

**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 are welcoming guests with a range of experiences and viewpoints; the views expressed belong to the guests themselves. And today, we are delighted to welcome our guest Dr. Lana Chahine.

Listeners, Lana is a Movement Disorders Neurologist and Associate Professor of Neurology at the University of Pittsburgh. Today, we are excited to speak with her about the development of a biologic definition for Parkinson's disease and a newly proposed staging system for "Neuronal alpha-Synuclein Disease" (NSD), which includes Parkinson's disease. And it's important to note that the NSD and the staging system are for research purposes only right now, and they are not yet ready to be implemented in the clinic. So, Lana, welcome to the show. How are you?"

**Lana:** Hi, Marie. Thanks so much for having me. I'm really excited to be joining you today to tell you about this new biologic definition and staging system.

**Marie:** Well, we are thrilled to have you here with us, and I'm looking forward to getting into some of the details. So, perhaps Lana, we can start with the background. Can you share with us why it was so important to develop a biological definition of Parkinson's disease and the staging system that's based on biology?

**Lana:** Yes. So, understanding what is so important about this staging system requires us to look back into history, and we'll do that a few times over what we discuss. Traditionally, Parkinson's disease was defined based on signs and symptoms. So the presence of motor features like Parkinsonism and non-motor features like cognitive impairment or hyposmia, and then other features like response to treatment, course over time, and so on. So, this approach was fraught because it was identifying people and diagnosing people with Parkinson's disease who had a very broad clinical heterogeneity, which we know occurs as part of this disease. And the subjective nature of that, combined with the subjectivity of how we assess Parkinson's currently and measure it, is really leading to a lot of heterogeneity.

Another limitation in these clinical diagnostic criteria was their lack of ability to really capture the earliest stages of disease. We now know that the pathology

underlying Parkinson's begins many years before signs and symptoms appear. So, in 2015, an attempt was made to put forth a criteria for diagnosing that period of disease, what used to be termed the "prodromal phase", and that relied on some symptoms and biomarkers, but it had several limitations. And along with the clinical heterogeneity and the heterogeneity of how we measure the disease and the variance in some of those measures, there is also this problem with terminology. Different people using different words to refer to different diseases, different stages of the disease, so we needed a common language in order to really move forward.

Similarly, up until now, when we think about Parkinson's severity, there are staging systems that exist already, but they're based on examination findings or maybe crude global metrics of mobility and function. One example is like Hoehn and Yahr staging. But these don't capture the broad range of functional measures that are important across the continuum, across the entire spectrum of the disease, and also may not account for what's clinically important and meaningful to patients in their day-to-day life. So, a biologic definition and a staging system based on biology could overcome many of these limitations that have existed to date because of clinical definitions of the disease.

**Marie:** Absolutely. I think you brought up some really important points there, and I'd like to touch on this idea of terminology and having a common language. I think this is critical in medicine as well as in the scientific research. So, let's talk about this term neuronal alpha-synuclein disease, NSD. Can you share what is the official definition that is being proposed for NSD?

**Lana:** NSD, or as you said, neuronal alpha-synuclein disease, is a term defined by biology and it encompasses all alpha-synucleinopathies with neuronal alpha-synuclein. That is, predominantly neuronal deposition of misfolded pathologic alpha-synuclein. So, the alpha-synucleinopathies with neuronal alpha-synuclein include Parkinson's disease and dementia with Lewy bodies, and are in contrast to other alpha-synucleinopathies that don't have a predominantly neuronal distribution of alpha-synuclein, such as multiple system atrophy.

**Marie:** Very interesting. And can you explain why having this term is, I guess, helpful in terms of moving forward and just integrating the descriptions of current diseases into this single unified term?

**Lana:** If you think about people with the clinical syndromes now encompassed by NSD, many, many terms have been used to describe those individuals. For example, we've used the term Parkinson's disease, dementia with Lewy bodies. In people with dementia, we've used the term Parkinson's disease dementia, and in addition, we've used many terms to describe the people in the earliest stages of pathology, for example, incidental Lewy body disease, premotor disease,

preclinical. Sometimes we've been a little more specific to speak about features in the early stages, such as REM sleep behavior disorder.

You can see how all this terminology can be very confusing, and people may be referring to the same disease with different terms or to the different diseases with the same term. And NSD addressed this by offering a unifying term with underlying biology that encompasses all these alpha-synucleinopathies with neuronal  $\alpha$ -syn, and importantly, allows us to then distinguish people who are not NSD. Individuals who have clinical signs and symptoms that are of course very important that sometimes appear as though they have a clinical diagnosis of Parkinson's disease, but they don't have NSD. And this definition allows us to identify this important subgroup that require further understanding and maybe even their own staging systems.

**Marie:** If you were to sum up then, Lana, what is the textbook-style definition that you would give people if they asked, what is neuronal alpha-synuclein disease?

**Lana:** The NSD encompasses three core tenets. First, that the disease is defined biologically based on biomarkers. Second, that the disease can be diagnosed in the absence of clinical features. And third, that clinical features in the absence of biomarkers are not sufficient to diagnose the disease. And understanding these three principles helps people understand the concept put forth under NSD. So, NSD is defined by three biologic anchors. The first is S, which stands for neuronal alpha-synuclein ( $\alpha$ -syn). The second is D, or dopaminergic neuron dysfunction, which may be present in a stage-dependent manner. And I'll go back to that later.

And the third component is G, which stands for genetic. And here I'll just briefly mention there are many genes linked to Parkinson's, but for the definition of NSD the fully penetrant disease-defining pathogenic variants in the synuclein gene are part of the NSD definition. And at present, the definition of S and D status is based on binary assessments of positive or negative, but our hope and our goal is to eventually have quantitative measures of these as time goes on, as we make progress in the field.

**Marie:** So, let's talk about these three biological anchors and what happens in cases where people may have one anchor, but not all three anchors. How do these anchors, I guess, contribute to the definition and defining whether people meet the definition or not?

**Lana:** So, the defining feature of NSD is the presence of abnormal neuronal alpha-synuclein, or what we call S-positive. And S-positivity can be assessed and determined by any rigorously validated and accurate biomarker for neuronal alpha-synuclein.

At present, the only biomarker that really meets those rigorous criteria is CSF alpha-synuclein seed amplification assay, but there are many other promising biomarkers that could be used to assess S. And any time those are validated, they may become part of the definition. So, the D anchor stands for dopaminergic neuron dysfunction or degeneration. And we've known for many decades now that degeneration of the substantia nigra dopaminergic neurons is the core pathologic feature of what we now call NSD.

Of course, it's not specific to NSD. There are other neurodegenerative diseases where there's nigral loss. And not everyone who is S-positive becomes D-positive, but it is the onset of D-positivity which defines progression along stages, which I'll go back to later. And at present, the most studied measure of dopaminergic neuron function is dopamine transporter SPECT scan, but there are other imaging measures that are being developed. And as I said, this is categorical, so it's either normal or abnormal dopamine transporter binding based on specific binding in the lowest of the two putamina adjusted for age and sex, but this definition may change over time, and hopefully will one day become quantitative.

Here I wanted to briefly mention that neuronal synuclein disease is a multi-system disease that affects not only the central nervous system, but also the autonomic nervous system and peripheral nervous system and importantly, affects both dopaminergic and non-dopaminergic pathways. So, in the future, we'll hopefully have NSD-specific measures of neurodegeneration that we'll be able to incorporate into the biologic definition and the staging system.

And finally, the last biologic anchor is G for genetic. And as I said, fully penetrant pathogenic variants in the synuclein gene are disease defining. They are NSD, but there are many other genetic variants associated with neuronal synuclein disease. So, if you take people who are clinically diagnosed with Parkinson's disease, about 15 percent have pathogenic variants in genes like the GBA1 or LRRK2 gene. And pathogenic variants in GBA1 have also been identified in individuals diagnosed with dementia with Lewy bodies. And beyond that, we know over 90 SNPs that may confer some risk for Parkinson's disease or earlier age of onset.

So, all of these genetic traits have variable penetrance. The penetrance does increase with age. And because of this, this low or variable penetrance of the many genetic traits associated with NSD, these are not considered disease-defining, though they may be incorporated into stages and inform aspects of staging now and in the future.

Here, I want to just briefly take a moment to mention that the majority of individuals with risk variants who develop dopamine loss and functional impairment will be S-positive. They will show N-a-syn abnormalities. But there are a subset of people who clinically are diagnosed with Parkinson's disease and have all the features that would otherwise indicate they have Parkinson's, but they don't have NSD. They don't have S-positivity. And these include people with pathogenic variants in the LRRK2 gene and then PRKN gene. And we can go back and talk about these individuals more later. But these people don't have NSD. And it's really important to understand what they have, what is causing the nigral loss of these individuals.

**Marie:** Certainly. I think, Lana, you brought up some really interesting points. And one thing that I would like to come back to is this idea that you mentioned that these are the definitions and these are the criteria. And these are the evidence components that we have to support these criteria right now. And I think it's really important to emphasize that the NSD, this is a working definition that's going to continue to evolve over time with the field.

**Lana:** Absolutely. This is an important initial step. We expect many future iterations of the NSD and NSD-ISS. And the beauty of the way it's designed is that it introduces this positive feedforward loop where the way it's designed actually will facilitate answering of the many key research questions and gaps that will inform future versions of it. Importantly, this is a research definition and a research staging system. It is not meant for clinical application. It requires a lot more study before we can trial it into the clinic. But again, it's a really important starting point.

**Marie:** Absolutely. And perhaps we can dive into the staging system next. So, we talked about the neuronal alpha-synuclein disease. Now there is this NSD-ISS, the NSD-Integrated Staging System. So, Lana, can you just walk us through what is the staging system, and what are the different stages?

**Lana:** NSD is a continuum. But defining discrete stages along the way is really important and will provide a research framework for many of the applications. So, the NSD-ISS, it's based on the biologic anchors I mentioned, S, D, and G. And then there is a stage-dependent progression based on presence or absence of D and then presence or absence of signs or symptoms and how they manifest with functional impairment. And I'll elaborate more on that as I describe each stage.

The NSD-ISS consists of seven stages. The first stage is stage zero. And this is the stage defined strictly by fully-penetrant pathogenic variants in SNCA. People who are stage zero are going to be very rare. As I said right now, stage zero is defined only by variants in SNCA. But it's possible that variants in other genes may also define stage zero in the future if they are determined to be fully

penetrant. And stage zero can be thought of as being analogous to stage zero in Huntington's disease.

Now, most people who have NSD will be stage one and beyond. Stage one and on require S-positivity. So stage 1A individuals are people who have S-positivity but are D-negative. They have abnormal synuclein but no dopaminergic dysfunction. Stage 1B are people who have S-positivity but also now D-positivity. And importantly, people in stage one have no signs or symptoms.

An example of someone in stage 1A would be an individual community-dwelling older adult, living in the community, completely healthy with no signs or symptoms, who let's say has a synuclein assessment as part of a research study and have a DAT scan as part of a research study, and they're determined to be S-positive, D-negative, completely asymptomatic fully functional. That's a stage 1A individual. And we believe that S-positivity precedes D-positivity if we have studies that are closely following people and assessing both of these frequently enough that we'll be able to identify that. And studies to date already indicate that, but more data are needed in this regard.

**Marie:** Absolutely. And then stage two.

**Lana:** Stage two is defined by the presence of signs or symptoms but that these signs or symptoms have not yet led to functional impairment. And what are some of the signs and symptoms that might define stage two? They may include olfactory dysfunction, autonomic changes, mild cognitive changes, or REM sleep behavior disorder. So, as you hear the list of these symptoms, many of them are nonspecific. They can happen in older adults who don't have NSD, but the lack of specificity is offset by the requirement for S-positivity in these individuals.

As time goes on and data evolve, we'll be able to further refine what defines stage two with greater specificity. Now similar to stage one, in stage two, again given that this is all based on the biologic anchors, we have two stage subdivisions in stage two. Stage 2A are individuals, again who have mild signs or symptoms without functional impairment and are S-positive, D-negatives, whereas stage 2B are S-positive, D-positive. So, to reiterate, everyone who's stage one and beyond is S-positive. Everyone who's stage 2B and beyond is S-positive and D-positive, which brings me to stage three.

So, in stage two, as we said, there are signs and symptoms but they're not leading to functional impairment. In stage three and beyond, there is functional impairment, and each stage is defined by increasing levels of functional impairment. The severity of functional impairment defines each progressive stage, and we're conceptualizing this qualitatively as progressing along the continuum of slight, mild, moderate, and severe. And here I want to pause and

acknowledge that this initial proposal that was put forth and recently published does not define what functional impairment actually is, and how do we define slight, mild, moderate, and severe functional impairment? But that will be a big part of future efforts using data to define what we mean for each stage.

The operational definitions of the anchors for the functional impairment in stages three to six were beyond the scope of this initial conceptual paper that were put out. I just want to give some examples of what kind of measures we might use today, keeping in mind that eventually we hope to have a quantitative biomarker that can be incorporated into the staging system to help define disease progression. But at this time, validated biomarkers of disease progression are lacking so we would rely on rating scales of function. An example of this is the Movement Disorders Society Unified Parkinson's Disease Reading Scale or the MDS-UPDRS. As many people know, parts one and two of this scale measure functional impairment.

And so, one starting could be to use parts one and two of the MDS-UPDRS, along with certain signs or symptoms, and measures of motor and cognitive function, other non-motor features, to define the different stages. Most people who we currently define as newly diagnosed Parkinson's, so people who just received the diagnosis based on clinical criteria will fall into stage three. But, and this is really an example of how this staging system can capture and call out the heterogeneity that clinical diagnostic criteria could not.

Most people with newly diagnosed Parkinson's will be stage three, but some who have no functional impairment will be stage 2B, and some who were just diagnosed but had more advanced disease could be stage four or even stage five.

**Marie:** Certainly, that makes sense, Lana. I like this idea of just thinking more about the different tools, the different things that are available, the different future quantitative measures that will be available to really break down what these later stages would be. I think that is going to be an important thing to keep an eye on going forward in the field. But let's maybe take a step back and talk about the Synuclein Seed Amplification Assay (SAA). How did the validation of this assay really change the conversation around staging and this biologic definition? You mentioned that S is, of course, one of the key anchors.

**Lana:** The validation of the Alpha-Synuclein Seed Amplification Assay, which I'll refer to as SAA, was really a turning point that brought us to this important moment where we can put forth a biologic definition and staging system.

Here again, looking back at history helps put things in context. So, over a century ago, Lewy bodies were first identified as the pathologic hallmark of Parkinson's

disease and later were identified in dementia with Lewy bodies as well. Then in the late 1990s, alpha-synuclein was recognized as the core constituent of Lewy bodies and Lewy neurites.

Then we were able to develop immunohistochemical methods to stain for it, and therein, efforts to identify and measure pathologic alpha-synuclein in vivo began. For many years, from the mid-2000s, efforts were underway with some success, but either the measures were lacking in specificity or they were not reproducible or scalable, meaning could not be reproduced in different labs in a manner that would allow their widespread application. Then a major breakthrough came, first starting in 2016, when an assay originally developed for prion disorders was applied to alpha-synuclein. From 2016 until 2021, this assay was tested on a few different cohorts.

Then in 2023 came the application of this SAA to over a thousand individuals enrolled in the Parkinson's Progression Marker Initiative or PPMI. Within just those few years, this CSF a-syn SAA was considered robustly validated and sufficient to actually diagnose NSD because CSF a-syn SAA is highly specific and sensitive. The assay is positive in more than 90% of neuropathologically confirmed cases of Parkinson's and dementia with Lewy bodies. Many people with REM sleep behavior disorder also have positive SAA. And importantly, it can detect people who go on to be clinically diagnosed with Parkinson's and dementia with Lewy bodies. Another key feature of this assay is that it distinguishes the type or form of alpha-synuclein present in NSD from a-syn forms in, for example, multiple system atrophy or MSA.

**Marie:** I think the SAA was a critical step in moving us towards being able to develop the NSD-ISS. But let's talk about that process. I know it happened relatively quickly. We're talking just a few years here, but what was the process, Lana, that you and the group took to really put this definition and the staging system together?

**Lana:** We first started informally thinking about and working on a biologic definition and staging system just in the middle of 2021. And by 2022, there was a broad consensus among really a range of stakeholders, and that would include neuroscientists, clinical neurologists who care for people with alpha-synucleinopathies, but beyond that industry partners, patients, their families, and foundations. A range of stakeholders who really recognized that a biologic definition and staging system was critical to advancing the field. And another, I would say, inspiration for this came from the biologic definition and staging systems put forth in other neurodegenerative diseases, that is Alzheimer's disease and Huntington's disease, and the success that that has brought in terms of advancements in their respective fields from the definition and staging system.



So in this context, The Michael J. Fox Foundation assembled a working group. And the NSD-ISS working group aimed to develop a biologic definition for the disease, to develop a framework or staging of the disease, and then to identify gaps in knowledge. In April 2023, an in-person meeting was held with global NSD neuroscience and clinical experts, members from the patient community, public and private partnership groups, representatives from industry, and importantly, regulatory agencies, as well as key patient advocacy groups.

So, a series of virtual meetings, face-to-face conferences were held, several virtual and in-person meetings were held, sometimes on a weekly basis. And this culminated in the first draft of the NSD and NSD-ISS, which was posted publicly in June of 2023 and allowed for public comment. After several weeks of public comment, the draft was revised. And so it really incorporated key feedback.

**Marie:** And I think it's really interesting that you were involving all of these different kinds of stakeholders. And I'm sure you were getting a lot of different feedback from all of these different stakeholders. So, can you talk a little bit about how these different perspectives kind of fed into what was ultimately published in this recent paper and just the iterative nature of the approach and the conversations that happened surrounding it?

**Lana:** Indeed, I think the diversity of opinions was invaluable to the eventual final draft of the NSD and NSD-ISS. At the core and at the base of all of this was a lot of consensus about the need for a biologic definition and a staging system. But there were discussions about what the best terminology is, what the best biomarkers are to define the disease. And so extensive literature reviews were conducted, scientists from different backgrounds consulted. And of course, the patient voice was front and center to how we define the disease and the staging system.

**Marie:** Absolutely. And I know The Michael J. Fox Foundation played a pivotal role, you mentioned, in bringing all of these different stakeholders together, can you comment on, I guess, just the impact that that had — being able to have this neutral convener in the mix?

**Lana:** The Michael J. Fox Foundation was really instrumental to this. I don't believe that the NSD and NSD-ISS would have been put forth and with such speed had it not been for MJFF. They facilitated meetings and communication. They interchanged with the many different stakeholders and ensured that all the different diverse backgrounds and expertise of the different stakeholders were accounted for. And again, really helped us to keep the patient voice front and center.

**Marie:** Well, Lana, it sounds like you had information and input coming in from a lot of different stakeholders, as we mentioned, and thinking about what the future looks

like for the NSD-ISS. So, can we just talk about what are some of the benefits of having this NSD (the definition) and the NSD-ISS (the staging system), as well as the potential impacts on both research and the clinical side of things?

**Lana:** In the short term, it will not have an impact in the clinic. It's really not for clinical application, but we hope and believe that it will have translation into the clinic in the future.

I mean, I think there are many potential applications of the NSD and NSD-ISS, but I'll give just three examples. The first pertains to understanding disease pathophysiology. Up until now, traditionally, we've conducted biomarker discovery or studies on pathogenesis in humans based on cohorts that were assembled based on clinical features. But given the heterogeneity underlying those cohorts, that may have hampered biomarker discovery and our understanding of pathogenesis. Now that we can identify people based on biology, we'll be able to investigate molecular changes and biomarkers within those groups that have a common biology. And in doing so, we can also identify people with different biologies, and that will inform our understanding of those diseases as well.

A second application that I think is really exciting and important, and probably has the most direct potential for translation to the clinic, is clinical trials. And there are many ways that the NSD-ISS can inform clinical trials. But for example, we might consider a trial that was enrolling individuals with NSD in stages one and two. So these are, we used to call them prodromal population, but now we'll be able to identify them and define them based on biology. For example, we might want to identify people with pathologic a-syn, that is, S-positive individuals, and test interventions to prevent dopaminergic dysfunction. So in other words, to study stage 1A individuals and prevent them from becoming stage B and beyond.

Or we may want to take someone who is stage 2B, for example, someone with REM sleep behavior disorder who is S-positive and D-positive, but has no functional impairment, and try to prevent or delay the onset of functional impairment. In other words, to delay progression to stage three and beyond. We used to call this phenoconversion.

You can see now how the terminology that the NSD-ISS provides us with allows for much clearer communication, and it's going to help facilitate the definition of criteria for clinical trial. And, which brings me to the third possible application, which is really defining stage-specific outcome measures. I alluded to this before, that different degrees of functional impairment, and how much one person versus another tolerates them or feels that they're impacting them day to day, will really vary. It's going to vary someone's super-healthy and functional. We may need an outcome measure that measures things like typing on a keyboard or threading a sewing needle, but in more advanced stages of the disease, we may need an

outcome measure that measures things like walking safely without an assistive device. There are many other potential applications of the NSD-ISS, but those are just a few.

**Marie:** That makes sense, and I think a clear benefit that comes out in terms of your response there is just moving towards developing more precision medicine approaches, therapies, and treatments for Parkinson's disease, and really facilitating or accelerating those clinical trials.

**Lana:** Absolutely. I think a very good example of that is, let's say, that there is a pharmaceutical agent being tested, which targets alpha-synuclein. Well, we would want to enroll people in that trial who have pathologic alpha-synuclein. On the other hand, if we're testing an agent against LRRK2 kinase activity, and we know that, as I previously mentioned, some individuals with LRRK2-associated Parkinsonism do not have NSD. They don't have abnormal alpha-synuclein.

We may assess for alpha-synuclein and then test the agent in those within and without S-positivity to really be able to understand how tailoring treatments to underlying biology modifies efficacy. While the NSD and NSD-ISS are really important advances in the field, it's important to keep in mind they're still in very early stages. They are not meant for clinical application at this time, though we hope that they will translate into the clinic eventually, but much work remains to be done before that's going to be possible. At present, we'll continue to diagnose Parkinson's disease and dementia with Lewy bodies based on clinical criteria. And biomarker assessments as put forth in the NSD and NSD-ISS may not be necessary or even appropriate in the clinical setting at this time.

**Marie:** That makes sense. I think an important callout there, Lana. And I know in the field, there have been substantial advances, particularly in recent years, and I think none of these advances comes out of nowhere. They build on previous successes in the science. So, can we talk next about just some of the tools, or resources, or collaborations that you think are moving the field forward and have maybe helped get us to this point?

**Lana:** I think prospective observational studies like PPMI, like the Parkinson's Progression Marker Initiative, have really helped inform the NSD and NSD-ISS, and similarly are going to help answer many key gaps remaining. And those, in turn, will inform the next versions of the NSD-ISS.

For example, the timeline of progression along the axis of biologic staging is unknown. We don't know, for example, of the maybe 5 to 10 percent of asymptomatic older individuals who are S-positive, D-negative, how many will actually go on to progress through the different stages? How many will become stage three, what we currently call clinically diagnosed Parkinson's? It's really

prospective observational studies like PPMI, which collect data with such rigor and multimodal data, deeply-phenotype participants that will allow us to answer those questions and in turn enable therapeutic development.

PPMI and similar studies, such as the DLB consortium and even data from clinical trials, will help us define specific functional anchors for stages three to six and possibly also help us develop new clinical rating scales and outcome measures to refine the definition of stages three to six. It was through the input of a variety of stakeholders in collaboration that this first version of the NSD and NSD-ISS was able to be put forth, and it is the inputs from a diverse group of individuals including scientists, regulatory agencies, and of course importantly the patient voice which will move the field forward, which will inform future versions of the NSD and NSD-ISS.

**Marie:** Well, Lana, I think that is so important. We appreciate you drawing our attention to some of these important resources, studies, and collaborations and I'd love to talk about the gaps, the unanswered questions. You hinted that there are still many. So, what do you see right now as some of the biggest unanswered questions or maybe areas of opportunity in this field of research?

**Lana:** I like that you called them areas of opportunity because I really believe that defining the NSD and NSD-ISS really helped point out to us the gaps in knowledge and provide us a framework within which to answer some really important questions. One really key gap that we need to fill relates to how to measure pathologic alpha-synuclein. At present, we need to obtain spinal fluid to test with the SAA. And while we know that that is possible and safe to do, having a more feasible and scalable measure for N-a-syn is necessary. For example, a blood test or a skin biopsy that could allow us to safely and quickly assess for S-positivity.

Along those lines, we also really need to understand the performance of these key biomarkers that define the biologic anchors in diverse samples, representative of the general population and also including research participants with a wider range of features and diagnoses including dementia with Lewy bodies, and in the real-world setting. Going back to my prior point, this will actually be enabled by scalable biomarkers that are more easily assessed than spinal fluid. I mentioned this before, but one of the key limitations in our field right now is a quantitative biomarker. We really need such a biomarker to measure not only disease onset and progression, but also response to therapy.

Finally, another key gap in knowledge that the NSD and NSD-ISS really highlighted for us are these individuals who carry a diagnosis of Parkinson's disease based on clinical features. And we know they have nigral degeneration

because studies like PPMI have allowed us to assess dopamine transporter SPECT scans in these individuals, but these individuals are S-negative.

So these are S-negative, D-positive, G-positive individuals, many of which have pathogenic variants and LRRK2 or PRKN. Understanding the biology of these individuals is really a very high priority, and the NSD and NSD-ISS allows us to do so. Finally, while the S, D, and G anchors are core components of the NSD and will likely remain so in the future, our goal is to incorporate biomarkers that reflect specific molecular changes that underlie the mechanisms of neurodegeneration. For example, biomarkers of mitochondrial or lysosomal function, biomarkers of inflammation, or other pathways that are NSD-specific and can be used to either define the disease or define progression along the stages.

**Marie:** Excellent. I think those are some amazing and exciting areas of active research right now in the field and I look forward to seeing progress in these areas in the future. But I'd love to talk about your work specifically, Lana. Can you tell our listeners how the work that you're doing is really bringing us closer to finding a cure for Parkinson's or contributing to improved therapies for people with the disease today?

**Lana:** So, the work that I'm doing with the NSD and NSD-ISS has many applications that are really going to advance the field. For example, they're going to allow us to identify individuals for clinical trials in the earliest stages of the disease. They may inform pharmaceutical development, outcome measure development, and really hopefully bring therapies to the clinic that will hopefully prevent or delay onset of neuronal synuclein diseases and improve the lives of people with neuronal synuclein disease.

**Marie:** Well, Lana, thank you so much for joining us today to talk more about this exciting development in the field and to share your insights.

**Lana:** Thank you for having me, Marie , and thank you to the listeners.

**Marie:** Well, Lana, I have truly enjoyed our conversation 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](http://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 and 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*.