification, and 48 that address specific symptoms. Todd, can you start us off by telling us what we mean by disease modifying therapies, and how these differ from symptomatic therapies?

Dr. Todd Sherer: 02:39

Sure. Thanks, Jamie. And thank you to everyone who's joined the webinar today. There's different types of approaches that

we take in trying to develop new treatments for Parkinson's disease. And I think the types that we're going to talk about today are really aimed at targeting and addressing the underlying biology that is leading to Parkinson's and leading to the progression of Parkinson's disease.

So the goal of the therapies that we'll be talking about today are really to intercede, intervene in that underlying process of the disease with the hope to slow down the disease process, and ultimately to slow down the progression of the symptoms of the disease. I mean, I think that's what we mean by the current term of disease modification.

The other treatments that focus on the symptomatic treatments, these really focus on trying to improve some of the symptoms of the disease, but may not be targeting the underlying disease process, in terms of the biology through which the therapies are working.

Jamie Eberling: 03:44 And can you just mention some of the challenges that are particular to disease modifying trials?

Dr. Todd Sherer: 03:50 I think what's difficult about disease modifying trials are a couple of things. One, we are still learning a lot about what causes Parkinson's, what the underlying biology that may be involved in the progression of Parkinson's disease. So there's quite a lot of risk involved in how you go about developing your therapy and what biology you're trying to target.

It's also quite difficult to run clinical trials looking at therapies that might be slowing the progression of the symptoms of Parkinson's disease. For a number of reasons, Parkinson's is a highly variable disease, so no two cases of Parkinson's are exactly the same, so that adds a lot of noise into the system to really understand the outcomes of a trial.

And also, luckily, Parkinson's can be a very slow disease in many people, but that adds a lot of time to a trial, because if we're really trying to look at the impact of a therapy over time, we have to watch and see as the symptoms progress over that timeframe.

So the trials, because of the variability and the need to look over a long period of time, can require a lot of participants, as well as a long duration. And that can make trials very expensive and difficult to initiate.

And finally, we still need to develop better and more robust outcome measures to really be able to determine that a therapy is having that effect on the progression of the symptoms that we're hoping for.

Jamie Eberling: 05:21 Great. Thanks, Todd. So let's talk a little bit more in detail about some of the ongoing trials. And I want to mention that most of the trials that are listed on this slide have links. You can click on the link once you've downloaded the slides and it'll take you to Fox Trial Finder or clinicaltrials.gov, and you can get additional information about the trials there.

So this slide summarizes the current trials that target α-Synuclein. As you may know, α-Synuclein is a protein that clumps in the brain of most Parkinson's patients. And scientists believed that these clumps of protein called Lewy bodies are toxic and harm cells.

So as you can see, there are three different approaches that are being tested in the clinic now. And these include vaccines, antibodies and drugs; and the trials are in different phases of development.

So Ken, can you talk to us about α-Synuclein and why we think this is a good target, and then tell us about what these different approaches aim to do.

Dr. Ken Marek: 06:31 Sure, Jamie. And again, it's a pleasure to be here this afternoon, and thanks, everyone for listening. I just wanted to go back to one of the comments you made at the start, which is that the pipeline for Parkinson's disease therapies is pretty full. And a reason for that is sort of illustrated by the number of trials that are on this slide, focused on synuclein. Over the past few years, there's been, really, a number of efforts to better understand some of the underlying causes and underlying pathologies in Parkinson's disease, some of which are related to genetics, some of which may occur in some individuals with a genetic mutation, but may be relevant to all people with Parkinson's disease.

So synuclein is really thought to fall into that category, that we now understand that in the majority of individuals with Parkinson's disease, we believe that there is the set of abnormal clumping or aggregation of this normal protein called synuclein, which becomes abnormal in individuals with Parkinson's disease.

And there are a number of different strategies that are now being evaluated to try to resolve that problem. One is a vaccine which would sort of prevent this abnormality from occurring in individuals in whom it might otherwise occur. The other is an antibody approach, which, and there are a number of different companies that have developed specific antibodies that specifically target synuclein, so they are injected into the blood, get into the brain, and their end would ... The goal of those of those studies is to try to reduce the amount of this abnormal synuclein in the brain. I would just parenthetically mention this is a similar strategy that is being used in Alzheimer's disease. We've recently heard about a success in Alzheimer's disease with a amyloid antibody targeting a different protein that's similar to synculein, but is relevant to people with Alzheimer's disease rather than Parkinson's disease. So this strategy, I think, is very exciting. And these trials are just underway, and we will begin to see the results of these trials over the next several months.

Yet another strategy is to rather than use a medicine which is injected into the blood, to try to use an oral medication, which would also have the same effect of reducing the number of these clumps of this abnormal protein. And there are a number of trials that are being planned with that in mind; these sort of small molecules that can be taken orally that might have the same effect. So I think we're really at a stage where there are a number of exciting ongoing therapies that are being tested, ongoing trials that are testing therapies in synuclein. It has a very strong scientific basis, and now we are eagerly awaiting some of the results of these trials.

Jamie Eberling: 09:58 That's great, Ken. And can you just tell us what is meant by phase one, phase two and phase three?

Dr. Ken Marek: 10:06 Sure. So when we think about doing a clinical development of a drug, there are a number of phases of that development. Essentially, phase one is testing in healthy subjects, just to be sure that the drug is safe. Phase two is when we try to evaluate the drug in individuals with the disease, by really trying to know what's the right dose of the drug, whether there are any side effects of the drug that we can recognize easily, and just sort of understand whether this drug really may be effective. Based on the information in phase two, which are studies which are reasonably small, maybe a couple of hundred people, there would be an effort to go into a larger phase three study, which is really designed to really acquire the data necessary to get the drug approved by the regulatory authority. So these are larger studies, sometimes longer studies, really to try to ensure that

these drugs might have the effect we now believe they would have from the earlier trials, but in a larger group of individuals who would be evaluated over a longer period of time.

So the synuclein therapies that are on this list are really either in phase one or phase two, really waiting to get the results to really provide the rationale for moving to the phase three studies.

Jamie Eberling: 11:45 Great. Thanks, Ken. Okay, so LRRK2 is another genetic target, and there are trials in the clinic right now. Two are testing LRRK2 inhibitors, and one is testing what we call antisense oligonucleotide. It's a mouthful.

Todd, can you tell us about LRRK2, and what these trials are aiming to do?

Dr. Todd Sherer: 12:11 So LRRK2 is another really promising area for Parkinson's research. It's one of the more common genetic mutations that have been found to increase the risk for getting Parkinson's disease. And what has been found is that the mutation in LRRK2 that leads to an increased risk for Parkinson's actually increases the activity of LRRK2. LRRK2 protein serves as a catalyst within chemical reactions and biological reactions within a cell. And what has been found in the laboratory is the mutations in LRRK2 that are linked to Parkinson's increase that activity, so increase the ability of the LRRK2 protein to function.

This has really led to an excitement in the ability to, then, develop therapies against LRRK2. When you have a protein that has too much activity, this leads to the hypothesis that a therapy could be targeted to block or inhibit or reduce the activity of that protein.

What's particularly exciting and interesting about LRRK2 is that this type of protein has been developed in the past, or has been targeted in the past, for therapies in other diseases, particularly oncology and cancer therapies. So there's a good track record for the pharmaceutical industry for developing therapies against proteins like LRRK2. So this finding that has linked the LRRK2 protein to a risk for Parkinson's, it's what they would call drugability, in that there's an activity that could be targeted by a therapy; has led to quite a lot of activity around LRRK2 therapies.

So it was very exciting, in this past year, to see that the first, really, LRRK2-based therapies are moving forward, now, into

clinical testing. Two of these approaches are using drug-based therapies, so this is the Denali studies that are looking at LRRK2 inhibitors, so these are pharmacological chemicals that are being developed to decrease the activity of LRRK2, to normalize that activity.

And then new, more kind of genetic approach, which is the the one on the antisense oligonucleotide approach, this is really to use genetic technology to decrease the production of the protein. So lower the amount of LRRK2 protein with the same goal of decreasing the activity of this enzymatic function of the protein.

I think what's also been really exciting about LRRK2 science over the last or two really has to do to the role that LRRK2 might be playing in Parkinson's, in individuals who do not carry the mutation in LRRK2. So there are individuals, as I mentioned, who have LRRK2 mutations, and that's probably leading to an increased risk for Parkinson's in those individuals. And as I mentioned, the mutation increases the activity of LRRK2.

What has recently been found in the laboratory is that certain environmental toxins that also increase the risk for getting Parkinson's, such as pesticides; these pesticides also increase the activity of LRRK2 in the same way that the mutation does. So what that is indicating is that perhaps inhibiting LRRK2 function in these LRRK2-based therapies may, in fact, have a benefit for individuals with a mutation, because they would have increased LRRK2 activity; but also others with Parkinson's who have more idiopathic or unknown causes, as we are finding the increased activity of LRRK2 in response to pesticides or in different biological samples from individuals with idiopathic PD; those without the mutation.

So this is a really exciting new area of research. Some of the trials ongoing, now, are recruiting individuals with Parkinson's and a LRRK2 mutation, but also testing these same therapies in those without the mutations. So this is a really important area, and I think there'll be a lot more activity in this area moving forward.

Dr. Ken Marek: 16:33 Yeah, maybe I-

Jamie Eberling: 16:33 Thanks, Todd. That-

Dr. Ken Marek: 16:34 Maybe I could just add that I think this concept that, as we are showing these studies in these trials today, we've separated, of

course, them into different categories, but I think more and more, we are seeing that there is sort of a phenomenon where the individuals with LRRK2 may be relevant to all people with Parkinson's disease, as we're going to talk about another mutation, GBA, in a moment, that also maybe relevant to therapies there, or maybe relevant to all people with Parkinson's disease. So there is a sort of coming together of these different pathologies that may help us to develop therapies that could be useful for not only individuals with a specific mutation, but with other individuals with Parkinson's disease, as well.

Jamie Eberling: 17:32 That's right. And speaking of GBA, that's the last genetic target we'll talk about. And as you can see, there are several therapies that are currently being tested.

Ken, what can you tell us about GBA and how it may contribute to the disease process?

Dr. Ken Marek: 17:48 All right. Thank you, Jamie. So GBA is yet another common mutation that has been recognized in Parkinson patients. You can see about as many as 5% of individuals with Parkinson's disease may have a GBA mutation. And it results, this time, in a lower activity of a protein in the brain, which in turn results in a cascade of events in a series of chemicals in the brain called the lysosomal system. And part of the goal of the therapies is to try to increase the activity of this protein, GCase, to normal levels; or, sort of restore the function of this system through working on the sort of downstream effects of this protein.

It is very exciting that there now are a number of therapeutic trials which are underway, that are really directly addressing this particular problem. And there are a number of strategies that have been taken, three are illustrated in this slide. One is to simply develop drugs which enhance the activity of this protein, which is lower because of the mutation, so GCase enhancers. And we see there are two therapeutic strategies that have been tested already, and are in early testing, the Lysosomal Therapeutics drug and Ambroxol.

Another strategy is to try to, not directly approach the GCase protein, but approach the effect of that reduction in protein. And that's a study which is ongoing by Sanofi. And Sanofi has taken this on with a lot of prior understanding of this particular problem, because they have had success with a similar treatment for a disorder called Gaucher's syndrome.

Dr. Ken Marek:	20:00	A genetic disorder called Gaucher syndrome, which also results in a reduction in the GK's protein in that case, causing a much more widespread problems. But they've learned from that effort and are now a very much bringing that forward to the Parkinson's therapeutic arena. And finally, there's a really exciting new therapy that is being tested by Prevail Therapeutics. This is a gene therapy really trying to use gene therapy to kind of restore or replace the defect, which is caused by the mutation to begin with. So this is yet another approach. This project has just begun and they are currently enrolling subjects to try to understand whether this strategy will be effective as well.
Jamie Eberling:	21:03	Great. So before we move off of the genetic target, can maybe you can just comment a little bit on what's being done in PPMI in terms of genetics and how what we learned from that study could support the clinical development of these types of therapies.
Dr. Ken Marek:	21:21	Yeah. So PPMI or the Parkinson Progression Marker Initiative is an effort that is sponsored by the Fox Foundation really to try to address an issue, which Todd mentioned earlier that is trying to develop better outcomes so that we can more easily and effectively understand whether drugs can slow or prevent the onset of disease. Again, since we're trying to understand whether a drug reduces the rate of progression in a relatively slow process. Having sort of objective markers to help us to understand whether the drug is having that effect would be very helpful. In that project. We have specifically targeted individuals with these genetic mutations with the GBA mutation, MARK2 mutation as well as the synuclein mutation to try to help us to understand whether we can measure changes that occur in these individuals with regard to their clinical findings, with regard to their imaging findings, with regard to their other biochemical findings to really identify in and pin down a specific objective markers that tell us about the progression of disease in these individuals both with Parkinson's disease and who may have the mutation but who are not yet developing Parkinson's. So even at this at stage that might ultimately enable us to develop a strategy to prevent Parkinson's disease. So we're using these genetic mutations to help us as a guide ultimately to all people with Parkinson's disease. But I think we're hopeful that by evaluating large numbers of individuals with these mutations, we can really develop these tools that we need to advance these disease modifying therapies.

Jamie Eberling: 23:31

Great. Thanks Ken. Okay, so let's move on to repurpose therapies. We hear a lot about repurpose drugs and these are drugs that were developed for one disease and then tested for another. So Todd, maybe you can talk about some of the potential benefits of this approach and also some of the challenges.

Dr. Todd Sherer: 23:52

Yeah, so as you mentioned, repurpose therapies have the goal of taking drugs that we already have developed that already are available or already moving through clinical development for one disease and test them to see if they could have a benefit or impact in another disease. And the rationale for this is that there actually is a lot of overlapping underlying biology that can go across different diseases and using that same drug, you might be able to target what's happening in more than one disease.

In theory, this is an interesting approach because of the potential speed that this could bring to drug development. We talked about, Ken mentioned before, the various stages of clinical trials. For example, the phase one, phase two, phase three. In many cases if we already have a drug that's already available, it's probably already or likely have already gone through many, many of these clinical testing phases. Many, many people have been exposed to the therapy and we could have a good understanding of safety issues, dosing that's required to get a benefit because it's already been developed.

So in theory there could be a shortcut in terms of developing this treatment for the new indication. I think one of the challenges to keep in mind is that as you are bringing a drug into a new indication, you may likely have to do some of those ... Go back in time and do some of those experiments over again. If there's a different type of population of individuals who are now being tested with the therapy.

So for example, there could be a drug that was previously developed for younger individuals and is available and now if we're trying to test it in a Parkinson's population where the people may be older or more elderly. It doesn't automatically mean that we don't have to go back and do some of the safety testing or dose testing. So I think there are pros and cons of doing repurpose therapies. The most significant pro is a potential to accelerate the development because we already have a drug in hand that we could move forward. The con is that we still have to do the rigorous testing. We have the same challenges of how we go about doing trials in Parkinson's and

we want to make sure we're still as rigorous and data-driven as we need to be.

Jamie Eberling: 26:26 Thanks Todd. Maybe one more challenge that I'll just mention is that a lot of the drugs that are being repurposed are drugs that were developed for diseases that don't affect the central nervous system. So these drugs need to be able to get into the brain for the most part in order to be effective for Parkinson's disease. And oftentimes they're specifically designed not to get into the brain. So dosing can be pretty tricky.

Dr. Todd Sherer: 26:54 Yeah. And just to add it. I guess another challenge that I was going to mention is that depending on how long the drug has been around, it could be that it is now a generic drug. So no longer on patent and it will require either foundation or government support to move that project forward because there's no longer the same incentives for pharmaceutical companies to continue to develop these therapies. So that's something else. And you'll notice in this slide a lot of these are more academic or foundation, government driven therapy trials that are being developed for the repurpose drugs.

Jamie Eberling: 27:35 Yeah. And two of the trials listed on this slide for nilotinib, I know there's been a lot of interest in those trials. Can you tell us anything about the current status?

Dr. Todd Sherer: 27:49 So for nilotinib, these are trying to develop therapies against the c-Abl target. This is another interesting drug target that's been linked to the underlying mechanisms of Parkinson's. And there are drugs that have been developed in cancer that target c-Abl, one of which is nilotinib and there are two trials going on right now, one from Georgetown, one from Northwestern and the Parkinson Study Group and my understanding is that the results of those trials are ... The trials have been completed and the results should be coming out pretty soon to understand the impact of nilotinib in Parkinson's.

Jamie Eberling: 28:34 Okay, great. Thanks Todd. Therapies against two other disease mechanisms, inflammation and oxidative stress are also being tested in the clinic and Ken, what can you say about the potential role of inflammation and oxidative stress in Parkinson's disease? Ken, are you on mute?

Dr. Ken Marek: 29:03 Yes, sorry. We now understand that many of the sort of general underlying sort of brain problems such as neuroinflammation or just sort of brain stress as it were. Can be relevant to Parkinson's disease. They are likely relevant to other neurodegenerative diseases as well. But there are now a

number of efforts, and some of which are listed here to try to directly test this hypothesis. That is to say if we can reduce the inflammation, which we know occurs in the brain as a result of neurodegeneration, can we, in that way also improve symptoms or slow down symptoms. And that's a really exciting new idea because it opens up many new types of therapies that can be tested. And you know this is a group of therapies that really approach inflammation from a number of different strategies and there are others as well that are in the wings.

So I think this is something that we're going to be hearing a lot more about over the next few months. These particular studies are still in their early phases of development. But I think the concept of neuroinflammation is something that is really taking off. I think similarly, the idea that there is what's called oxidative stress or you know essentially that some of the nerve cells are sort of working over time and as a result of some of the underlying pathologies in Parkinson's disease can cause some of the degeneration, which occurs in Parkinson's disease. This is a concept, which has been around for quite some time, but again a recent scientific data has led us to think about this more carefully. And there are a number of different therapies that are focused on this issue and others that are focused on improving kind of some of the area of the nerve cell called the mitochondria, which can be a sort of ... It's called a powerhouse of the cell and it's maybe responsible for this difficulty with oxidative stress.

So I think these are additional ways in which we can take advantage of the novel scientific information, which has been brought forward. That really directly provide us with therapeutic targets to test and are being tested right now.

Jamie Eberling: 32:06 And before we move on from discussing these ongoing trials. Ken, can you just talk about how long these trials take? How long does phase one versus phase two versus phase three?

Dr. Ken Marek: 32:19 Yeah, this is I think a really important issue in that it takes a long time and a great effort to move these trials through the current development scheme. So I think, it may take several years for getting drugs through their phase one studies to again to test safety through their phase two study where you're really testing the first evidence of efficacy. That process may take four or five years. And then to get us to a phase three study, which probably takes again another three or four years to accomplish.

So it's a major time commitment to get these projects from the scientific idea through the actual drug that can be approved and

available to Parkinson patients. So I think this speaks to the idea that anything we can do to speed this process would be very desirable. Todd already identified one possibility, which is to use drugs, which you know have already made it through phase one and phase two for a different purpose. And that way we can kind of speed the process.

Another important issue is that we want try to encourage individuals who might be willing to participate in clinical trials. To join these clinical trials because enrollment and recruitment is a major delay in the timing of getting these drugs through their clinical trial development. So I think that this is really a challenge for all of us to try to reduce the time it takes to get these drugs through the process.

Jamie Eberling: 34:19 And what about biomarkers? If we had better biomarkers, would that speed up the process?

Dr. Ken Marek: 34:28 Thank you. Yeah. So again, going back to this study that I mentioned earlier, which was the Parkinson Progression Marker Initiative, PPMI. That goal there is to identify again, objective markers that may change or may give us information much more rapidly than waiting for change in a clinical outcome. So, for example, rather than trying to understand whether a drug might slow down a change in a tremor or a change in walking. That may take 12 to 18 months, we might be able to say, let's see if this changes an imaging measure or a biochemical measure, which we can detect in just say two or three months. Obviously that would significantly speed the process. And that is certainly something that we hope to accomplish with that trial.

Jamie Eberling: 35:25 Thanks Ken. So what's coming next? We've talked about some of the therapies that are currently being tested in the clinic, but there are other approaches that are being developed and nearing the clinic. So Todd, can you talk about some of these other approaches and why we think they could work as well?

Dr. Todd Sherer: 35:44 Yeah, so I think, and this is something that was referred to earlier in the discussion. The science around Parkinson's is really growing leaps and bounds very quickly. The knowledge about what might be causing Parkinson's disease, causing the cells in the brain to degenerate as part of the disease. Has really become quite interesting and robust. And new targets are being developed and explored really on a monthly basis. Some of this is coming out of additional studies of genetics. So other genes like, Parkin and PINK1 that had been identified can reference some of the underlying cell biological pathways. The lysosomes autophagy pathway, which has to do with how the cell handles

proteins. Mitochondria, how the cell handles energy. These are all starting to come together in a very important and interesting way in the underlying laboratory science, which is providing a lot more robust basis for developing therapies around these new developments.

And it's brought more biotech companies into the space and more interest from the pharmaceutical industry to develop innovative new approaches. And I think what's most exciting is that there is this diversity of approaches being developed for Parkinson's. We know the disease is varied, so it may not be that one therapy or one biology, biological target will work for everyone. But also we know that this is a very risky field. So having a diverse set of approaches gives us more chances for success. More shots on goal towards the success we want.

And also the technologies are developing quite rapidly. We talked about for example, gene therapy and antisense oligonucleotide. These are really novel ways of developing therapies that don't depend on the historical pharmacological or drug-based therapies. Stem cell therapies are still being explored. Other gene based kind of gene correction therapies are also being explored and it really just expands the opportunities and these are moving quite rapidly towards the clinic.

I think what's important to the points that Ken was just making that as more and more of these novel therapeutics move to the clinic and through the clinic, we still need to come up with more efficient and appropriate ways to vet and test these clinically. So that we could do that at a lower cost and more quickly. And I think that's where a study like PPMI comes to play here. So we can move this whole process forward. But it's quite exciting. I'm quite optimistic about all these new approaches. The new biology, the new investment in Parkinson's. It's a robust area and I think it's something to really be optimistic about.

Jamie Eberling: 38:53 Yeah, I agree with you Todd. I think it's really exciting that there are so many ongoing trials but also so many programs that are nearing the clinic. So more to come for sure. Todd, Can you just mention how people can find trials to participate in?

Dr. Todd Sherer: 39:09 Yeah, so there is the ... As I think you mentioned Jamie in the beginning. We do have a program called Fox Trial Finder, which lists the Parkinson's trials that are going on and, which ones are recruiting and what types of participants they're looking for. There are ways to participate in these types of trials we talked about today, which are testing new therapies, but also studies

like the PPMI that Ken mentioned. That are just looking to understand Parkinson's disease. They're exercise trials, all sorts of different opportunities to participate. So I would suggest and recommend for those that are interested to look at Fox Trial Finder. There's also a study ongoing called Fox Insight, which is an online surveying type of study with a goal of just trying to understand better what it's like to live with Parkinson ...

Dr. Todd Sherer: 40:00

... full of just trying to understand better what it's like to live with Parkinson's, how the symptoms are impacting the disease, and that you can participate in right from your own home without having to go to a clinic. It's not just for Parkinson's patients. It's for people who care for Parkinson's patients, controls people without Parkinson's.

So, these are many, many opportunities to participate. The only way that we learn about these new targets and this new understanding of the disease is from people with Parkinson's. To the point Ken made, the only way we really understand whether any of these treatments are working is through the participation of those with Parkinson's as well.

Jamie Eberling: 40:43

Great. Thank you, Todd. Okay. So, we're going to move on to questions. You can still submit questions if you have one for our panelists, and we will try to get to as many as we can. If we're unable to talk about them on the webinar, hopefully we can get back to you in writing.

So, the first question comes from Dan. Ken, I'll direct this one to you. Are trial options limited after DBS has been performed?

Dr. Ken Marek: 41:19

Great. So thanks, Jamie. Yeah, so DBS, or deep brain stimulation, of course is an important therapy for Parkinson's in these patients. I think that in general, the trials that are available for all people with Parkinson's disease are, to some extent, dependent upon the stage of your illness, the age of the Parkinson's disease.

So after DBS, there are some trials that are still available, but that would need to be focused on those trials that would be viewed as useful as individuals who have also had that therapy. I think that while many of the trials that we have listed in the various slides you've seen already are focused on newly diagnosed or early patients, there are trials that are available for people at all stages of disease.

Jamie Eberling: 42:24

Okay. Speaking of different stages of disease, we talked about alpha-synuclein. That seems to be a very important target and there are a number of clinical programs.

Todd, can you talk about what types of patients are included in those trials, and do we think that those types of therapies could work very early on or is there an ideal patient population for those types of approaches?

Dr. Todd Sherer: 42:53

Yeah, the alpha-synuclein therapies are quite interesting when you think about who they might benefit over time. I think there's an important distinction about who are involved in some of the early testing of the therapies versus the ultimate goal of who you think that the therapies might benefit.

But, Parkinson's is one type of disease of a group of diseases that are all marked by aggregation of alpha-synuclein, so-called, synucleinopathies. Those can include other disease like Multiple System Atrophy. There's a very, very closely related syndrome to Parkinson's called Lewy body disease, which may actually be Parkinson's disease, but it's also marked by synucleinopathies, which again, is aggregation of this nuclein protein.

So, it has not really been determined yet which stage of Parkinson's, or of all the synucleinopathies, which benefits from which of these potential nucleintherapies. Those are all being worked out in testing now. So, some of the studies are looking for people early in the disease. Some of the studies actually are looking for people with multiple system atrophy.

So, there's still a somewhat diverse approach being taken on these therapies related to alpha-synuclein because of its involvement in across the broad spectrum of Parkinson's and related diseases as well.

Jamie Eberling: 44:32

While we're on the topic of alpha-synuclein, The Fox Foundation has invested a lot in developing an alpha-synuclein PET tracer. Ken, can you tell us why we think that would be important for these trials, and also just learning about the disease in general?

Dr. Ken Marek: 44:49

Certainly, yeah. Yeah, it would be wonderful to have an imaging tool that could be used to visualize alpha-synuclein in the brain in individuals with Parkinson's disease and, of course, in individuals who might be at risk for Parkinson's.

So, this type of strategy has been really helpful in trying to really have a window into the underlying cause of the illness in

someone who is sitting in front of you in your clinical office. In this way, you can, again, both understand. You might be someone who is going to develop the disease, but also maybe understand how rapidly it's changing over time, and most importantly, understand whether therapies that would be used, like the therapies we've been talking about for synuclein or any therapy for Parkin disease, might have an effect that you can detect in either the amount of synuclein in the brain or reducing the rate at which it's changing.

This is just as, again, as bringing this to another realm, this is exactly the kind of strategy that has been so helpful in the Alzheimer's disease therapeutic development of amyloid therapies where there is an amyloid tracer. We would expect that when we do have this synuclein tracer that it will also really be sort of a game changer for how rapidly and effectively we can do clinical trials in Parkinson's disease.

Jamie Eberling: 46:38 Okay. We have a question about genetic mutations. How can you find out if you have one? Todd, can you answer that?

Dr. Todd Sherer: 46:48 Yeah. So, there are different ways to find out if you have Parkinson's related genetic mutations. One of the things I would start by saying is that this is still a developing field in terms of understanding the genetic role in Parkinson's. So, we don't have a full understanding of all the genetic involvements in Parkinson's.

There are ways to get this done, if you're interested, by working with your neurologist at the clinic and discuss the pros and cons of sort of doing the genetic testing. There are ways for some of the genetic information about Parkinson's to learn through Fox Insight. If you participate in the genetic sub-study, which has a collaboration with 23andMe and reports some, but not all, of the Parkinson's genetic mutations.

I also think it's important to point out that there is a difference between doing genetic testing, which is what this question was really based on, "Can I find out if I have a particular genetic mutation?" and participating in genetic research in Parkinson's, where you don't have to actually find out the results. You could just submit your sample in and be part of the larger discovery effort.

In a study like PPMI where we are looking to recruit individuals with certain genetic mutations, there's also a mechanism to find out within the confines of those studies whether you have the mutation as well. But, a lot of this should be considered with

your doctor and your family to think through sort of how to go about doing this and learning about the information.

Jamie Eberling: 48:38 Okay, this question comes from Kent, and he wants to know, "Do people with Parkinson's have to change their current medications if they enter a clinical trial? Ken, can you answer that one?

Dr. Ken Marek: 48:51 Well, it would depend a little bit on the clinical trial and on the medication that you're taking. So again, there are clinical trials that have some restrictions with regard to medications, and that might require even a change in medication, but I think there are also many trials that would allow individuals to remain on the medication on the dose that they're taking and the clinical trial drug would be added to that mix.

So again, I think it would be important to, if you're considering clinical trials, look at The Fox Trial Finder to talk with your neurologist about opportunities for clinical trials, and I think that will be, I think, probably more specific information about what would be necessary in your case.

Jamie Eberling: 49:53 Okay. We've heard that no two Parkinson's patients are alike. How does this kind of heterogeneity affect clinical trials? Todd, can you answer that?

Dr. Todd Sherer: 50:05 Yeah. I think that the variability in the disease is one of the main challenges that we have in clinical trials for Parkinson's.

Jamie Eberling: 50:12 Yes, that's clinical trials.

Dr. Todd Sherer: 50:15 Because, due to the variability... Sorry, can you hear me? I think that the [inaudible 00:50:25] is down.

Jamie Eberling: 50:15 Yes.

Dr. Todd Sherer: 50:24 Okay. Because of the variability in the disease, in order to see an effect in a drug, we have to have more higher sample size. So, you need more, a larger number of people, in the trials to control for that variability so that you can really, if there's an effect, determine that effect.

So the fact that we need more individuals in the trials adds time, because we have to recruit all the participants, and then also adds costs, because the more people in the trial, the more expensive it is. I think one of the more important directions of research going forward, and this is a major contribution that the

PPMI study is doing, is to try to get a better understanding and handle on the variability.

We could be a lot more focused on who is brought into a particular trial to control for that variability so we can do the trials with less people. But in general, I think the main outcome of this, so the impact of this, is the need to have more individuals in the trial to control for that variability, and that just adds cost and time to the approach.

Dr. Ken Marek: 51:37 Yeah. I would just mention one other issue, which is that I think as we have come to learn that what we think about Parkinson's disease, has many different faces, that it's quite heterogeneous, that it is also possible that in a large clinical trial that some of the people might be responsive to a particular drug while other people might not be responsive.

If we can't separate those people effectively within a clinical trial, we can't see that. It's sort of in the noise. So, it would really be helpful if we kind of were able to understand better the individuals who were enrolled in a clinical trial so that we would be clear we're we're testing the drug in the best way possible.

Jamie Eberling: 52:30 Ken, do you think it's fair to say that a neuroprotective therapy could be developed before we even know the cause of Parkinson's disease? Is ii important that we know the cause of Parkinson's disease in order to develop these therapies?

Dr. Ken Marek: 52:46 Well, I think certainly we can develop a neuroprotective drug without a full understanding of the cause of Parkinson's disease. Of course, we have some understanding today, but certainly not a full understanding. I think that we should not sort of wait for all of the scientific information to be available before moving ahead to try to develop drugs that might slow or prevent the course of Parkinson's effectively.

In fact, if we could understand, if we could develop such a drug, it would have this huge effect of helping us to understand the science. So, it goes both ways. So, I think we need to move ahead as fast as possible to evaluate the current therapeutic targets to help us to develop these drugs.

Jamie Eberling: 53:44 Thanks, Ken. Todd, are there any therapies being developed for advanced stage Parkinson's patients?

Dr. Todd Sherer:	53:54	Yeah, I think as we mentioned today, we focus predominantly on the disease modifying, or the underlying disease type, of therapies. But in the introduction, we talked about a quite comparable and robust pipeline of therapies that are looking across the spectrum of disease. We actually have had in the last a few years a number of new drug approvals for managing the symptoms of the disease, particularly as the disease progresses, either to better improve our ability to treat the motor symptoms of the disease or some of the non-motor symptoms of the disease that people are also impacted by. So, there is a diversity of approaches being developed across the spectrum of the disease that is trying to target all different stages of the disease, and again, both the motor and non-motor symptoms.
Jamie Eberling:	54:53	So Todd, we've talked about a lot of different types of approaches, and it might be confusing to somebody who's looking to get involved in a trial. How does one choose what trial to participate in?
Dr. Todd Sherer:	55:08	Yeah, I think this is an interesting question. I think there's, as Ken mentioned, first of all, it's important to understand what type of patient the different trials are looking to enroll in the study. So, not every patient would be appropriate for every trial based on either the stage of disease that's being looked at, some of the potential side effects of the experimental therapeutic that's being developed. So, I think that's sort of one criteria to look at and understand and talk to the people at the clinical center. So, I think that's the other thing to consider is that not all studies are at every geographical location. So, to sort of understand what's available near where you would be able to participate. Also, different studies have different requirements in terms of what the expectations are for the participants. So I think ultimately, interacting with the site and understanding what the requirements are, the goals of the study, and matching that to what you are interested in participating in is probably the best approach. Now, certainly some of these studies, as we mentioned, are actively looking for individuals with certain genetic mutations. So, that's something to keep in mind if you either know you

have a mutation or are interested in finding out. That also would be I think of interest to consider.

Jamie Eberling: 56:36 Okay. Ken, again, we talked a lot about alpha-synuclein treatments today. Are there any alpha-synuclein treatments, which may potentially treat both Parkinson's disease, Parkinsonism, and Lewy body dementia? How do all those different diseases, how do they differ?

Dr. Ken Marek: 56:56 Sure, sure. So, the definition of these types of diseases is evolving as we learn more about the science. So, underlying pathology in Parkinson's disease is, of course, the clumping and develop of this protein synuclein, but that is also true in some related problems, like something called diffuse Lewy body disease, or DLB. There is some controversy as to whether those are in fact different from Parkinson's disease or just another variant of Parkinson's disease.

But in fact, it doesn't matter so much in the sense that if one has a diagnosis of that illness. It may well be that synuclein therapies could be of a value and that may similarly be true, or another disorder called, Multiple System Atrophy, or MSA, where we know that there is a synuclein pathology as well.

So, I guess one of the things I would just summarize we're learning is that our definitions are, of course, based on how we see patients in the clinic. But, another definition is to look at the brain pathology. Some of these disorders show a similar brain pathology and therefore, would be likely helped by these same types of drugs. So, synuclein therapies may well be useful beyond typical Parkinson's disease.

Jamie Eberling: 58:30 Thanks, Ken. So, we are nearing the top of the hour. I don't think we really have time for more questions. So, I just want to both Todd Sherer and Ken Marek for their expertise today for participating. We really appreciate it. Thank you, everyone, for joining us today. We'll be sending a link to the webinar so that you can listen on-demand if you missed something or if you want to share it with others.

Also, please mark your calendars for our next webinar, which will be on December 19th. We'll be hosting an Ask Us Anything Hour, so that we'll answer any questions you have. Thanks again and have a great day.