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. Now, we're welcoming guests with a range of experiences and viewpoints; the views expressed belong to the guests themselves.

And today we are excited to welcome our guest, Dr. Antonella Santuccione Chadha. She is co-founder and Pro Bono Chief Executive Officer of the Women's Brain Project, an international nonprofit organization studying sex and gender determinants to brain and mental health. And today we are excited to talk more about Antonella's work with the Women's Brain Project and their recent roundtable on enhancing care in Parkinson's disease. So, Antonella, welcome to the show today. How are you?

Antonella: I am fine. It is a wonderful Sunday day here in Zurich where I'm based. And I would like to thank you for this opportunity, and thanks to the audience for taking the time to listen to this conversation.

Marie: Well, we are so excited to have you today and to learn more about you and the work that you're doing. So, can you start by telling us a little bit more about your background, Antonella, and how you found your way to this current position with the Women's Brain Project?

Antonella: Delighted to. Well, I am a medical doctor and a neuroscientist who acquired also profound expertise in neurological and psychiatric disorders. To the question, why we started the Women's Brain Project? There is always a professional and a personal reason behind things. And after my career as a neuroscientist and as a researcher at the University of Zurich, where by the way I was part of the team of those who discovered the first disease-modifying treatment for Alzheimer's disease, I left while expecting my secondborn for a more, let's say, easier job.

And it was time for me to join the Swiss regulatory agency for therapeutic products approval. This is where we approve drugs, where we understand how they work and if they are safe or not. Of course, for the Swiss market collaborating with FDA and other agencies around the world. And it was at that time that my professional experience brought me to understand that profound sex and gender differences were existing in the way the drugs were acting on humans and also the safety profile of each single drug. And this piqued my

scientific curiosity, so I went back to my colleagues in the lab and said, hey, why don't we start an association to exactly study how sex and gender factors impact disease, function, and how we respond to treatment in general. And that's how it started. This is the professional part of it.

On a more personal note, and that's a bit more complicated for me to disclose because it opens a page where lots of emotion comes across. I was a young doctor, freshly married, and by the way, with an Indian husband. So, you can imagine the Bollywood/Hollywood part of the bringing the two parts together. The family weren't, I'd say, the happiest to begin with. So, newly married and also expecting my first child. Everything was going really well, and the pregnancy was advancing with success. This is when then I find out that the girl that I was expecting — they don't have the skull formed. The brain was just basically exposed to the amnestic fluid. And this was quite shocking. I will not disclose all the despair behind it because I think it is clear.

But I went back as a scientist home and I said, why? Why did this happen to me? And I started to read around, and research shows apparently that the brain of a female, it is, even in the early neurodevelopmental phase, more prone to this type of issues. And this is when the women's brain project really took life. It's how you transform a professional curiosity, but a personal tragedy into something constructive. And I was lucky that life brought me that far.

Marie: Absolutely. And Antonella, we appreciate you sharing this personal story. And I know that these personal experiences can really motivate or inspire dramatic changes in the field. So, you had this idea of "we need to start this women's brain project". Can you tell us a little bit more about the history? And then what happened next?

Antonella: What happened next was that basically we became an association. And we started to generate the science, the science behind the reason why the female brain might be more prone to certain types of diseases, such as Alzheimer's, migraine, depression. And I don't know if you ever heard about the very rare brain disease anti-NMDA receptor encephalitis that again, it is mainly female. And until a few years ago was considered like the brain of women on fire because they were hysteric. It wasn't known that it was just a physiological condition given to a tumor usually that produced antibodies against the brain. But that's how it started.

And for us, it was about facture. I mean, how can we generate the evidences to convince the scientific community that when talking about brain and mental diseases, we should focus on understanding how sex and gender impact them. It wasn't easy at the beginning. We had a little bit of reluctancy. Many peer or senior colleagues were asking, is it really needed? Does it really make sense?

But then, when we start to look at the scientific literature, we could prove that, for instance, Alzheimer's, is more predominant in women. But it's not only about that. It's about how symptoms differ, how the time to diagnose might be experienced differently between men and women. And when we put all those evidences, maybe we can discuss more in detail later, we came out with the first publication, which was in *Nature*. From *Nature*, the BBC came, and then the whole attention spiked. And that's how we started.

Marie: Certainly. And Antonella, can you tell us then what have been some of the key milestones that you've seen for the organization since it began?

Antonella: I can say that when we started, it was 2017. Since then, we came out with more than 100 peer-reviewed publications. We have been contributing and leading more than 50 policy reports. We wrote, I think, in total something like seven books or so. We have been instigating collaboration around the globe, conversations among scientists, policymakers, regulators. I mean, I think we are one of the few organizations worldwide that had two roundtables with regulators across the globe to speak about sex and gender precision medicine since 2020 when we started.

So, you know, I think considering that it was kind of a hobby, a pro bono work, mainly driven by collaboration with the scientists that voluntarily spoke and studied this phenomenon. We went really, really far to the point that from an association, we are transforming into a foundation. And the final goal, where I think we have to all be contributing for, it is to establish the first research institute for sex and gender precision medicine in the world. And I'm sure, Marie, that you are familiar with the concept of the research center for cancer, or for tropical diseases, or for HIV. Have you ever heard of a research center that is specifically studying sex and gender precision medicine?

Marie: I have not, unfortunately.

Antonella: I think that's the way to go about it. To start to have across the globe, not just a department, not just a group of scientists, not just an initiative, but really dedicate the funds that an institute, a research institute, can move for understanding the problem overall. Because it's a big unmet need for patients. At the end, what matters to me are the patients. I was myself truly surprised when I was hearing for the first time that Alzheimer's was female because I myself was having many patients with dementia and Alzheimer's disease. And I, as a young doctor, never posed the attention to the sex of my patients, to the gender of my patients. And I think this was eye-opening for me, because then I changed the way I look at my people and the way I was trying to address specifically needs that were related either to a man or to a woman.

Marie: Absolutely. And you touched on a little bit, just some of the examples of differences that you see, whether it's in prevalence of the diseases or disease characteristics. And I think it's really important when you're trying to treat these diseases. So, can you talk about just the importance of considering these sex and gender characteristics when developing medicines for diseases, but particularly these precision medicine approaches that I think the field is moving towards?

Antonella: The problem is really vast and broad. So, I would suggest to stay for the time being focused on Alzheimer's and give you the example on this specific condition. For instance, when you look at Alzheimer's disease, we already said it is more prevalent in the female population. By the way, majority of the caregivers, despite the medical condition we're talking about, are also female. Alzheimer's has specific symptoms for men and women, above all, at the beginning of the disease.

For instance, women tend to have more depressive symptoms. So, they go to the attention of the general practitioner with depressive symptomatology, and often they get treatment with antidepressant to realize a couple of years later that this was actually the beginning of mild cognitive impairment. One of the reasons, for instance, is the fact that the scales that we are using to recognize and diagnose these diseases in women were mainly developed back then in the 70s, where we were looking at other phases of the condition, namely dementia. And those scales are not accurate enough to characterize the symptoms that a woman might represent versus a man, which might be, on the contrary, more aggressive or having more of the kind of burnout at the beginning of the disease, and even prone to alcohol abuse, by the way.

So, what I'm trying to say is that the scales usually are not good enough to understand how women compensate, because women tend to compensate at the beginning of the disease with more verbal productivity. And it's also about the treatment response. If I tell you that when we talk about Alzheimer's, there is a clear trend showing that all disease-modifying treatment.

And as I said, I was on the team of scientists that characterized aducanumab, so I kind of know what I'm talking about, shows that they have a better action on the male populations versus the female one. So, it's not just about the symptoms, the time to diagnose, the prevalence, the numbers, it's really how we respond to treatment. And we want to bring treatments which work to the patients, treatments to which the patients ideally are successful and stay content on the treatment.

The same is true also for Parkinson's. We know that often the symptoms of a woman at the beginning of the journey of the disease differ quite a lot from the

one of a man. And it's about the depressive symptomatic again, the fact that there are more gastrointestinal problems versus the male population, who on the contrary, might have more of the cognitive deficit than a woman might face. And again, it's about how to recognize those symptoms, how to make a differential diagnosis that is timely and precise, and how then to tailor the treatment response. Again, in Parkinson's, what we know is that often the female population do not respond as good as the man population does to the treatment. We know that the safety profile, it is often much more severe in the female population versus the male one.

And now if you ask me, has this been taken into account in clinical development? Well, Marie, I have to say, unfortunately, not enough, and maybe not at all. And I pause here. It needs a reflection and we could talk about this issue on and on. And for me, it is a major issue because if you want to develop a successful treatment that really helps the patient, how can you not take into account those differences in symptoms, disease progression, time to diagnose, how a patient might have a different pharmacodynamic and pharmacokinetic as compared to another one. And again, the bigger world population that you can divide the human species, it's men and women. So, we should start from there to have that precision medicine approach because starting to analyze sex and gender, then it will bring us to even further consideration of how ethnicity, how the wealth of an individual, the way we live, the specific lifestyle might have an impact on a given condition, or how we can prevent those conditions to be, that's even more important to me.

Marie: Oh, absolutely. Now you commented, you brought up some really important points, Antonella, about the diagnosis, the symptoms, and the response to treatment that you see in men versus women. What are your thoughts on the data that we have so far for things like progression of disease for these neurological conditions, whether it's Alzheimer's or Parkinson's?

Antonella: Well, for example, what we know is that Alzheimer's does have a much faster progression in the female population versus the male one. So, in other words, women decline much faster than the men do. We believe that this can be due to the fact that women have a higher deposition of tau, which is one of the biomarkers for Alzheimer's, the toxic or the neurodegenerative type of proteins that get accumulated in the brain. And this means women decline faster in Alzheimer's. But Parkinson's, I think that what is a big elephant in the room is that we observe that a higher number of young female get diagnosed.

The reasons why we don't know, I mean, we know that certainly the environmental pollution might be one specific risk factor for Alzheimer's. And we said that the female brain, it is more dedicated in a way than the male one. So, it might be that it's these subjects, these patients, especially female, that start to

manifest these early symptoms. One of the reasons is due to the environmental risk. But what I wanted to say is that when a young patient, if a woman starts to manifest symptoms, what is known is that often they change based on the menstrual cycle they are in. And you will hear a patient telling you that often the symptomatology might get worse or that the treatment response might change the way it acts on her body. And I think this is what, again, must be taken into account, not to mention the fact that menopause, which is a physiological transformation of the female body, it's not at all taken into account when we do either drugs for Alzheimer's disease or Parkinson's.

And again, we know that in both these conditions, the menopausal transition, not only predisposes to disease women, but also might have an impact on the symptomatology or the treatment response. And I think that's what has to be changing as soon as possible.

Marie: Absolutely. I definitely agree. And I think these are some major changes that need to happen in how we're doing research to incorporate some of these factors in every stage of research. So, can you talk about, I guess, just the important role of whether it's funding agencies, or research institutes, or other organizations in really helping to move towards this incorporation of these factors in research?

Antonella: Absolutely, Marie. And I think this is a change that requires the entire community to acknowledge that this is a huge gap in medicine across the board, not only for neurological disorders, for mental conditions. This is a problem that goes really across the entire spectrum of conditions and even prevention. We need to have a dedicated approach within the laboratory where the research is done, considering that it's not only about the in vivo models, so the sex of the animals that we do study to understand better a given disease or a treatment response, but it's also the in vitro system.

So, it's about the cells, for example, that are used in the lab. We don't know exactly which is their sex. We know that while packaging those cells in our petri dishes, they might even change the chromosomal setting that they have at the origin, not to speak about the cells that derive from oncological cell lines that really you don't know anymore there what it is. It is a female or a male cell, or does it have a mosaic? What is it that you are considering in terms of sex in that case?

And then we need, of course, to change within the clinical developmental approach, meaning from phase one, phase two, above all. And then, of course, phase three, where things are getting a bit better, I have to admit, but phase one, phase two, there is still a lot to do to make sure that in the early phase of the development of a drug, enough women and enough men are considered and studied. I remember my days as a regulator where we were studying the potential

effect of a given treatment on the heart frequency, knowing that very often some drugs might give rise to arrhythmia, and those arrhythmia are mainly lethal for women. Well, we have recommendation guidelines that encourage in pharmacokinetic studies where you suspect that there is a possible effect on the heart rhythm that you include 50-50 in terms of men and women representation in the trial. But I find it not enough to say if you suspect that that might be that given effect.

First of all, how can I suspect up front? I mean, yeah, you can have a guess, and then it's a recommendation. It's nothing really like “do it”. Another thing when we speak about — this is clinical development. We spoke about what should happen in the lab, but then you said it. We need to be sure that when you allocate fundings, they are given to projects that take into account sex and gender.

When not, they have to specify the reason why, and there must be scientifically valid reasons why not to. And this goes also for investors. I advise pro bono many startups, and I always say, hey, guys, please consider the sex and gender approach in your scientific planning.

But it's not only to have that equity component that it's a must, but it's also because you might learn things that will surprise you. What if I tell you, Marie, that based on some machine learning exercise that was done to recognize early symptoms of Alzheimer's disease in men and women using digital biomarkers, what was found out is that machine learning was capable of recognizing subjective cognitive decline earlier in female only versus men, meaning that machine learning was more accurate than the doctor in objectifying those symptoms that women were reporting. Like, you know, I don't function as before. I might have a brain fog. I'm not the same person as I used to be.

And this is what you hear from women, mainly, you know, it's not about I got lost in my garden or I didn't find the way back home. That's already a phase of disease, which is pretty much advanced. So, I hope I gave you a flavor of what it takes. I want to conclude with this, what you also need, importantly so, is the participation of policymakers. Because without the allocation of the right resources from governments to allow the transformation of the infrastructure, I doubt that we can split up the process of diagnosing and treating people with precision medicine approaches.

Marie: Absolutely. And I'd love to dig into this development of digital biomarkers, because I think this is a fascinating area of research. And I think it can help potentially overcome some of the maybe biases that women may encounter in the clinical setting. So can you comment on that?

Antonella: That was one of the early work that we did at the Women's Brain Project. First of all, we were one of the first organizations in the world to bring the attention of our colleagues to the fact that big data might have been biased, especially when we are trying to use this big data or digital biomarkers for health management purposes, so from diagnostic to clinical endpoints.

So we said, watch out, because we have to be very careful on the type of data sets used to train this machine learning. And so, we published a *Nature* piece. I think it was 2020. I don't remember exactly. You see, my memory is starting to — I'm 50 years old, so the specific risk related to menopause might be applying also to me, hopefully not. But that said, about digital biomarkers and the potential they have in first of all, recognizing, I think, symptoms of diseases that we as doctors and humans do not even know. What I'm trying to tell you is that the power of digital biomarkers of measuring things that aren't obvious to my naked eyes or to neuroimaging or even to blood or cerebrospinal fluid puncture are enormous.

I strongly believe that most of the neurodegenerative and neurological conditions, but if you wish, even fever, are characterized by change in the way we move. And our study, we did another study published, I think, in 2020, to show that a machine learning using different types of digital biomarkers, which were captured using a portable device, which could have been an iPad or a smartphone, was able not only to do the job that it was meant to be doing, which means classifying people as cognitively impaired or non cognitive impaired, but most importantly, when I asked the scientists, can you please tell me if your machine learning piece can discriminate if the person taking the test, is a man or a woman? With big surprise, the machine learning, with a great level of accuracy, was able to predict the sex of the individual without knowing it, of course. Which means that those differences in the way we function are something that one can objectively measure.

And why I'm speaking about the fact that most of these neurodegenerative diseases and neurological conditions are based on changes in motoric functions. Because the main discriminator, it is about how we move. It's micro-tremors. It is really assessing parameters that no other tool can, if you know what I mean. Me as a doctor, I cannot really measure with a great level of accuracy in a fast fashion, how is the micro-tremor of the hand of my patients, if you know what I mean.

So, I think that this is the potential of those digital biomarkers, that if you use them in a routine setting, GP setting, they can already, with a great level of accuracy, tell you where your patient stands, which could be the disease underlying these disturbances, and recognize symptoms that we as doctors, I repeat, with naked eyes, without instruments or other tools are not able to assess. And we might learn that in addition to, I don't know, cognitive decline in

Alzheimer's, you also have micro-tremor of a certain level that we didn't measure before, like we do with Parkinson's, for example. That's how I see the future of medicine, that we will learn new features of diseases based on what digital biomarkers will teach us.

Marie: Oh, very interesting. Well, I think this is a fascinating area of the field. And we touched a little bit on the work being done in Parkinson's disease. I'd love to dig into this a little bit deeper. I know the Women's Brain Project actually recently held a round table on enhancing care in Parkinson's disease last November. So, Antonella, can you tell us why this round table was convened, and who were the participants who attended?

Antonella: So, the main reason why we did this roundtable — it is because we realized that there was a huge gap in terms of policy, but also research and clinical development, when considering Parkinson's with the sex and gender lens. And we already touched base on differences that we know do exist in Parkinson's when we speak about women and men. We said, for example, that women might manifest different types of symptoms. We said that, yes, it's true that the disease is more frequent in the male population, but women do respond less to a given treatment and might experience more side effects.

What we also know is that women represent the majority of paid or unpaid caregiving for Parkinson's. So, we thought, let's bring this topic in a roundtable where we put together — and again, that's the way we succeed also in the Women's Brain Project — where we put together the patients first. And then we have the specialist, and then we have the policymakers, and then we might have other stakeholders around the table where everyone discuss on those unmet needs to educate the, let's say, medical experts to specific needs of a patient, but also to educate the policymaker on what it needs for a man or a woman with Parkinson to have a better quality of life, to have an infrastructure in place that allows to have the best possible life. And also to have a treatment that functions because that's also a major point. And that's what happened.

This was at the end of November. I think we are the first organization, as far as I know, that took this approach to Parkinson's disease. And let me tell you one thing that was a learning also for me, because yes, I had in my old days Parkinson's patients, but they mainly came to my attention when they were much older and eventually with symptoms of dementia. What I myself learned in that circumstance is that the numbers of Parkinson's — because, you know, I had always the impression that the Parkinson's patient was mainly an 80 years old plus person coming to my attention back then for help and for treatment, mainly a man, really big curve. You know, this is a picture of the Parkinson's patients that one might have.

And then I realized that in fact, it's completely different. You have that even the proportion of men versus women. It is not that big as we think. We brought a report with the Economist Impact Unit, and there we put some numbers, black and white on paper. Actually, there are 4.6 million patients with Parkinson's, which are male and 3.8 [million], which are female. So, the delta is not so huge as one can think, because well, we see your Parkinson's is predominant in men.

Yes, it is, but a little delta. That was the discussion we had. I mean, if there are also all these women that experience Parkinson's, which are the specific needs, which had a policy in place to facilitate patients who are men and women specifically to navigate their journey, which is the time to diagnose. We heard that many, many women get the diagnosis much later than a man will do.

Also, because of this bias, I just told you the bias that you picture your classical patients as a man, 80 year plus, and you don't think that a woman with 45 might already have Parkinson disease.

Marie: True. Yeah, I think that's so important. So, can you share, then, you were having these conversations with patients, with policymakers, and with diverse stakeholders within the field. What were some of the main findings or outcomes that came out of this conversation?

Antonella: What we heard and what we decided to put in black and down in a call to action, which now we're trying to publish in a peer review journal, by the way, is that we need specific approaches to study the disease in men and women, starting already in preclinical development to then go towards clinical development. We know that drugs don't work that good in women as they do in men.

This is not acceptable. So, we need to really change the approach to research and clinical development. What we learned is that when women do have roles as caregiving for people living with Parkinson's, they usually have the consequence of having stepping down from their work, and they basically are at higher risk, even of neurogenerative diseases, because you might well know that social isolation is a specific risk for depression, depression is a specific risk for Alzheimer's disease and dementia, et cetera, et cetera. Also, the fact that the body doesn't move because you are caregiving 24 hours-seven, and that's often the case for women more than men. So, we advocated for policy that would globally have specific solutions for the female population that is is caregiving mainly. We also discussed about the fact that there must be more, bigger awareness to symptoms of this condition that speed up diagnosis.

Of course, the funds and involvement of governments to drive these policy changes at the local level, each local level, considering that each country, each geography might even have their specific needs in terms of infrastructures, and

there are different healthcare systems, some are more advanced, some are less advanced. And I think that time is now. I want to quote the testimonial of, by the way, a patient, a woman. We had one patient sharing with us, for example, her story. She wasn't a patient only. She was also a medical doctor. So, let's say, a person that was very knowledgeable, even on the science behind the disease. What she told us is that she was diagnosed when she was 33 years old and while being pregnant. The first symptoms she had was micrographia. So she was writing with a very small cramped handwriting. Let's put it this way.

And nevertheless, at the beginning of her symptoms, she wasn't taken seriously enough. And because she was then pregnant, the whole diagnostic process couldn't take place because it was too invasive, right? She was expecting a child. So, just to say that there are specific needs around women with Parkinson's that must be taken into account. And if we don't do this, we have a huge missed opportunity to ameliorate life of men and women around the globe.

Marie: Absolutely. I think you did a great job of highlighting these key points. This patient-centric care is absolutely critical. Thinking about, not only the sex and gender of the patients that you're working with, but whatever their particular circumstances might be. Like you said, someone who is of a particular age, whether they're pregnant, all of these different lifestyle factors also factor in as well.

Antonella: No, absolutely. Because I mean, the need of a 33 year old lady won't be the same needs of an 80 year old person. And it's so different the life that a person might face at a given age that we have to tailor approaches, care, and the treatments based exactly on that. And that's what we didn't do yet. We didn't do this so far. So, we need to have that change.

Another thing that came out of the roundtable, of course — it is the huge stigma around these diseases. Stigma is still a major personal issue. And I can tell you that I can speak also because of personal experience. Of course, I didn't live [through] Parkinson's, not even Alzheimer's. I've lived other things. And when it was about myself, you feel very much stigmatized. You know, that was my story, for example, with my child when there was this anencephaly. How do you speak about it? Whom are you going to tell? This is such an unspoken thing that you feel kind of ashamed.

You feel like people won't understand. And you try to hide, and you feel pretty much alone. And again, the stigma around any disease, but especially a neurological condition, must be finally removed. And we need to educate the younger generation. We need to educate across geography, across professional roles, everywhere in the schools, in university, what it's all about and make a society that is friendly for people living with these conditions.

Marie: Absolutely. And I think that stigma goes multiple ways. It might prevent someone from going in when they start to notice some symptoms that might be triggering flags. And even from the physician perspective, there may be hesitancy to give certain diagnoses because they know that there's a worse prognosis, for example, unless they're absolutely sure, which can be difficult.

Antonella: Absolutely. And even for me, when I was at the hospital before posing a certain type of diagnosis, I was pretty hesitant because I knew that, first of all, it's a stigma. Second, I didn't have good treatments to give hope to these people. And I also, this was about 12 years ago - 13 years ago, didn't have the diagnostic tools, which were making me believe that this was really the right disease I was seeing.

So, to your point, this is a missed opportunity because we know that time is brain, brain is time. And the more you wait, the more those diseases advance. So, we have to empower not only the patients, but also the doctors with tools that are powerful in giving a diagnosis and discriminating among a disease versus the other. So, differential diagnosis is so important. And also about treatments, because if you don't have good treatment options for your patients, you're hesitant because then you prefer to say, okay, come back soon in six months and see what happened.

Which shouldn’t be. Because, especially women, hear this too often. I heard from the patients in the room, very loud and clear, the fact that often the general practitioner says, come back in six months. And this is what we can't allow to be. I said it also earlier that often the case can be that patients, at the end of a journey, even like with Parkinson's, my experience, dementia symptoms. And I don't know, Marie, if you know that within the OECD countries, we have that women have a higher number of dementia versus men.

We said it already, and this would imply also dementia due to Parkinson's disease, Alzheimer's, Lewey body, frontotemporal. We don't know exactly, but the numbers are higher for women. And then what the OECD also show is that the majority of the patients that are institutionalized, meaning either in an elderly home or in a nursing home, are again women. And they also get a higher prescription of antipsychotic. And antipsychotics are a proxy indicator of poor standard of care.

So, the problem is huge because women are the ones that have a higher number of dementia when they get old. Women are the ones that are the most institutionalized, and they are the ones that get higher prescriptions of antipsychotics, which is not really a cure, which is not really a treatment for the specific symptoms of that disease. It is just a way to remove the behavioral

component of those diseases to keep the patients calm and living in these houses, in these nursing homes.

Marie: Absolutely. And as you mentioned, this is a really big problem. And I think to solve a really big problem, you need help from a lot of different people. We highlighted that there are diverse stakeholders being brought together to have these conversations and to work towards a solution. Can you talk about what that process has been like and how you've been able to bring people together to rally everyone behind this cause?

Antonella: Well, I think that the first way was really to produce the scientific evidence needed to convince that this was a matter of concern, that it was real, and that science was speaking for this. So, we really, as I said, published a huge pipeline of peer-reviewed scientific publications. When you bring data and science on the table, everybody's convinced. With those types of evidence, then we started to work together with everyone around the table, including media, because we had a strong trust and relationship with journalists, which helped us scientists to educate also the lay public on this unmet need. And that's how the momentum started.

Now we are, for instance, part of a global alliance for women's health that has been launched at the World Economic Forum. If you would have asked me seven years ago, Antonella, will you make it to bring this topic to the attention of the policymakers at the top of the world in Davos for WEF (World Economic Forum)? I would have said not so sure. We made it. We made it because you need to be vocal. You need to be convinced, passionate. You need to be credible.

Marie: Right.

Antonella: And you need to do what is needed. At the end of the world, it's not even rocket science. It's common sense. I mean, we are different. Women were not included enough in clinical development and research, and it's time to reverse the narrative. It's not rocket science. I always say that every scientist who wants to make an academic career, and therefore needs publication — you know how it is in the scientific world — they just should look at sex and gender differences in any experiments they do. Because they will have material to publish. Because wherever you look, you find those sex and gender differences.

Whether it is a treatment response, or your in vitro cell system, or your patch clamp, or whatever you do as a scientist, if you start to look at those sex and gender differences, you will have material enough to have a decent scientific publication. So, it's a joke. But in the end, that's what you need to make that revolution happen.

Marie: Absolutely. And I think the revolution can't happen without, whether it's resources, collaborations, tools, and other previously funded research. So, can you talk about what sorts of things do you see benefiting your own work and kind of moving this cause forward in terms of those veins?

Antonella: Yeah, this is a good question, but it requires a very transparent answer. I think I've mentioned to you that the Women's Brain Project, it is an association. We got established in 2017. It was mainly pro bono work, volunteering scientists from all over the world who responded to our call and said, yes, we're going to help, yes, we're going to publish with you. So, we did a lot based on our own goodwill, on our invested time, invested resources, and we grew. We grew exponentially, unexpectedly even because I would have never said that this group of three scientists then would have brought the organization that far with time. Of course, some people stayed, some people left, and that's part of the growth. But we really went for it.

And what we need today, we need to move from that, let's say, pro bono type of work into now an organization that has the funds to move the research institute that I was talking about earlier. We need unrestricted funds to make the jump from mainly a pro bono, volunteering organization into now a well-organized and structured organization. And why that? Because we move science. We work, we mentioned, with regulators, with pharmaceutical industry, with media, with the lay public. You need to put in place lots of things from the good legal framework to the good HR. It's time to be more robust. And we are doing that. We are trying to establish the research institute, looking for sponsors, investors, people who believe in this cause that want to contribute from one little penny to maybe the million we need, because research costs.

That's also another statement I want to bring across. And I stand behind these words. I often get upset because the perception, especially in the population or people that come from other fields, is that research doesn't cost much or researchers shouldn’t earn so much. I mean, research costs. And we need to allocate the right funds to pay those brilliant minds who will take care of our health to develop those treatments and solutions needed.

I myself as a young scientist worked basically for free for many years. I was passionate. I believed in the cause, and I had a family supporting me. So it's fine. I was a couple of years financing fully my learning in North Germany as a biochemist in a prion lab, and all was wonderful. But this shouldn't be. Actually, you should allocate great resources to pay for the science we need to make human beings live healthier, longer. And if you wish, you're so happy.

Marie: Absolutely. I think it is an investment in the future is how I view it.

Antonella: Absolutely.

Marie: So, Antonella, can you comment on the relationship between the Women's Brain Project and The Michael J. Fox Foundation — how these two organizations got connected and whether your work has benefited, or you could see it potentially benefiting, from some of MJFF's tools, resources, and collaborations?

Antonella: I think, as I said, we need a lot of help. And I think that The Michael J. Fox Foundation will certainly and hopefully contribute to this type of help needed. It was kind of a first for us because we would have never expected that because of that roundtable that we initiated based on our understanding of what was missing on the field, we would have then come to this type of collaboration. We are very proud and privileged. We would have not expected it.

And we recognize that maybe what we did really was of importance because look at sex and gender differences in Parkinson's. It is an unmet need, especially when we look at the policy strategy. And what we are trying to do, as I said earlier, is to publish this learning from the roundtable as a paper into a peer-reviewed journal to have, again, that type of credibility that then can change, really, the status quo.

Because when you bring the paper from *Nature, Lancet*, *New England [Journal of Medicine]*, whatever, then people listen with a different level of attention. Above all in the field of academia, from a pharmaceutical industry where science is mainly done. So, as I said, we hope that the collaboration with The Michael J. Fox Foundation will help us to find the means and the resources needed to bring this work further.

This work was sponsored by pharmaceutical industry originally. And now we're looking for new sponsors to continue it. What I think we should be also doing together, we have looked now very much at the European perspective. So, this was a roundtable done mainly with European healthcare professional policymakers, patients, representatives, and patient organizations.

I think we should be replicating the same exercise in the US territory and other areas around the world because, Marie, whether you believe it or not — I'm sure you know about it, actually — if you take the US situation versus the European one, low and middle income country, Asia, it is all so diverse. And what I need here as a patient 50 years old, diagnosed with Parkinson's, won't be the same as what I might need in a low and middle income country, whether a man or a woman. So, it will be nice to replicate the roundtable, considering different geographies and bringing experts and patients around the table to see which are the specific local needs.

Marie: Absolutely. And I think there is a lot of work to do as you hinted at Antonella, but a lot to look forward to as well. So, when you look at the field today, what do you see as the biggest areas of opportunity, or perhaps unanswered questions in Parkinson's disease research, perhaps related to this topic?

Antonella: One very easy thing that we should be doing as scientists, as experts in the field is to go back to our own lab journals or our own record, our own data and reassess everything under the sex and gender perspective. Because lots of data do exist already.

We have those repositories, those data related to clinical trials that might have worked or failed. I would encourage to pose the question. What if? What if I would have considered sex and gender as a factor in this type of experiment? Would have I obtained different results? Would I have obtained results specific for men and women? Or maybe I learned that I should include more women to generate a different type of learning.

Of course, then we need also new research. Because we need to account for what we spoke earlier — hormonal changes in the life cycle of a woman, but maybe even of a man. I mean, men have andropause. And how a patient with Parkinson's being a man with 50 years old, would not necessary be the same as patients with Parkinson's with 80 years old, where andropause kicked off and took place significantly. So, I think that we have to redo a bit the science. We have to reanalyze the data we have with that type of question.

And that's the type of change I envision. Of course, we spoke about digital biomarkers. So, I think that digital solutions will transform profoundly the field because digital solutions will be used not only as early diagnostic tools, but also as new clinical endpoints, of course, validated by regulators. That's a must. But we will learn things that we do not know yet because the scales we use today, I repeat, they are obsolete and designed for diseases that were different from the diseases we watch today because those diseases were for a more advanced type of patient. Now we can recognize Parkinson's, Alzheimer’s much earlier than it used to be.

I think that's the type of transformation I need. And if you ask me how the study should end, well, my hope is that in 10 years from now, the topic of sex and gender in any disease will be obsolete. The next chapter to speak, it's about ethnicity because we know that ethnicity is a major component. So, I think that we solve sex and gender, and then we have to continue the deep dive into how ethnical differences, different origins might predispose us to disease differently and respond to treatment differently.

Marie: I think that's wonderful. I think there's a lot of exciting research being done on this front. Can you share, as one kind of parting comment here, how your work, Antonella, is bringing us closer to whether it's finding a cure for Parkinson's or just contributing to improving therapies for people with Parkinson's?

Antonella: I think that the learnings generated with our roundtable, a first of this kind of king of sex and gender differences in Parkinson's and bringing patients at the center of the discussion as well as policymakers, will be a great lesson of what it needs to bring sex and gender precision medicine approaches into Parkinson's disease.

Not yet really studied, not yet really discussed abundantly in the field. We need to do more. So, I think that our first will be the first of a series of those types of discussions across patients, healthcare professionals, policymakers that will radically transform the field towards an inclusive, precise approach to even Parkinson's.

Marie: Excellent. And if our listeners want to learn more, Antonella, about the Women's Brain Project, what is the best way for them to do so?

Antonella: Well, we have a website, and we're also present on social media. Our website is www.womensbrainproject.com/. And we are present on LinkedIn, Instagram, Facebook. But of course, you are very welcome to drop us an email at info@womensbrainproject.com. And we will respond the best possible way. Of course, we have lots of educational material available on the web. We wanted to actually interact once again with our guests that joined the roundtable discussion. This happened under the white Chapman rule, to have educational video exactly on what we discussed. And this requires an additional type of work. So, we need funds for that. And if you're interested, reach out to support our research.

Marie: Phenomenal. Listeners, definitely check out that website. Get connected if you have questions or want to learn more. And Antonella, thank you so much for sharing your insights with all of us.

Antonella: Thanks a lot. It was a great opportunity to showcase the work we do at the Women's Spring Project. I want to thank the listeners, and I hope there will be a future occasion where we will discuss how we solve the problem together.

Marie: Well, Antonella, it's been such a pleasure to have you on the show today. 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*.