Dave Iverson: 00:01 This is Dave Iverson. Keeping everything that's happening in the world of Parkinson's disease research can be challenging. The good news is, that means there's a lot going on. But it can also be a bit head-spinning to synthesize all the new developments. Recently I sat down with Mark Frasier, vice president of Research Programs at The Michael J. Fox Foundation to get some help in putting the Parkinson's picture together.

Well, Mark Frasier, it's a pleasure to be able to talk to you about the progress in Parkinson's disease. Thanks for doing this.

Mark Frasier: 00:31 Yeah. Thanks for having me, Dave. It'll be fun.

Dave Iverson: 00:36 I remember a presentation that you and, I believe, your colleague Brian Fiske did, oh, probably as much as a year ago for The Michael J. Fox's Patient Council. One of you described the challenge of Parkinson's disease research as essentially being like figuring out one of these 10,000-piece or 10 million-piece in this case, I suppose, puzzles. Only you didn't have the advantage that you normally have when you're putting together one of those gigantic puzzles, because you didn't have a picture on the box to tell you what it was going to eventually look like, nor did you have corner pieces or straight-edge pieces to at least give you a place to start.

I thought that was a great way to envision what our challenge is, but it also seems, at least in the last year or so, particularly perhaps even more recently than that, that we're beginning to sort of fit more of the puzzle pieces together. Do you share that sense, Mark? If so, what are the pieces, I guess, that we're beginning to understand?

Mark Frasier: 01:39 Yes. I think that's absolutely right, and I share that view. Figuring out Parkinson's, like any disease, is like doing a puzzle without knowing the picture. I think in the last year or 18 months there has been a lot of progress. I would say that a lot of the corner pieces are some of the genetic data that has been discovered in the last decade and some of the environmental risks that we've known about for quite some time. But now we're starting to put those pieces together and fill in the blanks a little bit and see how these different genetic discoveries may be linked to each other and how some environmental causes actually may be linked to some genetic contributions.

So, we're starting to fill in the blanks a little bit and really understand the disease not just from a clinical perspective, for example, someone having slowness or stiffness or tremor, but also at the molecular level. What's happening to cause the
disease and what's contributing to the progression of the disease. There's still a lot of work to be done, but we've started connecting some of those dots.

Dave Iverson: 02:59

When we talk about, then, the corner pieces, that, let's say, genetics in particular helps us understand, on the one hand, we've always thought of genetics ... Well, we used to think that it didn't play any role in Parkinson's. We've learned, of course, in the last 15 years or so that that's not the case, that it does play a role, but only a role. So, what is it about genetics that helps you begin to discern what's going on? Is it because genetics gives you a specific target, a specific piece that you can actually look at more clearly, and that in turn unveils some of what's going on at that molecular level you're describing?

Mark Frasier: 03:42

I think of genetics as shining a spotlight on primary actors in the disease. So, what the genetic discoveries have done in Parkinson's disease have really highlighted a major actor that contributes to the development of Parkinson's disease. For example, alpha-synuclein is a gene that was identified in the mid-90s, and that really shined a spotlight on the gene. As we started learning about alpha-synuclein, we realized that alpha-synuclein actually accumulates in the brains of people with Parkinson's disease.

So, with this spotlight, it uncovers new things about the disease and our understanding of the disease and increases our understanding of the disease; but, then, what's really exciting, as you indicated, it provides an actual target that drug developers can go after to treat the disease. There are a number of clinical trials underway now testing alpha-synuclein targeted therapies that are determining whether you can modulate alpha-synuclein and actually slow the progression of the disease.

Dave Iverson: 04:58

The interesting part about that also is that, even though that genetic mutation that in a very, very small percentage of people in the alpha-synuclein gene causes Parkinson's disease, as you say, we've now learned that that clumping of alpha-synuclein is a common denominator across everyone with Parkinson's, regardless of whether they have that gene mutation.

So, is the thought then, Mark, that some of these gene mutations, even though they may be rare, can tell us something about what goes amiss? Is it that these gene mutations point to ... For example, one of the problems I often hear about is that there's something that goes wrong with our ability, when you have Parkinson's disease, to dispose of certain cells, to get rid of
the garbage that's going on at the cellular level. Is that what those gene mutations are helping us discover? How those mechanisms work?

**Mark Frasier: 06:02**

That's right. They're clues to show researchers and help us understand what actually goes wrong at the cellular level. We identify a certain gene first through large genetic studies and analyzing thousands and hundreds of thousands of different people, their DNA. Then, by uncovering these different mutations, it shows us what goes wrong in the cell. There are mutations that are associated with the garbage disposal mechanism of the cell. These have been implicated in Parkinson's disease. I mentioned alpha-synuclein, and we now understand that alpha-synuclein accumulates in everyone with Parkinson's disease. So, it really highlights what at the molecular level and what at the cellular level is going on.

One of the things that I think is really exciting in genetics research is that there are genes that have been discovered that may be very rare, as you indicated, but confer a large risk for developing Parkinson's disease. We've talked about some of these in the past: alpha-synuclein, \textit{LRRK2}, \textit{parkin}, \textit{PINK1}. Now where the genetic research is going is, now that we've found all of these genes that confer a large risk, but are relatively rare, we're now studying hundreds of thousands of genes that may confer a small risk and occur pretty common in the population; but, when you combine these different genes together, you may develop Parkinson's disease.

So, the research is at a point where we're looking at many, many cases, many, many individuals and trying to put these puzzle pieces together, where you may have multiple different genetic risks that are very common that are contributing to developing Parkinson's disease.

**Dave Iverson: 08:03**

When you say "small risk, but common," that means we might find this mutation in a lot of people, and it might only contribute a little bit toward your risk of Parkinson's. But if you start putting more of those together ... if you have, for example, several of those, plus, as you were mentioning before, you add in a known environmental risk, let's say, like pesticide exposure ... you start adding that up, and you're getting closer to the whole? Is that a way to think of it?

**Mark Frasier: 08:36**

That's right, and the puzzle is becoming more complete. Our understanding of the disease is becoming more holistic.
What, then, do we still need to know? If we’re getting closer to our understandings of these pathways ... as you look at this, Mark, as you and your research colleagues look at this ... what's the next horizon that we need to have become more clear to fill in the next pieces?

Well, I would say a couple of things. One is we need more data. I said we've been studying thousands of people. We need hundreds of thousands of people contributing their information, and data, and DNA to really understand these different connections, these genetic connections that may contribute to Parkinson's disease. We also need better measurements of the disease. You and I have talked about this in the past, but one of the main challenges in Parkinson's disease is, really, measuring its change over time. Having more objective measurements, things like sensors, or brain imaging, or a blood test, that actually track the course of the disease more objectively is going to be key to making new advances in Parkinson's disease. Lastly, I would say we need a lot of researchers, not just people focused on Parkinson's disease, but computational researchers, big data researchers, analyzing all of this data and developing new tools to analyze this data. That's going to be really key in making new breakthroughs.

In a way, we need a really big team, both on the patient side and on the researcher side. Is part of the reason for that, Mark ... I think this is also a really fundamental, newer understanding ... is that Parkinson's disease is really not a disease, a singular phenomenon? There is such variation. It's an old joke that we talk about in Parkinson's, that if you meet one person with Parkinson's, you've met one person with Parkinson's, because everyone's experience is so different. Is that also why we need so much data, because it is so varied?

It is so variable, and that's exactly right. We need lots and lots of data to really dissect this-

We need lots and lots of data to really dissect this variability and break it down into several different diseases. The exciting news right now is that, actually, there are trials underway that are targeting certain forms of Parkinson's disease.

You may have heard about the GBA gene. There is a trial targeting individuals that have the GBA gene with the expectation that they may respond to this treatment more effectively than people without the gene.
And so targeting the treatments based on a particular genetic status or a particular symptom is really important. And that's where the field of precision medicine is moving to be more targeted with medicines.

Dave Iverson: 11:49

And in that way, are we beginning, then, to have a sense that this great variation, that you have one person with Parkinson's who has a tremor, but someone else might not have a tremor, they have a problem with rigidity. Someone else might have a problem with balance and gait. Someone else might be more inclined to have cognitive difficulties, and so on.

Are we beginning to, then, get at the point, Mark, where you can you discern those differences, not just at the clinical level, at the observational level, by seeing someone in action, are you beginning to be at the point where you can understand those differences at the biological or molecular level? In other words, are we getting to the point where biology can predict symptomology, if that's even a word?

Mark Frasier: 12:38

Yeah. No, that's exactly right. And we are right in the beginning, at the tip of the iceberg in this area. There have been reports in the last year or so that have suggested certain proteins in spinal fluid can predict whether certain individuals develop cognitive impairment.

There's other reports that other proteins may actually be predictive of an individual that has more gait impairment over tremor. And so you can imagine a world where proteins and genes and molecular characterization actually predict certain symptoms before they may occur.

And then the natural next step would be to tailor treatments based on that molecular signature or molecular fingerprint. And this is really exciting, because this is where medicine is going. You can imagine having more effective treatments. You can imagine treating individuals at an earlier time point to prevent certain symptoms from developing. So we're at an exciting point here.

Dave Iverson: 13:54

One of the huge hurdles in getting that deeper understanding has always been our inability to really see the disease in a way that, for example, you can see cancer. You can MRI a tumor, and you can see what's going on. And then you can see how effective the treatment is, because you can then MRI that tumor again. We've never had that same ability, those kinds of biomarker abilities in Parkinson's. And I know this is an area
that's been of enormous interest and focus for you in your own work, Mark.

You mentioned that we can now kind of measure protein levels of spinal fluid. That's not quite the same as being able to image the brain and see what's going on with alpha-synuclein clumping, which would be, perhaps, an equivalent to an MRI. Are we getting further along in that way so that you could, with a much more precise eye, discern what was not only going on with the disease, but then also discern whether or not a treatment was actually being effective?

Mark Frasier: 14:56

Yes, you're right. It would be ideal to have a biomarker or an imaging agent or an ability to actually measure what's happening in the brain in real time and understand whether a treatment is making a difference. We've supported many, many millions of dollars to develop a imaging agent that could actually visualize the alpha-synuclein clumps in the brains in living people.

I'm excited to say that there has been progress. Just two months ago, there was announcement that a company developing a imaging agent for synuclein is moving to human testing of their agent. And it seems to be promising. We've supported this company called AC Immune for a while. And we're excited to see the results. This is just the first step, and I would imagine that they may need to optimize the chemistry once the human tests begin. But it's really exciting to see this move into human testing.

I would also say, Dave, just something that we have not talked about, but some of the data that is emerging around dopamine imaging is exciting. It was previously thought that once individuals were diagnosed with Parkinson's disease, the dopamine imaging agent couldn't really detect any change over time.

But the PPMI study and other studies are teaching us that actually early in the disease dopamine imaging does change about 10 percent in the first year and another seven to 10 percent in the second year. And so this is really exciting, because this could be used as another outcome measure in clinical testing to determine whether your experimental medicine is rescuing dopamine cells from further loss. So we're starting to develop multiple different tools in our toolbox that can be used as biomarkers to understand whether these new treatments are actually slowing the progression of disease.
So there are these newer kinds of scans, like a DaTscan and others, that you've used. You mentioned PPMI, the Parkinson's Progression Markers Initiative. These are those kinds of scans, and they're much more precise, because we used to say you couldn't really ... the only way you could diagnose Parkinson's was by clinical observation. There wasn't a way to really determine it with a particular scan. You're saying those scans are getting much more refined now and can be used, perhaps, in diagnostic ways but also to measure whether or not how someone's disease is progressing?

That's right. As we gather more data on DaTscan we're understanding its strengths as a potential tool. And what we're seeing is that certainly it can be used to assist with a diagnosis. It's not the gold standard for a diagnosis. You still need to have a neurologist assess the symptoms. But it also can be used in clinical testing, and is being used in clinical trials, to determine whether the DaTscan changes over time and the intervention rescues some of the dopamine cells.

I want to return for a moment, if we could Mark, to the cancer analogy, which gets used often. But I think it is helpful in that, not only in cancer are you able to image something, see what's going on, therefore, not only diagnose, but see whether or not a treatment is effective.

In cancer, they've also been quite successful in developing new, very specific therapies that, just like we're saying Parkinson's is not one disease, but many, so it is with cancer, that in breast cancer, for example, there're many different kinds of breast cancer.

And so they've been able to develop particular therapies targeted at those, that if you have a particular hormone receptor on your tumors, one that's called HER2 for example, there's now a drug, Herceptin, that fights that particular kind of cancer.

Is that a useful model to think of? Is that where we want to go with Parkinson's? And then of course, the big question is how far we are from that, but is that the approach in the end, that precision medicine approach that you were describing earlier, that we want to be able to get to?

Yes, that is the exact model that we're headed toward and actually is becoming more of a reality in clinical testing. I mentioned certain trials that are selecting only individuals that have a GBA gene. That is an example of precision medicine.
There are also other trials that are selecting individuals that only have a LRRK2 mutation. And so this notion of tailored treatment based on a molecular diagnosis, in addition to a clinical diagnosis, is becoming more and more the reality. And today's oncology is tomorrow's neurology. That's where we're moving.

Dave Iverson: 20:12
I like that phrase. Let's kind of pull back a bit, Mark. We've talked a lot about this idea now of what these genetic changes can teach us and, in a sense, also provide a way to develop a kind of precision medicine approach.

But if you step back and say that for most people, LRRK2 only represents, what, something like one or two percent of all Parkinson's GBA, perhaps even less than that, right? But you were saying before what's fascinating now is that there may be scads more, that's not a very precise term, but you know what I mean, of genetic mutations that just convey a little bit of risk. And so it's that much more complicated in a way.

The puzzle gets more complicated again, because there's so many factors involved. How are you trying to put that together, that there might be all these different little gene mutations that convey a little bit of risk, that we haven't even discovered yet, but in combination with anything from drinking well water, to pesticides, to whatever, might put you at risk? That just seems enormously complicated. So how are you trying to approach that?

Mark Frasier: 21:19
Yeah, it's a great question. And it is complicated, but we are making progress in that. So oftentimes when people think about understanding or doing biology research, I think oftentimes people think about understanding disease in a Petri dish or doing some animal studies.

But real biology is understanding from the human experience. And so as we gather all this genetic data, we take that genetic data and then understand the different genes and their connections in a cellular model or in an animal model and then develop new treatments and translate that back into humans. What is happening in Parkinson's disease ...

Mark Frasier: 22:00
... back into humans. What is happening in Parkinson's disease is that there are connections being made across these different genes that are actually converging on similar pathways. So, for example, there's been some data showing that the LRRK2 mutation increases its activity of the gene and its protein. Some data suggest that pesticides also might increase its activity. And when you block that activity, it can actually rescue the cell loss
that occurs from pesticides. So, this is in cells without a mutation.

There is also connections between GBA and alpha-synuclein. So, in a cellular model, GBA mutations increase alpha-synuclein. We know that alpha-synuclein increases in everyone with Parkinson's, whether you have a GBA mutation or not. So, we're starting to see these pieces actually converge on similar pathways, which suggests potentially that similar treatments may benefit individuals with certain mutations and potentially without. But by building these data and understanding the genes at a cellular level, we can understand how the pathways converge with each other.

Dave Iverson: 23:27  
In a sense, while we need a precision medicine approach because Parkinson's is so varied, the thought is that some of these precision approaches, like a LRRK2 drug for people with LRRK2 mutations could potentially benefit those who perhaps whose Parkinson's was prompted more by environmental exposure. So, it might be a two for one. Is that right?

Mark Frasier: 23:53  
That's right. I think that it is a leap. And while there's still a lot of work to do, the first steps of course, is to do a smart experiment and test a LRRK2 drug in individuals with the LRRK2 mutations. But as we build this data set, we think that these LRRK2 drugs may actually benefit individuals without limitation. So, we have to make those connections and build the data set. But it's an interesting paradigm where we want to develop precision medicine approaches, but also understand how these genes are connected to each other, so that these medicines actually may benefit more than just the mutation carriers.

Dave Iverson: 24:39  
Yeah. No, it's fascinating. Let's begin to wrap up Mark, by coming back to this big picture again, and the big data that you need. I think when you think about this, and this enormous variety, it really does make the point and we've talked about this for years and the Parkinson's community of how important it is for people to participate in research. Can you just underline that a bit further and perhaps say something about the ways in which people can participate, and why everyone's data in this case is so important?

Mark Frasier: 25:16  
Well, because Parkinson's is so variable, we really need a lot of data to understand the Parkinson's experience. By that, I mean the experience of individuals that have the disease, their journey, their molecular information, their brain information, if you will, and only by doing that, we will have a large data set to really put the pieces of this puzzle together.
There are a number of ways that individuals can participate in research. The easiest way is through an online study. You can participate in research through your own home. We are supporting a study called Fox Insight, where we're collecting information on individuals' experience, where they enter information and fill out surveys about their disease and their symptoms. There are other ways where individuals can volunteer for clinical trials to testing experimental treatments, new treatments for Parkinson's disease. And then there's other ways where you're just contributing additional information, blood samples, or imaging data, or wearable sensors wearing through a smart phone or smartwatch. All of these possibilities contribute data in a way that is going to make new discoveries and new insights into the disease.

We have a tool called Fox Trial Finder that is a match.com for clinical research. So, if individuals are interested in participating in clinical research, you can punch in your zip code and a little bit of information on this website and see all of the different possibilities, many of which I described are available in your area.

Dave Iverson: 27:12

And then finally, Mark, similarly just as you need this huge amount of participation on the patient side, as we've also alluded to, you need a lot of participation on the scientist side. And that you not only need neuroscientists like you and your colleagues, you need now computational scientists. You need scientists across many different disciplines, because it is so complicated. So, describe that part of the challenge, that you need a big team too.

Mark Frasier: 27:42

We need a big team and with many different expertise. This is an area that the Fox Foundation has prioritized, particularly in the last two years or so. Through data challenges, we've invited and welcomed a new audience of researchers, mathematicians, computer scientists, biologists, neuroscientist, and they have all become Parkinson's researchers by stimulating their research and bringing them under the tent to really analyze all of these robust Parkinson's data sets that we have developed.

Many data scientists have commented to us that we have some of the most robust data of all medical research just in Parkinson's disease. And these guys handle terabytes and terabytes of data every day. And so, they are really salivating at the idea of analyzing these data sets and uncovering new insights. So, it's been really exciting to see this field emerge in parallel with a lot of the Parkinson's data sets that are being developed.
Dave Iverson: 29:00 And in the end then Mark, that's how the puzzle gets put together. I mean it really does need to be team Parkinson's on both sides for the puzzle to really be completed.

Mark Frasier: 29:12 That's right. I think that is the wave of the future, is doing team science alongside large data sets that only are exclusively dependent on patients contributing their information.

Dave Iverson: 29:29 Well, Mark Frasier, as always, a great pleasure to talk with you today. I'm glad we're on the same team. Thank you, Mark.

Mark Frasier: 29:38 Thanks, Dave. Good to talk with you.

Dave Iverson: 29:41 That was Mark Frasier, vice president of Research Programs at The Michael J. Fox Foundation. For more information about the latest in Parkinson's disease research, and to find out how you can participate in that effort, visit michaeljfox.org. I'm Dave Iverson.

Michael J. Fox: 29:58 This is Michael J. Fox. Thanks for listening to this podcast. Learn more about the Michael J. Fox Foundation's work and how you can help speed the cure at michaeljfox.org.