Marie: Hello and welcome to *The Parkinson's Research Podcast: New Discoveries in Neuroscience*. I'm your host, Dr. Marie McNeely, and I've partnered with The Michael J. Fox Foundation for Parkinson's Research to bring you to the forefront of the field of neuroscience to discuss the latest advances and discoveries with leading experts.

The Michael J. Fox Foundation created this podcast for researchers, clinicians, and industry professionals with the hope that these conversations and the resources we share will advance your efforts and partnerships to improve brain health. We're welcoming guests with a range of experiences and viewpoints. The views expressed belong to the guests themselves.

And today we are thrilled to be welcoming our guest, Dr. Charles Adler. Listener's Chuck is Consultant and Professor of Neurology in the Department of Neurology and The Wayne and Kathryn Preisel Professor of Neuroscience Research at the Mayo Clinic Alix School of Medicine at the Mayo Clinic in Arizona. And today we'll be talking more about some of the research projects that Chuck has been working on, as well as his perspectives on the clinical side about Parkinson's disease biomarkers. So, Chuck, welcome to our show today. How are you?

Chuck: I'm doing well. Thanks for having me.

Marie: Well, we are thrilled to have you with us, and we're looking forward to learning more about you and the amazing work that you've been doing. But let's start with introducing listeners to you if they haven't met you yet. So, Chuck, can you tell us about your background and perhaps some of these steps that you took to get to your current position?

Chuck: Well, I always had an interest in science and medicine. I had multiple people in the family that were physicians, so I always had that interest. What got me really interested in neurology and Parkinson's disease in particular was my grandfather had Parkinson's disease.

He passed away when I was 13 years old. So, that had a tremendous influence on what I wanted to do with my life and my career, which was find a cure for that disease. Especially back then, there was levodopa and pretty much nothing else to treat the disease. So, fortunately, we've made major gains since I've taken this interest, but unfortunately, have not gotten to the point of curing the disease.

Marie: Absolutely. And how did you find your way to the Mayo Clinic?

Chuck: So, I started with the MD-PhD at NYU and moved back to Philadelphia where I had grown up to do my training at the University of Pennsylvania, which was really phenomenal. And at the time, the question was — stay on staff there or

move to a warm climate? Mayo Clinic in Arizona had recently opened. They opened in 1987 or so, and I became the 95th doctor to join staff at Mayo Clinic in Arizona and just have loved it and stayed. Never went anywhere else.

Marie: That's wonderful, and you have been quite busy over the years. I know one of the big studies you've been involved in is the Arizona Study of Aging and Neurodegenerative Disorders. You're actually co-principal investigator, along with Thomas Beach. So, Chuck, can you provide an introduction to this study for any listeners out there who might not be familiar with it?

Chuck: Well, back then, Sun Health Research Institute had begun a brain donation program under the leadership of Dr. Joe Rogers. And they were doing autopsies of individuals who were controls, meaning had no neurologic disease that they were aware of, as well as those with Alzheimer's disease and dementia. And in 1997, Tom Beach came to the Institute as the neuropathologist. And I joined the research team as the neurologist with the idea that we wanted to do exams on all the people who had signed up to donate their brains.

The reason is that at that time, and even now, most brain and body donation programs do not do neurologic exams on the people who are donating their organs. So, many people have movement disorders that have not been diagnosed. You wouldn't see in the chart that they had movement disorders. You might not see what their cognitive status was in the chart.

We began doing movement exams, neurologic exams, and cognitive testing once a year on everybody who had signed up. And then in 2005, with the help of The Fox Foundation and the grant that we received from them, we went to whole body donation with the idea that Parkinson's disease, and some of the other neurodegenerative diseases, may not be just brain only, but they may be systemic diseases. And having organs from people with Parkinson's, people with Alzheimer's disease, as well as controls could potentially lead to very important findings.

Marie: Certainly. And I know this study has been going on for quite a number of years. So, Chuck, what have been some of the key milestones or achievements of this particular study?

Chuck: We have been together — it's over 27 years. So, milestone number one is the number of brains and whole bodies we have autopsied with detailed neurologic clinical information. It's over 2000 at this point. So, one of the biggest milestones or main goals of this study has been to provide tissue to scientists around the world with really detailed clinical information to be sure that people have the diseases that we say that they have.

The reason that I say it that way is that we have looked at diagnostic accuracy of a clinical diagnosis of Parkinson's disease. And we are very clear that even though we in the clinic can be very good at making the diagnosis. Early on, the diagnostic accuracy may be as low as 70%. If you follow somebody from the first visit to the time of autopsy. And then for somebody who has had Parkinson's disease for 5-10 years, let's say, responds really well to carbidopa-levodopa or other Parkinsonian medications, we still are incorrect about 8 - 10% of the time. People have other neurodegenerative disorders or other pathology that is underlying their Parkinsonian systems. And should we keep calling them Parkinson's disease or not is unclear because they certainly look like, and act like, and respond like Parkinson's patients.

But one of the milestones, I think, of our program is showing that they don't have Parkinson's disease, at least by current criteria. So, I would say that's one of the major things that we've found. The other major thing is the topic we're going to talk about afterwards, which is biomarkers. So since 2005, as I mentioned, we have been doing whole body autopsies. And from that, we can determine that we can find alpha-synuclein in tissues other than the brain. We have helped pioneer work in submandibular gland biopsies, looking at alpha-synuclein, CSF, looking at alpha-synuclein in skin. So, we feel very fortunate to have been at the forefront of that due to the donations that people have made of their bodies and brains.

Marie: Absolutely. Well, I think this study has made amazing progress so far. And like you hinted at, you know, some of these major milestones are really giving us information to move the field forward. But what does the future look like for this study?

Chuck: So, the future is bright. As mentors of mine told me early on in my career, when it was slow going, when it came to writing papers and having data, this is the gift that keeps on giving. So, when we tell our patients that or our subjects that, we truly believe that the cure for Parkinson's disease is going to come from Maricopa County, Arizona. Because in order to find a cure, you're going to have that scientist that use tissue to detect biomarkers, to detect changes, to detect ways of stopping progression of the disease. And this tissue will keep on giving in that regard. The expectation is this program is going to continue as long as it remains funded and there are scientists and clinicians willing to continue working on the project, which I don't see a reason why that's not going to happen.

Marie: Well, I think this Arizona study of aging and nerve generative disorders is a really important and exciting study to be working on. But you've also been leading efforts at the Mayo Clinic there in Arizona in participation in the Parkinson's Progression Markers Initiative and the development of PD biomarkers. So, this is a really important area of research as well. So, perhaps can you give us an

overview first of the role that your site there at the Mayo Clinic has played in this large-scale PPMI study?

Chuck: Sure. So we're one of the clinical sites. Here in Arizona, we actually have three clinical sites for PPMI: Mayo Clinic, Banner Sun Health Research Institute, Barrow Neurologic Institute. One of the beauties of Arizona Study of Aging and Neurodegenerative Disorders is that we are a collaborative program of those three sites. And I think it's rare in a city to see all three major Parkinson's centers be collaborating. And we collaborate on many aspects of things.

So, PPMI is just one of those. The project at Mayo Clinic has been going for a number of years now. We have collected data, including DAT scans, and CSF, and blood, and do the periodic exams as one of the major clinical centers and have been really, really excited about what has come out of PPMI to date and what will be coming out of PPMI in the future. I would just add that in addition to PPMI from a biomarker standpoint, The Michael J. Fox Foundation funded the S4 study, which was a biomarker study that we helped lead. It was done at a few sites around the country and we did submandibular gland biopsies, colon biopsies, skin biopsies, collected CSF, collected blood. And data from that study has really helped inform the field in terms of where alpha-synuclein is located in multiple tissues. It was a small study and certainly PPMI builds on that study tremendously.

Marie: Absolutely. And I think these findings in the submandibular gland biopsies were particularly interesting. Can you maybe go over what the key findings were?

Chuck: Sure. So, when we started doing the whole body autopsies, Tom Beech had chosen a number of different peripheral tissues to look for alpha-synuclein staining (phosphorylated alpha-synuclein). Looked throughout the GI tract, looked at skin, and submandibular gland was one of the areas of the body that had the highest density of alpha-synuclein staining of any tissue that he looked at. Because of that and because of its location where one could do peripheral biopsies in living humans, this was the most translational research project that we have done, which is we started doing biopsies in submandibular gland in patients with advanced Parkinson's disease and then moved to patients with early Parkinson's disease.

And we were able to show that most of the patients had evidence of synuclein staining in the submandibular gland. So, we had a high positivity rate. We thought it was a tremendously valuable diagnostic test for research purposes. What we were happy to see is that other tissues such as skin, and CSF, and maybe blood may also have as high positivity because those are a little bit easier to gain tissue from than submandibular gland. We need an ENT doc to be able to do the biopsies in submandibular gland.

Our research, however, has continued to do submandibular biopsies because one of the things that we believe is really critical is, is there a way to use any of these different tissues to follow the progression of disease? So, does synuclein aggregation increase over time in any of these tissues? So that we could: A, watch progression (because we don't have that ability at this time), and B, if there is a treatment that's stopped or slowed alpha-synuclein aggregation, could one of these tissues be used to monitor the progression of disease and show that that treatment actually stopped or slowed aggregation of synuclein? So, we've continued, I think we're the only group still continuing to do submandibular gland biopsies. And the hope is that, again, skin, or blood, or CSF will be fruitful. But if it's not, and if submandibular gland is fruitful, then we won't have lost any time.

Marie: That makes sense. And I think being a part of these large-scale research initiatives is really exciting and perhaps really rewarding because they have this collaborative element and you're able to work with people, not only just across the US, but around the world as well. So, can you comment on what it's been like for you and your team to be part of studies like PPMI?

Chuck: It's been tremendously satisfying. I think that the overall way one looks at how to do research has changed during the course of my career. So, certainly early in my career and in most people's career back in the ‘80s and ‘90s, everybody was pretty much siloed off. You wanted to do your own research. You wanted to protect your data. You wanted to protect your samples. You wanted to gain notoriety, gain the ability to publish your data.

And a lot of that had to do with how funding was generated. So, if it wasn't your data, you weren't necessarily going to get funded. But if it was your data, the chances of getting funded certainly increased. That has completely changed, certainly in the Parkinson's disease area. Because what we've seen between the Parkinson's study group and The Michael J. Foss Foundation, even at NIH, is doing these collaborative studies. So, the whole or sum is much, much greater than the parts. There's no question.

We can't collect samples at Sun Health Research Institute in AZSAN to the numbers that we can collect if we do it as a joint program. We, early on, calculated to get enough samples to make a dent in some of these types of research. We'd need 10,000 subjects in our study. The only way to gain that sort of number is to do collaborative work. And PPMI has certainly shown that we can do that internationally. And I'm at a loss right now to tell you exactly how many individuals have been enrolled in PPMI, but it's in the thousands. And that means the number of samples are in the ten thousands, and that's the only way we're going to make headway. And I am tremendously excited and pleased that

collaboration is really the way to go rather than separating yourself out and doing your own research.

Marie: Well, I definitely agree with you. And I know, Chuck, you split your time between these important research endeavors as well as time in the clinic. And I'd love to talk a little bit more about the clinical side of biomarkers and maybe the application of some of the work that's been done in this area. So, I know biomarkers have just, in general, been a hot topic in the Parkinson's disease field. And as researchers are identifying and developing these biomarkers, it's important to keep in mind how they could potentially be used in clinical settings. So, what do you see as some of the most important considerations regarding the clinical utility of these potential biomarkers?

Chuck: So, I think there are a tremendous number of considerations that the field needs to think about when it comes to these various different biomarkers. One of them is ethics. And ethics comes in because at this point in time, we do not have any treatment that will slow or stop the progression of PD or cure PD. So, having a clinical biomarker to identify somebody who is at risk for the disease has many ethical implications. In terms of that same or a similar biomarker to confirm that somebody has a disease, at this point in time, we still need more data.

And the reason I say that is the majority of the biomarker studies that have been done to date have utilized a clinical diagnosis of Parkinson's disease as the gold standard, as opposed to an autopsy or neuropathologically-confirmed diagnosis of Parkinson's disease. And we certainly are concerned about that in the sense that we have seen, as mentioned earlier, that not everybody that looks or acts like they have Parkinson's disease — acting, meaning responding to medication — actually has Parkinson's disease. So, the biomarkers, if we only use a clinical diagnosis, are going to be inaccurate.

And I think we still need to continue the research to the point of individuals coming to autopsy to prove that the biomarker is absolute. So that's a long-winded answer for you, but I have plenty more I can add to that.

Marie: Yeah. And I think a lot of that's centered around these ethical questions. And I think there are maybe other domains or other areas that you have to think about in terms of these considerations. And one is just the clinical reality or logistics. So, can you comment on that area as well?

Chuck: I think we're fortunate here in the United States to have a number of different tests currently available, currently marketed. Many places in the world don't have the ability to do that. But currently there is CSF testing for alpha-synuclein, there is skin testing for alpha-synuclein, and there are imaging tests, such as the DAT scan. So, we have biomarkers that may be able to help us clinically in

determining whether somebody has Parkinson's disease. But I would say they are helpful in diagnosing Parkinsonism.

The issue for me has been, how does using the biomarker actually affect how you're going to treat an individual patient? So, while some clinicians are using all of those biomarkers for any patient that comes in looking like they have Parkinson's disease to help “confirm” the diagnosis, I find that since there is no difference in the medications that we can offer people at this point, I'm not using most of these biomarkers for diagnostic purposes. I use them in abundance when it comes to my research, but have not been using them very much when it comes to clinical use.

Marie: Definitely. And I think that covers, of course, the ethics, some of the clinical realities. And I think another thing, just when we think about the clinical care environment compared to a research environment, is starting to think about the policy, the reimbursement, the insurance. Can you comment on how you see that working out in the future, or what it's like right now when you have these potential tests you could offer people?

Chuck: I know most of them have been covered to date by most insurance companies, including Medicare. But to be honest, I'm not an expert when it comes to reimbursement for the tests that I've just mentioned. But I believe most of them have been covered. Again, to me, the question is, what is the utility? Somebody has bradykinesia. They have a rest tremor.

They have rigidity. They have signs of Parkinsonism. I'm not 100% sure what the utility is of doing some of these clinical biomarkers to make a diagnosis when, for any reason, a patient looks like that, we're going to go ahead and utilize treatments such as carbidopa-levodopa, or a dopamine agonist, or some form of therapy that we use for Parkinson's disease.

So, for me personally, I've had trouble believing that we should be doing these tests, spending money on the tests when it doesn't necessarily change my clinical care. For sure, if somebody has tremor alone, so all I see is a rest tremor or action tremor and rest tremor, and I don't see anything else. And I'm not sure whether I want to go treat the patient with medications used for essential tremor versus medications used for Parkinson's disease. In that case, it may be worthwhile to use one of the biomarkers. It may also be worthwhile on some of our Parkinsonism patients who have not tolerated medication very well. So, they develop severe nausea, or vomiting, or whatever the side effect may be that limits my ability to raise the dose or treat them. Using the biomarkers to help say, hey, listen, this is the right treatment. We really need to get you to tolerate this. That's another clinical use of these biomarkers.

Marie: Definitely. And I know you touched on this earlier, Chuck, but the source of the biomarkers is important. And I know there's a lot of research being done in this area, but I'm not sure what the status is in terms of actually incorporating some of these different matrices, if you will, into clinical use. So, can you comment on what the mix of the matrix use is, whether it's biofluids, tissue biopsy, imaging, genetics, etc., actually in clinical use today?

Chuck: If we start with genetics, certainly younger individuals who come in with Parkinsonism, there are genes that can be identified that could tell us that that's the disease they have. Certainly people who come into the clinic and have strong family histories for Parkinson's disease or Parkinsonism, genetic counseling and genetic testing is a very reasonable avenue to pursue. Again, there are a number of different genes that have either been proven to lead to Parkinson's or are at-risk genes. And so, genetic testing is certainly something that is worthwhile doing in some of our patients.

Imaging was the next thing to come along. DAT scan has been something that has been around for a number of years and is very effective at determining whether somebody has a decrease in dopamine neurons, which is a non-specific finding in individuals. So, there are many reasons why somebody can have a loss of dopamine neurons. But I think it's something that is valuable in terms of some of the clinical comments that I made earlier. So, it's sensitive, but not necessarily specific.

In terms of tissue biopsies, skin biopsies, as I mentioned, is now clinically available. There is data to show that that is also very sensitive in Parkinson's disease. It's also been shown to be sensitive in some patients who are at risk for Parkinson's disease, such as REM sleep behavior disorder patients who do not have any signs at the time of dementia or Parkinsonism. Again, that's where ethics may come in, in terms of we don't have anything to slow or stop the progression of people with RBD from developing dementia or motor impairments of Parkinsonism. But I would say skin is certainly something that has proven, at this point, to be useful. And then from a biofluid standpoint, CSF would be the one that has been shown pretty well at this point in time to identify individuals who are both at risk for Parkinson's disease, as well as those who have Parkinson's disease.

Again, sensitivity is really high. I think specificity for some of these biomarkers still needs to be looked at with some of other Parkinsonian disorders and making sure, for those of us who do autopsy studies, one of the big things is co-pathologies. So, that's something that is being talked about more and more in our field is the fact that people with Parkinson's disease, people with Alzheimer's disease, people with other neurodegenerative diseases — when you autopsy the brain, there's a tremendous amount of overlap or findings of other pathologies.

So, how these biomarkers work in people with co-pathologies is going to be really critical.

Marie: Absolutely. And I think being able to differentiate whether it is a particular disease, the other disease, or a combination of the diseases is something that's still kind of a sticking point or a difficult thing to do in the field.

Chuck: It's tremendously difficult and may also be really, really critical for research into causes. So, why do certain people have both Alzheimer's disease pathology and Parkinson's disease pathology? Or we've seen a number of people that have PSP pathology in the same brain as somebody with PD and/or AD.

So, pathophysiology of those diseases is important. And then that leads to what are we going to do when it comes to neuroprotective treatment trials or trials to try to slow or stop the disease? If we are able to determine with these clinical biomarkers that somebody has synuclein pathology and maybe Alzheimer's disease tau pathology or amyloid pathology, is that group of patients going to respond differently than somebody who only has synuclein, or only has tau, or only has amyloid? And I think that what's going to happen in the near future is combining all of these current biomarkers, tissue, biofluids, and imaging to try to get as clean a population of patients that have these various pathologies as possible for both neuroprotective trials as well as for symptomatic trials. So, somebody with Parkinson's disease who has dementia — will they respond the same to medication as somebody who has Parkinson's disease with dementia, but also has Alzheimer's disease pathology?

That's something we can see — probably about half the brains that come to autopsy in our program that have PD with dementia also meet neuropath criteria for AD. So, are those patients different during life? We haven't found much differences when it comes to their neuropsych testing and their motor testing. There may be some differences in rate of progression of those patients, but not necessarily in the actual symptoms. So, I think all of these biomarkers are going to be really, really critical when it comes to trying to identify the right patients for the right protocols.

Marie: That makes sense. I think these are really important questions that you've raised and you walked us through just some examples of when it might be appropriate to use particular biomarker tests clinically. And I guess for you personally, you sort of hinted that there might not be as much value at the moment of incorporating some of these biomarker tests clinically, particularly for diagnostic purposes. But what does it look like in your clinic in terms of biomarker use, and what would it take maybe to use them more often, or what would be most valuable in terms of these biomarker tests for you?

Chuck: I tell you, I'm in the minority at this point, as best I can tell, because the majority of patients that come to our clinic. At Mayo Clinic in Arizona, we're a tertiary care center. So, most patients come either as referrals or have seen their primary care provider or a neurologist in the community and want another opinion. They want to come for research purposes. They want to come to see a Parkinson's disease specialist.

I would say the majority of them, at this point, have had DAT scams. And we're seeing more and more people come in with skin biopsies and some with spinal taps and CSF synuclein testing. So, even if I'm not the one who is ordering the test, many of these individuals have already had the test when they come in to see me.

What would it take for me to want to use these more frequently would be the issue of being 100% sure they are diagnostic and that the specificity were 100%, rather than specificity not being 100%. And I really think it needs to change my clinical care of the patient. Until somebody can prove that clinical care changes — I have heard from some colleagues around the country that they feel that patients have the right to know. They have the right to know if their skin biopsy is positive, or their CSF test is positive, or their DAT scan is positive. But that right to know doesn't necessarily change how we treat the patient. And that's what I find is the most crucial issue. How is it going to change how I treat my patient?

For sure, if we had a medication to slow or stop the progression of disease, that is going to be critical in terms of using biomarkers to determine who should be on that medication. I'm not sure how else to better answer that question because again, I feel like I'm in the minority at this point when it comes to using the biomarkers clinically, even though I'm one of the ones who helped develop them.

Marie: Well, I think these minority perspectives are important because they shed some light on different areas of the field or different ways of thinking about these sorts of things that other people may not have considered. So, when you think about this idea of clinical care needing to be changed by having this information from a biomarker, let's say we get to that point. At that point, what would you then see as some of the biggest barriers to you actually implementing those biomarkers into the clinical setting?

Chuck: So, I think if we're at that point, there's almost no clinical barriers. It depends on which tissue it is. So, at least here in the United States, again, we have skin, we have CSF. Skin biopsy is by far the easiest thing to do and probably has the least side effects in the overall scheme of things. Spinal taps, while patients may not like spinal taps, spinal taps are also fairly easy to do, have minimal side effects, so it’s just a matter of having a place where that can be done.

When it comes to submandibular gland, if that was the one that needed to be done, that's much more difficult in that you need an ear, nose, and throat surgeon to be able to do those biopsies. And there's a bit more side effects in the sense that there is some bleeding and some swelling that can occur in those sites.

And then there's blood. And I think all of us would say that if we had a blood test, if the blood test was shown to be not only sensitive, but specific, that's by far going to be the best way to do it. I don't think there's anything that would limit us, other than potentially insurance costs or out of pocket costs to patients. But if I had a blood test to do, and it was going to change my clinical care, there's no question that a blood test would be done. I would say that these biomarkers, as much as I'm talking about not using them in my clinic, the biomarkers are going to revolutionize various different clinical trials, because there is no reason not to consider using these biomarkers when entering patients into studies. And that's been clear with PPMI and other studies that we're doing is that we are using these biomarkers to decide who gets entered into studies. So, that to me is tremendously clear.

Marie: Definitely. And looking at the biomarkers that are in these various stages of development right now today, Chuck, what do you think are the most promising, whether it's from this research perspective or the clinical perspective?

Chuck: I think blood is very promising. I think that it's a matter of time until all the kinks are worked out and the reproducibility is there to be able to utilize that. CSF seems to be extremely good. Again, it’s being done by multiple different labs. We know that the data is not always reproducible, and that's something that we need to be careful of. We need to make sure that the methods used are very reproducible. And then you have skin. So, I think all three of those are strong potentials to be continued. I don't see a reason that any of them are not going to be continued for the near future.

So, in these various different tissues, the goal is to identify abnormal alpha-synuclein. And that can either be via biopsying the skin and submandibular gland, and staining the tissue and looking for phosphorylated alpha-synuclein, or various different abnormal aggregations of this synuclein. And in the various tissues, such as CSF, blood, skin, submandibular gland, we're also doing seeding amplification assays in which we are looking for amplification of alpha-synuclein signal to say that that is abnormal, and that there’s an abnormal abundance or abnormal type of synuclein in that tissue. And then the goal would be: A) identifying it, and, B) finding one of those methods to be able to determine that there is a change over time, so that that would monitor the progression of the disease.

If blood becomes the test of choice, I think the others will potentially go by the wayside, because why would we do skin or CSF testing if we could do a blood test? I'll go back to what I said early on though. That's as a diagnostic biomarker. I think that we still don't have a progression biomarker, and many of us are working on that. So, I think it's still going to be really important to try to determine which one of these tissues, either using staining as is currently being done in skin, as well as the seeding amplification assays, which are done in skin, CSF, blood, submandibular gland — can we make those quantitative enough to be able to determine a difference over time?

And if we can do that, that's going to also change the game. So, if blood is great as a diagnostic marker, but CSF is a better progression marker, you're going to have various different uses of these different biomarkers.

Marie: Very interesting. And are there any other biomarkers, Chuck, that you'd like to mention that you think are particularly promising?

Chuck: So, in addition to the biomarkers which we've talked about extensively, the one I haven't mentioned to date would be alpha-synuclein neuroimaging. So, much like we have in Alzheimer's disease where we can do imaging of amyloid, I think the gold standard for Parkinson's disease would be alpha-synuclein imaging. So, if we had a ligand that we could inject into patients that would bind up to synuclein: A) in the brain, and B) it would be great if we're in other tissues as well.

But if we could image abnormal alpha-synuclein in the brain, then we would have a non-invasive way of diagnosing and potentially monitoring progression of disease and even potentially monitoring response to treatment. Whether that would completely rule out the use of CSF, or blood, or skin is very much unclear. But there are a number of groups that have been working on trying to get an alpha-synuclein neuroimaging test up and running. And I think that will be a complete game changer if that's successful — or I should say, when that's successful.

Marie: Well, Chuck, I think there are a lot of really exciting areas of research in this biomarkers field, but thinking about what we've accomplished so far, what do you see as some of the tools, resources, or collaborations that have really helped make a big impact?

Chuck: The tools, resources, and collaborations that are moving us forward are multiple. First of all, tools. While seeding amplification assays did not become available or had not been worked out for alpha-synuclein until about eight years ago, that is the tool. And so predicting what's going to be a tool five years from now or 10 years from now is somewhat hard to do because I don't think anybody predicted seeding amplification assays being a tool back 15 years ago. Resources: we

need funding. There's way more funding for research in Alzheimer's disease and dementias than there are in Parkinson's disease and related disorders. So, resources are really critical.

And I think that we see tremendous value in The Michael J. Fox Foundation. They have been tremendously supportive. Again, they have funded PPMI and multiple other studies like S4. I think they've done a great job in bringing industry to the table. So, industry has a tremendous interest in finding a cure and neuroprotective treatments. Obviously, there's financial gain for them, but there's also funding they provide to scientists and clinician-scientists around the world in terms of trying to get to that point. So, partnering with industry is really critical.

The NIH and other governmental sources are tremendously critical to be able to fund the basic science that is needed to get to these points. We have funding from the state of Arizona. The Arizona Biomedical Research Commission has funded us for over 20 years. Their funding has been utilized for our brain and body donation program. That's our program, and other brain banks around the country have a tremendously difficult time getting funding because who wants to fund the resource as opposed to the science that utilizes the resource? So, that becomes really critical.

I know that there are other funding agencies internationally. There's a group in Europe that we have been asked to provide tissue for that was recently submitting grant applications to a European Association. So, I think it's really critical that funds be made available for both the procurement of tissue as well as the utilization of the tissue.

Marie: And I know Chuck, you've been heavily involved in collaborative research. So, can you comment, perhaps, on the role of collaboration that you see going forward?

Chuck: As we discussed earlier, I think the sum is much greater than the parts. And it's going to be critical for the Parkinson's community to continue to do these various different collaborative efforts. Again, there are multiple different longitudinal studies going on, other than PPMI. PPMI is one of the largest. There are European programs going on. There are other programs in the U.S. And finding ways to continue to get collaborations together, support collaborations, and to continue having the various different labs that value collaborations is going to be critical to finding better treatments for our patients.

Marie: That makes sense. And I definitely agree with you. And we touched on some really exciting areas of research in the Parkinson's field. I think many unanswered questions remain. So, for you, Chuck, what are you most excited

about? What are these future directions or areas of opportunity that you see as the most promising?

Chuck: So, I think the most promising has been the ability to identify individuals who are at risk for developing Parkinson's disease and other neurodegenerative disorders. Individuals who have clinically REM sleep behavior disorder, we've been working with a number of different colleagues around the country looking at the sense of smell — that's been done for the last 25 years, both here in the United States, as well as internationally.

So, taking individuals, we know people with Parkinson's disease lose their sense of smell. So, starting with loss of sense of smell, and then working forward to find other biomarkers that can help identify people at greater risk. Once we have that population that's at greater risk, we need better treatments to try to slow or stop progression to those diseases. I think that there are multiple different treatments that can be tried in this hyper-focused group of individuals. And I know that industry, NIH, Fox, as well as other groups are looking at ways to enroll patients in those studies.

What the biomarkers may help with is the fact that many people who are at risk for Parkinson's disease don't develop Parkinson's disease quickly, which is a great thing for them. But when it comes to trying to identify treatments to slow the disease, the slower individuals progress, the larger one’s pool of patients needs to be, and the longer you need to follow them. So, if any of these biomarkers that we talked about were able to identify patients at greater risk for the disease, we might be able to shorten the time that it takes to study drug X or treatment X and decrease the number of patients that need to be put in the study. So, I think that is, to me, the most important and most critical unanswered questions. We have pretty good treatments right now for symptoms, but we really need something to slow or stop the progression.

Marie: Certainly. And Chuck, it's been great to hear your thoughts and just to wrap up our conversation here. Can you summarize how the work that you're doing is bringing us closer to those big picture goals of finding a cure for Parkinson's and contributing to improved therapies for people who have Parkinson's today?

Chuck: So, I think the key to our work — Tom Beach, and I, and the rest of our group — is to continue collecting clinical data and the tissue needed for scientists around the world to access Parkinson's disease as well as control tissue and try to determine the changes and the differences. I think that my role and our role as sites in these various different studies is critical.

But again, to find a cure, I think we need to understand the disease better, to understand the disease better, we need tissue. And so I think the greatest

contribution I and my colleagues can have is to provide that tissue. And as I mentioned earlier, I think the cure for Parkinson's disease can come from patients from Maricopa County, Arizona, and they take pride in hearing that. And they are willing to step up to make the ultimate gift, which is they give the gift of their bodies to science with nothing expected in return for them as individuals. And there can be no greater gift in my mind. And hopefully my work and our work will lead to that cure.

Marie: Well, Chuck, I love it. And I really appreciate the work that you, your colleagues, and your patients and participants have been doing to move the field forward. It's been a pleasure to have you on the show today. Thank you so much for your time.

Chuck: Thank you very much for having me. It was a real pleasure and hopefully scientists, researchers, clinicians who listen to this will be encouraged to continue moving this field forward.

Marie: Well, Chuck, once again, it's been a pleasure to have you on the show. And listeners, it's been great to have you here with us as well. If you want to know how The Michael J. Fox Foundation can help your research, please visit michaeljfox.org/researchresources. And you can find new episodes of this show each month on the MJFF website or on your favorite podcast platform. When you have a moment, please subscribe to our show to make sure you don't miss our outstanding lineup of upcoming episodes. We look forward to connecting with you again in our next episode of *The Parkinson's Research Podcast*.