Multi-Jurisdictional
Contractor Advisory Committee (CAC) Meeting

Meeting Date & Time: August 20, 2026, 2–4 pm CT
Topic: Biomarkers Utilized in the Diagnosis of Synucleinopathies-Transcription

Jo Gilbertson

Contributing CMDs include Dr. Dr. Rajadhyaksha from Noridian, Dr. Patrick Mann from Well Point Federal, Dr. Earl Berman from CGS, Dr. Miguel Brito from Palmetto, and Dr. Luke Barre from Noridian. We thank them all for their hard work.

I will be assisting the MAC to facilitate this meeting. We would like to thank our CAC panelists who have taken time out of their very busy day to join our meeting and to share their expertise on today's topic. We also welcome those attending in listening only mode and sharing interest on this topic. Dr. Rajadhyaksha will have some introductory remarks and then introduce our CAC panelists. Discussion questions will be asked of the CAC panelists.

Key Question surveys will be taken and some closing remarks.

All lines are muted except for the CAC panelists and the meeting facilitators. Chat feature within the meeting is to be used for technical issues only. Questions regarding the discussion topic will not receive a response. The meeting is being recorded as required by CMS. Recording, transcript, transcript, key questions, and bibliography will be available after the call.

By not speaking, we ask yourself to place yourself on mute to minimize your background noise. We have collected all conflicts of interest. If there are additional COIs, please indicate when Dr. Rajadhyaksha announces you. Throughout the call, we ask you to announce yourself prior to speaking so it is clear for the audience

and the recording who is providing each comment. Lastly, to ensure we are able to discuss each question today, we have set an estimated time frame for each topic of discussion. When nearing the end of that time, I will interject to communicate that we are low on time or someone else will.

I will now turn this meeting over to Dr. Rajadhyaksha.

Dr. Rajadhyaksha

Thank you all for joining our Contract Advisory Committee meeting. The meeting was implemented January 8th, 2019, and the purpose of this meeting is to discuss evidence or literature on a topic. The CAC member's role is advisory in nature and comments, opinions, or the evidence of literature is utilized by the contract medical directors to determine if a proposed LCD should be developed and supplements the Medicare administrative contractors' internal expertise as subject matter experts to ensure an unbiased and contemporary consideration of state-of-the-art technology and science.

Next slide, please.

So, we have certain CAC panelists here, which I would like to introduce, who we are very grateful for their expertise and participation in this. We have Dr. Michiko Bruno, Dr. Christine Dos Esper, Dr. Dr. Chu, Dr. Eric Wong, Dr. Eric Loo, Dr. Jessie Iregui. Next slide, please.

Dr. Katherine Coerver, Dr. Kyra O'Brien, Dr. Michael Okun, Dr. Lawrence VandeVrede. I hope I'm pronouncing your last name correctly. Dr. Shino Magaki, Dr. Soeren Mattke, and Mr. Victor Nussbaum as a patient advocate.

Next slide, please.

So at this point, while we go through the evidence and we have, we talk through it, we are going to start with some questions. And let me take, hand over the, I guess, microphone to Dr. Patrick Mann to start off with the first set of questions.

Thank you.

Dr. Mann

Thank you very much, Dr. Rajadhyaksha. So, we'll start off with question number one. We have various of the CAC members assigned to speak to these, but other CAC members are more than welcome and encouraged to speak up as they see

things that they would like to comment on. Our first question, set is addressed to **Dr. Mattke** and Dr. Wong. And it starts as, what kind of study design would you want to see for a biomarker evaluation in a neurodegenerative condition, and then what metrics would constitute statistical significance in the evaluation of diagnostic accuracy? So **Dr. Mattke** or Dr. Wong, the floor is yours.

Dr. Mattke

Hi, Soeren Mattke. Study design, you mean to determine the accuracy of a biomarker, correct?

Dr. Mann

Correct, the evaluation of the.

Dr. Mattke

the clinical validity.

Dr. Mann

Well

Dr. Mattke

I mean, in neurodegeneration, I think that should go against neuropathology. That is sort of the only gold standard that we have in other indications where the field has more evolved, like Alzheimer's. Sort of imaging parameters like amyloid PET can be used to evaluate blood tests. But since we are starting from scratch here, it would have to be neuropathology, in my opinion. I mean, statistical significance is probably not the right term, because there's no statistical test that says this accuracy is sufficient.

It would depend primarily also on context of use. Is it a triage test to rule out the presence of a pathology or confirmatory to rule in the pathology? And also, in which context is the test used, is it like initial evaluation in low suspect populations, say in primary care, or in sort of patients with a likely clinical condition is evaluated in specialty care. Because the positive predictive value and the negative predictive value will depend not just on the test, but also on the pre-test probability of the presence of the condition, and that tends to be considerably higher once you go down to specialty care.

Dr. Mann

Great, thank you. Well, go ahead, please. (talking over each other)

Dr. Mattke

Before I give the numbers around, I want to wait for my colleague to weigh in on the criteria.

Dr. Wong

Okay, this is Dr. Eric Wong. I can offer my comment. Can everyone hear me okay?

Dr. Mann Yes, yes, we can hear you just fine, Dr. Wong.

Dr. Mattke

Yeah.

Dr. Wong,

Okay, so I think we have to back up a little bit when we talk about biomarkers. So my understanding of biomarkers is that there are three types of biomarkers. There is the predictive biomarker, which will predict whether or not patient would respond to treatment. So we are talking about disease modifying therapies, which we do not have for synucleinopathies. So for this type of biomarker, we need survival, overall survival or progression-free survival. So, but we are not talking about that.

But in case, if we have a disease modifying therapy, that's what, that the kind of metrics that we need to use for a predictive biomarker. The second type of biomarker is a prognostic biomarker, whether or not a patient is going to live longer or shorter.

Whether or not the patients will progress sooner or later. So, that, the metrics for measuring a prognostic biomarker is also a time-based metrics. So, but we don't, we, we probably at the current time, I don't think there is a very, very clear-cut prognostic biomarkers for synucleinopathies. So I think what Dr. Mattke was referring to was a diagnostic biomarker.

That's the third category. And I totally agree with him that the gold standard is compared to pathology. Okay. So that's postmortem. It may not be realistic because we have to wait a long time. Patients may survive 2 decades, 3 decades, 4 decades.

And so that means the field will move very, very, very slowly with time. So, however, we can have a diagnostic biomarkers based on well-accepted criteria, in the movement disorder field, synucleinopathy, clinical synucleinopathy field. So for example, using the Movement Disorder Society Parkinson's Scale, there are these scores that one, that one can use in terms of diagnosis, so, so to do that, I would place these patients into three separate categories, positive, negative, and indeterminate. Okay? So, and just think about this box that you have.

true positive, positive ones, and also according to the biomarker, positive, negative, indeterminate, and then, in the, in your gold standard, positive, negative, and in an indeterminate, you have a three by three box. And then you can do a Chi-Square test and then test for, test for the significance. So, so that's how I would think about it.

Dr. Mann

Thank you very much. Dr. Mattke, did you have a rejoinder?

Dr. Mattke

Yeah, I think that I agree with the approach. I just think there's a difference between statistical and clinical significance when you talk about biomarkers, right? Because yes, you may have like a positive test, like a hypothesis test, but unless you reach a certain level of accuracy, like sensitivity and specificity, that doesn't tell you much, right? Partly because the indeterminate category could be quite large, right? You could massage your cut-offs so that you get in the clearly determined positives and negatives, a fairly high sensitivity and specificity. But if half of the patients cannot

be sorted, that doesn't help you. So I'm a little skeptical about the statistical significance. I'd rather go by cutoffs that sort of make clinical sense.

Dr. Mann

Thank you. I see that Dr. Okun has his hand raised. Go ahead, Dr. Okun.

Dr. Okun

Just a really quick, just want to add a couple points on here.

Dr. Mann

Please.

Dr. Okun

Independent validation of a cohort, you know, with as much longitudinal follow-up as possible, and that takes time to get longitudinal follow-up and neuropathologic confirmation when it's available. Okay, so, I think we should be reasonable, you know, in thinking through, you know, like what we can do for any biomarker. And I agree there are three different types of biomarkers in all of the all of the discussion that's going on. The result changing a clinical decision is important. And remember that performance of biomarkers varies on what the phenotype looks like, what the genotype might be, what a comparator group is, what the assay is, and what the disease stage is. And these are things that we would consider for peer review in a journal article, particularly independent validation, because you aren't going to get pathologic follow-up on biomarkers, you know, a lot of it immediately that comes later. So I just want to add that to the discussion.

Dr. Mann

I really appreciate it. Thank you. I'm going to move on to the next question. I think that some of these questions will intersect with each other. So let's keep the moving and then we can revisit some of these things as well as we go. The next question is, next slide, oh, perfect, already. So Dr. Mattke again and I, Dr. Jessica, would you please help me pronounce your last name so I don't destroy it?

Dr. Iregui

Sure, it's Iregui.

Dr. Mann

Iregui.

Dr. Iregui

Yes, thank you.

Dr. Mann

Okay, Dr. Iregui, what are the statistical standards?

that are acceptable given that these are rare disorders.

Dr. Iregui

Yeah, I'd like to add to what Dr. Mattke was just saying,

Dr. Mann

Please.

Dr. Iregui

and I wouldn't make statistical significance the primary criterion. A biomarker can produce a highly significant p-value and still have insufficient clinical utility or poor generalizability. But in rare diseases, a clinically important effect may not reach conventional statistical significance because the study is underpowered. So my first thought would be to prioritize effect estimates, confidence intervals, diagnostic discrimination, and as Dr. Mattke recommended, clinical relevance.

Dr. Mann

Thank you.

Dr. Mattke?

Dr. Mattke

Yeah, I mean, are these synucleinopathies that rare, right? I mean, Parkinson's is not that uncommon. It's not like Alzheimer's disease, but rare disease I would think like it's more like really rare things.

Dr. Mann

Yeah, no, that's fair. I would say that subsets of synucleopathies could be considered more uncommon, but I guess we're thinking in terms of that you would have a large population which would not end up with, you know, it's the, as you were talking about earlier, your pre-test likelihoods.

Dr. Mattke

Right. I mean, the sensitivity and specificity, of course, is not affected by pre-test probability. It's the PPV and the NPV.

Dr. Mann

Yes.

Dr. Mattke

And so, yes, that is going to be tricky if it's really rare or one of the rare sub forms. But I think cutoffs for sensitivity, specificity, we can still say, well, for clinical decision making, either rule out or rule in, we can set thresholds based on consensus. There's probably no mathematical way to arrive in my mind at a threshold.

Dr. Mann

Thank you. I see that we have a hand from Dr. O'Brien. Dr. O'Brien, please.

Dr. O'Brien

I agree with Dr. Mattke. I would just say that we, you know, interpret these tests in the context of the clinical picture and other things. So I'd don't know that the disease being rare should really impact our use of these things. And it's really like the genetic subtypes where we might worry about that or MSA. But like Parkinson's is like the second most common neurodegenerative disorder. Lewy body is more common. So

Dr. Mann

Yes, thank you very much for clarifying that. I appreciate that. Let's go to the next slide then. I think we've already touched on this one, Dr. Mattke. What are the gold standards that should be used with these biomarkers, particularly the diagnostic biomarkers for synucleopathies? Is there anything beyond what you were saying, the gold standard being neuropathology, is there anything beyond that that you would like to say? And if anyone else would like to weigh in, please do.

Dr. Mattke

I made my case.

Dr. Mann

Yeah, I figured you did. I just wanted to make sure. As I said, I think that some of the questions intersect. Anyone else? Oh, go ahead, Dr. Okun.

Dr. Okun

Yeah, thank you. I just want to say again that autopsy is unavailable during a period when a biomarker is clinically useful. I just want to go on record saying that, because I think, and then avoiding, you know, circular validation, which is your biomarker is judged against a diagnosis that was influenced by the biomarker. Right? So that's why you need independent verification. So of course, neuropathology is a gold standard, but it's not really a gold standard in real time that you can use on something like this. So we just have to be careful of that. Yeah.

Dr. Mann

Thank you very much. Dr. Wong.

Dr. Wong

Yes, thank you. I just want to make sure that this is on record that, yes, there's a clinical phenotype, but there's also a proteotype, right? Because there are certain

other neurodegenerative diseases that may look like Parkinson's disease or

or some synucleopathies. And this is where biomarkers is going to come in to help distinguish, to put it into different bins. So if I may use the word proteotype, I mean, I'm inventing a word here. But that's the fundamental issue. There are different protein aggregates that are giving rise to different phenotypes. So I just want to put it out there.

Dr. Mann

No, I really appreciate that, given the fact that there are studies showing that the aggregates form different fibril structures and the like, and also appear in different parts of the brain depending on what disease or condition we are talking about.

I see the next hand up is, sorry, I'm just letting the mouse hover over it. Dr. Beach.

I'm not sure Dr. Beach is a presenter. I don't believe so.

Not sure though. It shows no camera, no microphone. Please correct me if I'm wrong. Jo? Is Dr. Beach in the audience?

Okay, I will for now assume that's true. It looks like our next hand up is Dr. Mattke. Please.

Dr. Mattke

Yeah, just one point on the impossibility of neuropathology confirmation. The only neurologic disease I know is Alzheimer's disease because I'm a cardiologist by training, so I'm pretty clueless here. But in Alzheimer's, much of the validation was actually not done contemporaneously, but with donated brains and frozen samples. So things that were old and put aside in the hope that these biomarkers might emerge. And I don't know whether any of these options exist for synucleopathies, but that would allow to do actually a true gold standard, because I agree with Dr. Wong that the clinical picture can be misleading in neurodegeneration.

Dr. Mann

Right. Thank you.

And then, finally, before we move to our next question, Dr. Iregui.

Dr. Iregui

Yeah, I just wanted to comment on the few comments that were made about Parkinson's being

relatively common and some of these being more rare. But I think it's important to remember that a test like this would perform relatively well against healthy controls versus Parkinson's or Lewy bodies. But when you're comparing

Parkinson's or MSA or DLB, PSP, any other atypical Parkinsonism's, many of those people are misdiagnosed as something like Parkinson's about 30% of the time before they reach their final diagnosis of that rare disease. So considering that there are some relevant disease mimics, that would be important to put greater weight on some of those studies for when you're comparing to healthy controls versus similar disease presentations.

Dr. Mann

A great point. Thank you very much.

Next slide, please.

So, question #4, this would be for Dr. Wong and Dr. Iregui: What demographics should be considered in supporting studies? We've already started talking about this with Doctor Iregui. So, if only a subset of represented population has been included in the validation, how do we address this demographic evidence gap and whether coverage will be restricted pending more diverse validation studies. So, please go ahead. Dr. Wong, I see you talking, but you're muted. You might need to unmute before we can hear you.

Dr. Wong

Yes, I can go.

Dr. Mann

Thank you.

Dr. Wong

So, so, so this is in an older population. However, I just want to add that if there is a family history of Parkinson's disease, if there is a like relatives with Parkinson's disease, I think you should factor into the demographics because some synucleopathies, at least based on the MPTP data and also the genotype, you know, there is an interplay between environment and genetics. Okay, so I think family history should be there. I think there are certain telltale neurological signs, like RBD, anosmia, smell problem, constipation. So this is a battery of histories that a neurologist needs to get to see whether or not there's more or less likelihood. If every box doesn't check off, then I think we can go to, we probably would not order the biomarker. However, at what level should we order it? Where the cutoff is? That's where I'm not clear. Okay, so there's a battery of clinical symptoms, demographic data I think it is where the clinical studies will need to address in terms of where to draw the line.

Dr. Mann

Thank you. And since this is yours and Dr. Iregui question, I'm going to go straight to Dr. Iregui. And then I see Dr. O'Brien and Dr. Bruno, I'll have you guys go next. So Dr. Iregui, please go ahead.

Dr. Iregui

Sure, yeah, I agree with Dr. Wong. I think that conventional demographic variables are important for equity and generalizability, but genotype can have a direct biological relationship with the disease and the biomarker. So we have evidence that LRRK2 associated disease can have different alpha-synuclein SAA positivity than sporadic disease. So I would want to see studies that characterize relevant genetic subgroups when feasible versus your conventional demographics.

Dr. Mann

Thank you. Dr. O'Brien, please.

Dr. O'Brien

Just borrowing from the Alzheimer's literature here, but I think it's also important to consider medical comorbidities, so we definitely need studies looking at how these tests perform in people with CKD, obesity, which probably, I would guess, affect blood biomarkers more than CSF. But it's still something that needs to be looked at.

Dr. Mann

Thank you. Dr. Bruno.

Dr. Bruno

Thank you. I really appreciate having this question in the first place. I just wanted to go on records that I represent Hawaii where the race and demographic is very diverse with Native Hawaiian Pacific Islanders population as well as Asian Americans that may have a very different, not very, but some difference in clinical and genetic phenotype, as well as risk factors. For example, PINK1 gene, which is a rare genetic variant in general, but common in our population and present younger. So there are other, this is more not like, I guess, a suggestion, but just hope that more inclusive studies in the future will include more diverse population. Thank you.

Dr. Mann

Thank you.

Dr. Coerver.

Dr. Coerver

Yes, I just, I wanted to echo some of those statements which have already been made. I am more, you know, Alzheimer's disease than synucleinopathies, but I do know them too. But this is an ongoing issue and I agree completely that the problem is that we do not have enough representation of different ethnic groups and that we need to try to increase our ability to recruit individuals. So we do understand how these diseases present in every person in the population and not just a select subset. But also I agree that the comorbidities, especially with the plasma biomarkers and Alzheimer's disease can be a very large problem. So this has to be looked at in a variety of people with a variety of different medical conditions.

Dr. Mann

Thank you very much. We'll take two more for this question, then we'll move on. I see Dr. Mattke is next.

Dr. Mattke

Yeah, I completely agree on the comorbidity questions. I wanted to qualify a little bit the question of representativeness. I think the, the relationship between the underlying biology and the positivity, negativity of a test, in particular a blood test, is probably not determined by racial, ethnical, ethnical factors. We had a lot of these debates in Alzheimer's disease where of blacks and Hispanics with similar clinical presentation were less likely to be positive on these blood tests. And some people concluded the blood test doesn't work in these minorities, which is incorrect. They just have a different clinical picture and are thus less likely to have a positive blood test and the blood test works. So I think, we need to be careful to not conflate test performance with diversity of clinical presentation and potential differentials by race and ethnicity, how the patient looks, but keep biology as biology.

Dr. Mann

Thank you.

And then finally, Dr. oh, sorry.

Dr. Mann

Sorry, say that again, Jo.

Jo Gilbertson

We're running out of time.

Dr. Mann

I hear you, so let me let Dr. Iregui get a comment in, and then we will move to the last question of this set.

Dr. Iregui

Yeah, thank you. Dr. Mattke actually said exactly what I was going to say, that I think there's an important distinction between a lack of evidence and evidence that the test performs differently based on demographics. But Dr. Mattke beat me to it.

Dr. Mann

Great. Thank you very much, both. Let's go to the last slide of this section.

So, this is for Dr. Wong and Dr. Iregui again. When evaluating evidence for outcomes based on

diagnosing a neurodegenerative disease with no disease modifying treatment, what metrics do you consider relevant to measure?

Dr. Wong

Okay, well, I can go first. This is a very difficult question, and I come to the conclusion that, I cannot identify in metrics to measure outcome when there's no disease modifying treatment. Now, I have to qualify for that because this is a chicken and egg issue. Without A biomarker, you're not going to get disease modifying treatment. So either one has to come out first, okay? So, I think it will be, in my opinion, just for surveying the literature, it's easier to get a biomarker out first, to get a test out first, and then disease modifying treatment, and then investigators can go back to improve the biomarkers and go through a number of iterations. So that's my comment.

Dr. Mann

Thank you.

Thank you very much.

Dr. Mann

Dr. Iregui.

Dr. Iregui

Yeah, my first thought is I agree that it's chicken and egg situation, but one of the most important outcomes may actually be avoiding inappropriate treatment. So we saw in the literature that in Lewy body disease, neuroleptic sensitivity can be severe. So if a biomarker helps clinicians recognize LVD and potentially avoid harmful medications. I would consider that a meaningful clinical outcome, even in the absence of disease modification.

Dr. Mann

Thank you very much. And then finally, we'll do one more with Dr. Bruno to keep us on time. Go ahead, Dr. Bruno.

If you're talking Dr. Bruno, you're on mute.

Dr. Bruno

Oh, sorry about that. Yes, I agree with Jessie's point. She beat me on the Lewy body point. But change in management in general, change in medication, as well as complication like fall planning, also patient reported outcomes may be important in quality of life, which there is not as much study. But, you know, even if there is, these are like hard scientific numerical values, but there might be other category, anticipatory guidance type of thing, which I'm not sure how to design the study, but just wanted to comment that.

Dr. Mann

Thank you very much.

All right, so this completes this section of questions. I would like to reintroduce Dr. Rajadhyaksha and please take over. Thank you.

Dr. Rajadhyaksha

Thank you. Thank you, Dr. Mann. So, I'm going to start, switch gears a little bit, and this question, I guess, is to Dr. Please help me pronounce your last name, Dr. VandeVrede.

Dr. VandeVrede

That's pretty good. Yeah, it's American pronunciation of a Dutch name, so VandeVrede here, just Ren is fine.

Dr. Rajadhyaksha

Thank you. All right. So let me start with you. Synucleinopathies may present in a wide variety of ways. What are some of the most common presentations you do see in your practice?

Dr. VandeVrede

Yeah, so this is a good question, kind of fundamental. We kind of alluded to it's an integrated diagnosis, a clinical pathologic diagnosis, because synuclein refers to the protein aggregation as Lewy bodies or MSA, but really what we're observing in the clinic is the clinical syndrome. So the most common clinical syndrome that you see is Parkinson's disease, but there are other presentations of synuclein diseases like dementia with Lewy body or Shy-Drager or pure

autonomic failure, and it can also occur as a co-pathology with Alzheimer's disease, that's actually quite common. About 40% of cases of Alzheimer's have comorbid synuclein disease. But it begins with the symptoms. All the syndromes have since sort of core features associated with them, and there are diagnostic criteria for each of these clinical syndromes that we diagnose. Very common to have motor, cognitive, especially autonomic behavioral features. And in some ways, those presenting symptoms are who drives the management and evaluation. So if it's primarily movement, they're seen by movement. If it's cognitive behavioral, perhaps they're seen by me. Sleep specialists might see them for the REM behavior disorder initially, but it's usually driven by the symptoms. But then the syndrome, is identified and then that's used to predict the etiology of the underlying protein, which is often synuclein and diseases with strong associations like Parkinson's disease, where there's a very strong association with synuclein and the classic presentation of it. But the best clinical diagnosis is only right about 80% of the time. This is true in Alzheimer's disease as well, where we had a typical amnestic presentation that was usually associated with Alzheimer's disease, but there are mimics that are important. I think some of them were mentioned. The evaluation of the patient starts with taking a history and doing a neurologic examination. This is usually a neurologist. Ancillary testing, I think MRI is pretty typical. There are the biomarkers, I think, that are increasingly being used, though more in the context of research and clinical trials.

The criteria, I think I mentioned that there's individual criteria for the clinical syndromes. There are also overarching criteria that were recently proposed, like synergy and the integrated synuclein staging systems, which start with the diagnosis of synuclein. Those, I think, are really mostly used in research, but they are a different sort of criteria for understanding and evaluating the diseases. But the management is typically the same people that evaluate them, though an ancillary care team is often used, like including PT, OT, and other specialists, but the initial diagnosis is usually done by neurologist, a sub-specialist if available. But Parkinson's disease is common enough that even PCPs, certainly primary care, can recognize it and consider treatment options.

Dr. Rajadhyaksha

So in a follow up to that question, what do you do with non-specific symptoms that may come? You know, something mentioned is REM sleep disturbance and things that the way you don't really know what's going on and you're trying to figure it out.

Dr. VandeVrede

Oh, sure. Well, I mean, I presented sort of that ideal academic framework where everything was easy and fell neatly within the diagnostic criteria. The reality of it is that the patient can often present with multiple co-pathologies, have obscuring medical conditions, and might not fit this neatly. And this is where sort of the Bayesian integration happens at the clinical level as you kind of take in the entire case and try to come up with the best fit, and I think often if it's a pretty clear, sort of maybe more vanilla presentation, especially for Parkinson's disease, you know, asymmetric tremor, instability and rigidity, responsive to Sinemet, it's pretty straightforward. I think it's often in those atypical cases, where it becomes more challenging, where there's incomplete fulfillment of the diagnostic criteria. Maybe you want some early diagnosis and early identification. And then there's all the atypical presentations, the things that I actually think a lot about. And dementia with Lewy body is kind of tough because the core clinical criteria aren't very good.

The penetrance of the symptoms as a result of the Lewy body is sort of incomplete and patients often don't meet the full criteria until relatively late in the disease. So I think in some ways your question is just highlighting where biomarkers can be useful to increase that diagnostic certainty when the clinical presentation is not as clear.

Dr. Rajadhyaksha

Thank you. And in follow up to that, Dr. Okun, you know, we alluded, I mean, Dr. VandeVrede alluded to the criteria. So what do you use, you know, when you have these wide variety of symptoms? How do you, you know, when do you know which criteria? Because you have criteria for different synucleinopathies, but

You know, as Dr. VandeVrede said, there are so many different presentations. How do you try to see what box they fit into?

Dr. Okun

Yeah, so I just want to echo, I agree with 100% of what was said for time. I would say Movement Disorder Society criteria is what's most commonly used for Parkinson's disease. Some people still use the UK Brain Bank criteria. There's consensus criteria published by the Movement Disorder Society and other groups. So the MDS is probably the one that's used the most for DLB, for MSA. And then folks, as was mentioned, are going to add, you know, ancillary things to help make

their diagnosis, imaging, autonomic testing, sleep studies. They may use genetics, they may use synuclein biomarkers, but all in an effort to answer a specific clinical question.

And then to answer the last part of this question, these patients are typically managed by neurologists, not always, because there's a shortage of neurologists. They do better than data suggests when they see a neurologist at least once a year based on Medicare data and Allison Willison, some great studies from Penn. Gerontologists see them, internists see them. Ideally, movement disorder specialists would see them. There aren't there's a shortage of them, cognitive specialists, as was mentioned, sometimes autonomic and, you know, in the ideal world, a multidisciplinary team. Longitudinal follow-up is what is going to really separate whether you have these diagnoses correct, and you'll get more correct over time.

Dr. Rajadhyaksha

Thank you so much for that. Dr., sorry, Victor Nussbaum, do you have a question?

Or a statement, you're on mute.

Still, yeah.

Mr. Nussbaum

Yeah, and speaking about the diagnosis being clear cut, I've met in the past 4 1/2 years, hundreds of Parkinson's diagnosed people where their symptoms start years before, and they go through the PCP, the back surgeon, you know, a number of specialists. And sure, it's clear, give him a Sinemet, three years into it and their tremors stop, or they haven't smelled anything for 20 years. So shortening that road prior to getting or getting to the movement disorder specialist is an important piece of this. It's not quite as clear cut as what you were talking about.

Dr. Rajadhyaksha

Thank you very much. We can go to the next question.

Sorry, I put myself on mute. Dr. Chu, this question for you. What type of imaging is currently available to evaluate suspected synucleinopathies? What are performance characteristics of these imaging modalities, including false positive? I guess, trying to figure out what does it capture, what doesn't it capture, and to see where these biomarkers would fit in into this spectrum of workflow. Thank you.

Dr. Chu

Thank you. No, thank you for the opportunity to speak here. So I'll give a brief introductory statement for myself in terms of my background and sort of how I'm answering this question. So currently I'm practicing in an academic setting at the University of Washington as a neuroradiologist, but after having practiced in private practice in the community for about 10, 15 years. So the patients usually that are referred to us for imaging are those that it's more to confirm a diagnosis of a particular movement disorder or particular neurodegenerative disorder or to rule out

other potential clinic entities that can mimic it. So for example, PSP or progressive supranuclear palsy. So there are some of these disorders have particular volume loss in particular parts of the brain. Some have particular imaging findings. But most of the time it is to look for or exclude the other disorders that may mimic clinically what's going on. There are some interesting things that are occurring now with

higher field magnets, but really right now, because in clinical practice, it's mostly 1.5 Tesla and 3 Tesla units. So for example, for Parkinson's disease, there have been signs described in the substantia nigra, but these are more for research units, I would say. In terms of false positive and false negative, I think, I don't think of imaging as a test that sort of confirm a particular disorder, but it can help in terms of excluding other clinical entities that may be, that may mimic it.

Dr. Rajadhyaksha

Thank you. So as a follow up, I think we disagree segway into the next question.

You know, we addressed the different co-pathologies. You know, you're trying to figure out, is this a combination of Alzheimer's diffuse Lewy body or is this MSA? Wherever we are, especially with Parkinson's and these other synucleinopathies, there are so many different co-pathologies. Where do you see in your experience that the percentage of cases you find them as indeterminate, you still can't figure out what's going on?

Dr. Chu

That's a good question.

You know, a lot of the time we aren't here to necessarily confirm a particular diagnosis, but to rule out other ones. I think in terms of the indeterminates.

I would say many of my tests are indeterminate in that I can't say confirm a particular diagnosis, for example, of Parkinson's disease. I think that's the best way I could answer it. Sometimes there may be another clinical entity that may mimic it and that we can actually see a particular spectrum of imaging findings that we can use for

to confirm a particular disorder, but that's not often the case. So in terms of ballpark figure, I think we would confirm or have supporting imaging findings maybe about 60% of the time, 70% of the time, but that's basically just on my experience.

Dr. Rajadhyaksha

Thank you. That's really helpful. Dr. O'Brien.

Dr. O'Brien

So, you know, we use MRI a lot to rule out vascular disease as a cause of Parkinsonism. You know, we can see findings of MSA sometimes, PSP sometimes, but often it is not that helpful metabolic PET we use often to look for hypometabolism associated with Lewy body disease, probably in 20% of cases, especially if it's earlier on in the disease course where they don't have as many features of Lewy body, it can, you know, be normal or unremarkable or show sort of a non-specific pattern of hypometabolism. So that's probably the figure I would give. Same with DAT scans. Like if a patient has Parkinsonism, we might get a DAT scan, but you know, that can be negative again in like 15, 25% of cases, I would say.

And we're still left with someone who has clear Parkinsonism and imaging studies that don't help us.

Dr. Rajadhyaksha

Okay, thank you so much. Dr. Wong.

Dr. Wong

Yes, thank you. I just want to make a comment that some synucleinopathies, the way that I understand it is that it is distributed in both the central nervous system and the peripheral nervous system. And I have ordered tests by skin punch biopsy to look for synuclein phosphorylated synuclein aggregates as well as DAT scan. And also there's the seed amplification assay that is coming into the clinical pick, the clinical diagnostics right now. So I don't see these tests as mutually exclusive. One can use one test to diagnose Parkinson's disease or a specific type of some synucleinopathies. I see them as a complementary test, because these protein aggregates are distributed in both central nervous system and peripheral nervous system. Thank you.

Dr. Rajadhyaksha

Thank you. Dr. Okun.

Dr. Okun

Yes, I just wanted to add briefly to this discussion that when we think about, you know, these imaging cases, it's important to integrate your history, your exam, and, you know, and you have to look at this not in isolation. And I will also

mentioned that there's an FDA class 2 approval now for MRI, you know, if you're symptomatic with Parkinsonian symptoms for telling the difference between Parkinson PSP and MSA. And so it's evolving but should not be used in isolation.

Dr. Rajadhyaksha

Thank you so much. We can go to the next slide.

Okay, the question is, how are indeterminate cases managed? We have symptoms, we have, you know, but we are not completely sure, right? So, I guess this question is for Dr. Coerver. How would you manage indeterminate cases?

And which specialty would follow them? And then I would let Dr. Bruno also opine. Thank you.

Dr. Coerver

Unfortunately, there's a decent number of indeterminate cases that come out, as we've discussed,

that sometimes the clinical presentation is different from what you see with the biomarkers or you don't have the biomarker confirmation. And the way that I would attack that particular problem is you treat them symptomatically. You try to address any underlying symptoms that they have, sometimes that can actually help you to determine a little bit better what the underlying problem might be. And as to what specialty would follow them, that, again, would depend if what their primary symptom is and so who they started with and then who feels comfortable actually treating those particular symptoms. We've discussed about how, you know, behavioral sleep disorder and how, you know, that can be, you know, one of the symptoms and would that be followed more so by a sleep specialist? If you have somebody who's comfortable with the treatment options for it, that might be a neurologist who is following it. If you have somebody who primarily has a movement disorder who has problems with balance and tremor, that might be a movement disorder specialist. So, I think it depends on the symptoms themselves. My area, I'm cognition, and so I end up having people that have a variety of symptoms that don't fit into one box. I'm the one that manages them but sends them out to other specialties as needed.

Dr. Rajadhyaksha

Thank you so much, Dr. Bruno.

Dr. Bruno

Yes, thank you so much. Yes, I completely agree that this is 1 toolbox, as in addition to the clinical evaluation of history, examination, and other imaging. So we synthesize them and with the co-pathology and comorbidity, sometimes it does not fit into one box, especially early in the diagnostic process. So I would divide certain clinical specific scenario. We may use the biomarkers, for example, if they have clinically classic PD and the synuclein biomarkers negative, then I think that is still clinical Parkinson's, possibly without synuclein pathology. So we would treat them as Parkinson's symptomatically.

And then if we are suspecting is this even neurodegenerative or there are other etiology like vascular or drug induced, or then we, if they have positive, then we may have to follow them more closely for the progression and possibility of neurodegenerative disease. And I think the challenging part, and then even in possible MSA situations, cerebellar syndrome, that's kind of another bucket, another category that kind of calls it to attention as well as other atypical Parkinsonian cases, which is slightly different from the Parkinson question. So I think all in all, if there's a discordant, they would warrant follow up, but with, as we discussed, which specialty follows is a kind of actually a challenging question because we do need to follow them, but we also have limited resource, so it depends on their, I guess, most significant symptom, whether it's cognitive or movement.

Dr. Rajadhyaksha

Much. Thank you so much. We can move on to the next slide. I do know that there's less time available. So I'm going to combine a couple of questions to gather here. And I'll start with you, Dr. Okun. The definition of synucleopathies is complex. There are multiple diseases, as we know, multiple symptoms.

Would a biomarker be needed to diagnose, needing to diagnose synucleinopathies need to encompass all of them? And really, how would you see this being involved in the evaluation and management of patients suggested with synucleinopathies? I'll let you come in and then Dr. Loo, I'll ask you a follow up question.

Dr. Okun

Yeah, I'll try to be pithy, as they say in Latin, for time. I wouldn't expect one biomarker to perform equally well across every synucleinopathy, so I'd be cautious about requiring that before considering any test as useful or stamping it as useful. They share biology, synuclein biology, as has been mentioned many times now on this meeting, but their location, the burden, cell types, possibility of confirmational strain of synuclein, they all differ across PD, DLB, and MSA and any other related syndromes. I would say in general; the literature shows that performance can be excellent in things like typical Lewy body Parkinson disease, but

it's lower in genetic subgroups, much lower, like if you have an LRRK2 mutation. And if you have multiple system atrophy, it might require an assay that's capable of recognizing different synuclein signatures. So a biomarker in general,

would be good for identifying underlying synuclein pathology without being able, by itself, to determine an exact clinical syndrome. And I think that's sort of really important to think about. And so for me, the right framework is indication specific validation rather than expecting a single universal, you know, synucleinopathy test to answer every diagnostic question.

Dr. Rajadhyaksha

Thank you. So you would expect something to be validated for disease to see where the utility and the validity would be.

Dr. Okun

Yes.

Dr. Rajadhyaksha

Okay. Thank you. And so as a follow up of that question, Dr. Loo, what would you like to see in such a biomarker?

Dr. Rajadhyaksha

As far as.

Dr. Loo

Oh yeah.

So, as he was saying, I don't think that there's a single biomarker that would be helpful to identify all of the synucleinopathies. You know, the alpha-synuclein does seem to be fairly robust in CSF. There was a clinical chemistry study a couple of years ago that showed that, you know, if you had CSF, you could undergo several freeze-thaw cycles and stuff and not affect the kinetics of the seed amplification assays. You know, so it seems to be okay, as long as the biomarker can help to differentiate things. The seed amplification assays, the kinetic curves apparently can help to differentiate between some of the subtypes of the synucleinopathies, but again, you know, you'd have to have a lot of standardization between laboratories for the assays, because there are things that can alter the kinetic curves, like, if there is blood contamination, if you have presence or absence of glass feeds, the pH that the thing is being run at. So there would need to be standardization for the assay, you know, people would need to be trained to be able to interpret the thing, of course, you know. Determining a tissue type to perform the study on would also be good.

It would be problematic for a clinical laboratory, for example, to need to do a validation on an assay when the sample types are extremely scarce or things of that sort, but again, like a single biomarker probably would not be entirely helpful. There are other biomarkers that you would probably want to assess in addition to like alpha-synuclein, you know, at the same time somebody might have coexisting Alzheimer disease, so you might want to look at, you know, beta amyloid and tau and that kind of, and stuff for folks with the atypical Parkinsonism versus normal Parkinson disease, you might want to look at neurofilament light chain. So, I guess it's kind of, it's dependent, I guess.

Dr. Rajadhyaksha

Perfect. Thank you so much. So, I'm going to get, give the next set of questions to Dr. Brito to take, to talk more about biomarkers. Thank you.

Dr. Brito

Thank you Aparna. So, Dr. Loo, you sort of stole some of the thunder of mine question here. So, we're talking about the performance characteristics of these tests and are they considered sufficient to make a diagnosis of synucleopathies? I think, is this test interpretation straightforward? What are the things to keep in mind when assessing the test report and realizing that, you know, this disease can either be glial or neuronal? How do these two tissue types, where a lot of the focus has been, which one of them should be used or should they be both used? Or is there one that's superior to the other? And of course, depending on the type.

Now, Dr. Loo you start.

Dr. Loo

Come, come again, sorry.

Dr. Brito

No, I said you can start your discussion on this. We're basically trying to understand which one of these tests is superior or are they for specific types? In other words, should only CSF be used for certain types of synucleopathies? Should skin be used for others? Or should this be a grouping of both of these, depending on what factors? And those are the factors that we're trying to find out.

Dr. Loo

I see. Well, it does seem like CSF has been the most robustly studied substrate for the diagnosis of the synucleinopathies using the seed amplification assays. You know, the sample collection needs to be very clean though, apparently a very little amount of blood contamination, like 0.01%, can drastically affect the kinetics because there's, you know, red blood cell contribution of that into of, of alpha-synuclein into the substrate.

Let's see. As for skin, I know that there have been a number of studies using skin, submandibular gland biopsies, nasal swabs, and that type of thing. But the, I guess, strength, for the assays isn't quite as robust as it is on the CSF.

Dr. Brito

Dr. Magaki, do you have anything to add?

Dr. Magaki

Hi, so I agree completely with what Dr. Loo has said. So, Dr. Tom Beach had recently published some studies comparing CSF seed amplification assays with skin, and as Dr. Loo mentioned, CSF seems to outperform the skin, although there's high sensitivity and specificity for detecting late stages of Lewy body disease. It's less so in earlier stages of the disease. Also, the seed amplification assays have been validated against autopsy studies. However, there's an immunofluorescence test on thick skin sections that have not been validated. So there's different types and certain ones seem to do better than others. And CSF, for example, CSF seed amplification assays.

Dr. Brito

Dr. Esper, you have a comment?

Dr. Esper

Yeah, so I think we all agree that the CSF is a more superior study. But something to keep in mind if we're thinking about this to be used universally in the clinical setting, there are a lot of limitations with performing these types of studies.

And that's why a lot of people favor the skin tests. But in the setting of using the skin test, we do need to be careful about the limitations that we discussed and broadly using the skin test in that type of setting.

Dr. Brito

Dr. Okun, you have a comment?

Dr. Okun

Yeah, I want to agree with what Christine said, just add one quick point, which is remember the clinical matters and the smell, you know, like if you add smell to it, you know, if they have smell dysfunction, not everybody has it, then your specificity jumps to like 96% from like 87 or 88% in that original study. So just keep that in mind.

Dr. Brito

Thank you.

Dr. Loo

Oh, I guess one quick other thing, I guess the biological location of where the protein is misfolding, you know, varies across the disease subtypes, so CSF might, the sensitivity of detection would drop if it's like present in the amygdala or in the limbic system, compared to, you know, other locations.

Dr. Brito

OK, thank you for that. The next question.

So, this is for Dr. VandeVrede and Dr. Bruno. The relationship between biomarker positivity and clinical diagnosis requires clarification, particularly in discordant cases. How is this information derived from these tests integrated in determining the clinical diagnosis of Alpha synucleopathies.

Dr. VandeVrede

I'll start. So it's integrated in the way we were talking about before. I think genetics was just alluded to is that you interpret it in the context of the clinical case and the presentation. You take

into account what your pretest probability was, the relative prevalence in that population, the presentation, the specific context of use, the

test performance data, the validation data, all of those things are part of this Bayesian calculation that happens in the mind of a clinician when they're interpreting all of the relevant data to come up with a clinical diagnosis. A biomarker in and of itself does not make a diagnosis, doesn't wear a stethoscope. It's a tool that we use to make a clinical diagnosis. And so if it disagrees, so we have high clinical suspicion, but a negative biomarker, I think sometimes that forces us to reconsider.

our clinical diagnosis and think about, you know, alternative or atypical presentations or ideologies for common clinical genetic causes, I think was one that was mentioned. But sometimes you go and you get orthogonal tests to look, you know, for a different way to get the same information to be able to add in and either strengthen or weaken that clinical diagnosis. You know, the other would be, you know, if you have a positive biomarker in an atypical syndrome, well, that might be representing that it could be an atypical cause of it or an early presentation potentially. But in general, that's this is the sort of reasoning that takes place. And sometimes tests are wrong and sometimes, sometimes we're wrong.

Dr. Brito

Thank you for that.

Dr. Bruno

Yeah, thank you. Yes, I completely agree. Just to be, I guess, time sensitive, I kind of separated, if you clinically really suspect Parkinson's and the synuclein is negative, then of course, yeah, we would revisit the differential, consider 2 possibilities that it is a non-degenerative mimic or it is genuinely neurodegenerative, but not necessarily Lewy body driven or other genetic causes that's synuclein may be negative earlier. So, it doesn't change the fact that you have clinical Parkinson disease, but that you would still, that would prompt a structural reconsideration of the alternative diagnosis or at least the etiology. If the, and then if the if you're suspecting Lewy body disease, if the, but the synuclein comes back negative, you may want to start considering Alzheimer's, other tauopathies, comorbid, mixed pathology, but also still keep DLB on the on the tape as differential as a plausible false negative. And then MSA, if the presentation is very cerebellar dominant, consider genetic or other ataxias. If it is more atypical Parkinson's presentation, you may want to consider tauopathies, but as already discussed, sensitivity for MSA is not as high, so MSA is still on the table. Now, if the test is positive, but clinically a little bit atypical, then that is also, I think you would consider co-pathology, comorbidities. So, just kind of depends on how atypical and what is driving the discordance. But I also want to say one thing, that if the person this happens a couple of times, if the person is asymptomatic, we would have to be really careful with that because that is that, that identifies positive tests identify risk, but not necessarily or not diagnosing a disease, at least clinically. This is kind of a research versus clinical criteria. So we have to be super careful with that, I think.

Dr. Brito

Thank you for that point.

So moving on to the next question. There are several types of synucleinopathies where the performances of the biomarkers are not as robust. You folks have alluded to that in mutations with, you know, LRRK2 and PRKN in hereditary Parkinson's and

obviously, MSA. What is the etiology behind this and are there concerns that reliance on these biomarkers may lead to misdiagnoses? And is there ongoing research to how to best detect these particular subtypes?

And this would be directed to Dr. Magaki and Dr. Esper.

Dr. Esper

I'm happy to go first. I would say the first thing to keep in mind is that we are talking about pathological biomarkers, not for universal diagnosis of Parkinson's disease. And when we talk about these assays, we're detecting a specific Lewy body type alpha-synuclein. So, in some of the examples that you mentioned, like LRRK2, it can be variable. So yes, you can have a negative test with, and we have had studies that have demonstrated that it can be 68% positive in LRRK2 PD, but again, it's much lower in those that are, that can't smell. And I think Dr. Okun had alluded to this as well. When you think about Parkin, Lewy bodies are often absent. So again, the test can be absent. And then for MSA, while it is a synucleinopathy, the aggregates are actually in a different location or different, they're cytoplasmic inclusions, so they also may not be detected with that test. So, that being said, when you ask about the research, yes, it's moving in the right direction. They are developing a CSF assay that's promising in terms of distinguishing the Lewy bodies

versus the MSA glial inclusions. But at this point, I would say they're not ready for a, in the clinical setting.

Dr. Brito

Thank you. Dr. Magaki, do you have anything to add?

Dr. Magaki

Yes, I agree with that. There's a more recent study that a colleague forwarded to me last week, published last week on a skin test for differentiating between Lewy body disease and MSA, but and previously it hadn't been, there was no difference, but there's some pre-analytical variables, such as the process of collection and processing that if they eliminated the outliers, there was some difference. So as mentioned, it's still in development, but seems promising.

Dr. Brito

Thank you very much. All right.

No other comments? We'll go on to the next question. So in the workup of a patient, where do you see these biomarkers being utilized and who should be ordering these tests? Dr. Okun?

Dr. Okun

Yeah, so thanks for the question. And, you know, I think that, to be, you know, succinct on this, I would say at present time, I would favor placing synuclein biomarkers after, you know, what I would term a competent clinical assessment. And before moving to, you know, more invasive, expensive other types of testing, I think the result should be used to define some question that's being asked. I think they're reasonable for uncertain cases of Parkinsonism, for things like suspected Lewy body disease and cognitive presentations, for selected prodromal syndromes that we've talked about. You know, the prodromal symptoms, I don't know if we said them concretely for the record, but things like constipation, dream enactment, acting out of your dreams, REM sleep behavior disorder, smell we've discussed, but also some mood and other syndromes can present early and also for trial eligibility. I would think that ordering should initially be concentrated among clinicians who understand a phenotype. And the clinicians, as has been discussed here, need to understand there are limitations to any assay and they have to take the time to understand what those limitations are. Certainly, it'd be nice to have neurologists, specialty neurologists with expertise in movement disorders, but there's a shortage of them. Cognitive disorder doctors, as we've heard, speak here very eloquently on these topics, also could be qualified to do this, people with expertise in autonomics or related fields, but also people can be trained, but again, understand the phenotype, understand the limitations, and over time, I think it will broaden, the ordering may be reasonable, especially if interpretation becomes a little more standardized and there's clear decision, support pathways for folks. So that's kind of how I would think about it.

Dr. Brito

Thank you very much. And last for Dr. VandeVrede and Dr. Okun again. In patients diagnosed with dementia, without, would identification of the alpha-synuclein co-pathology influence management decisions, and in those cases where multiple co-pathologies are suspected how do you, multiple biomarker tests impact the results and subsequent patient management?

Dr. Okun

Where do you want to start on that one?

Dr. VandeVrede

Go ahead.

Dr. Okun

Okay, I'll just say, you know, you know, like, potentially, you know, it could potentially influence management, right? So, you know, so Lewy body co-pathology, for example, was common, particularly in cognitively impaired folks and in populations.

And this could provide some influence over like phenotypes, prognosis, medication sensitivity, you know, in these cases. If we take a dive into the literature, we see that really only a minority of biomarker positive patients in some of the memory clinics, at least where they report cohorts are clinically recognized as PD or DLB, but that you can have combined Alzheimer's and Lewy body pathology, and that some of the emerging literature is showing, for example, this can be associated with faster cognitive decline. So, coming to a, you know, a point as to what we know from where we are now, I think if you know there's synuclein or alpha-synuclein co-pathology, it could do things like sharpen your counseling, increase your vigilance for hallucinations, you

know, it can help you with understanding fluctuations, Parkinsonism, dream enactment, autonomic issues. It also might influence your decisions in cautioning with using dopamine blocking drugs. And so, knowing those things could be important. And as I said before, and I'm going to repeat it because I think it's important. Amyloid, tau, synuclein, you know, biomarkers, you know, whether there, you know, imaging or they're in serum or CSF, whatever, they should always be interpreted, your data should be aggregated together and over time, and mixed pathology is common. It just is common, because we could go on for an hour about how common it is across these degenerative diseases. And we have to make sure that we're clinically informative without, you know, boxing ourselves to single labels. So I would leave it there.

Dr. Brito

Thank you.

Dr. VandeVrede

I agree completely with Dr. Okun. It makes this very easy. I can maybe just emphasize a couple of points. I think this is commonly, happening in patients with dementia because of the reasons that Dr. Okun mentioned is that we do know trajectories are different to potentially even responses to our disease modifying therapies are different with synuclein co-pathology, and for those management concerns, understanding of the prognosis, all of those I think could potentially influence it. And this is where I'm seeing it be used more often. In fact, we rarely see patients get a lumbar puncture for AD biomarkers because there's blood biomarkers and PET are so much easier. But oftentimes this is the clinical question about whether there's a co-pathology. And the multiple biomarkers, just to emphasize again, I think this is exactly right, being able to identify all of the different neuropathologies that are present would be ideal. And then we would just integrate that into the clinical picture to understand the individual trajectory, potentially treatments, hopefully.

Dr. Brito

Thank you very much for all your opinions, and I will cede the questioning now to Dr. Barre.

Dr. Barre

Thank you so much, Dr. Brito. So I think we're continuing to move a little bit more into the clinical utility type of questions. And the first question is for Dr. Christine Esper. And I think we've touched a little bit on this throughout some of the discussion. But the question is, is the evidence mature enough? That is, are there longitudinal studies performed to endorse use of biomarkers and risk stratifying patients? And as an example, those with rapid eye movement, sleep behavior disorder, and recognizing that we have discussed diagnostic accuracy, but less about prognostic utility. So for individuals with, you know, isolated, you know, REM sleep behavior disorder or other prodromal symptoms, is there sufficient longitudinal evidence that a positive biomarker predicts progression to clinically manifested synucleinopathy.

Dr. Esper

Thank you for the question. I think this is a very important topic. So I would say the longitudinal evidence may support for some counseling, but not for routine prognostication for every single person with isolated RBD. That being said, studies

have shown that, I think it's about 85, 86% of people with RBD or hyposmia did have a positive seed amplification assay study. So I would say that's pretty good support for identifying a prodromal group.

However, you know, we still do need to consider the limitations. The studies are not yet validated at the individual level. And when you consider the timetable for PD versus DLB versus MSA, it's unclear if repeat assays are, will be stable or if they can track these changes.

So, I think when you think about this topic, it really should be targeted. And if you can confirm that an RBD phenotype is biologically consistent with a synucleinopathy.

What can you do about that and how would that change your management or patient outcomes? And some of the things that we've already discussed, would this guide counseling, would you avoid certain medications? You can enroll these patients earlier in clinical trials when applicable. But again, this is something we need to look at over a long term rather just rather than just equating risk with utility.

Dr. Barre

Thank you so much. It's very helpful. As a follow-up to that, so assuming a biomarker is positive, where in the diagnostic workflow should the result actually influence care? Is it, you know, at initial

evaluation or in those indeterminate cases? Or is there some other clinical scenario?

Dr. Esper

You asking me?

That's a tricky question. So, as Doctor Okun, I think many have mentioned.

Again, we're talking about pathological biomarkers, and you really need to consider the big clinical picture. How the patient is presenting and why are you ordering that study? Now, there may be very specific indications. People have mentioned co-pathology. And is it possible that this is an ADPD type of scenario? How would that help?

Also trying to distinguish, you know, is this DLB? Certainly there are certain medications that you would avoid in that situation. But again, a specific positive or negative would not necessarily guide that treatment. It needs to be used in conjunction with the clinical exam and history and other parts of the patient's presentation.

Dr. Barre

Thank you. And sorry for the ad hoc question. Next slide, please.

So this next question is directed towards Dr. Bruno. So do these tests have potential uses in monitoring disease progression as well as in treatment success?

Dr. Bruno

So yeah, so thank you. The answer, so far, at least based on the evidence in my clinical practice is no. So I do not use it for monitoring disease or progression or treatment success until we see some specific, and this is not because the test is negative, it's just that we don't, I haven't seen much guidance on that. So I would use it more for diagnostic purpose at this point, and guiding that, guiding that treatment decision as well as counseling. Possibly I may repeat it if their clinical scenario changes and I have a specific clinical question, but I would not use it for monitoring disease progression or treatment success at this time.

Dr. Barre

Thank you so much, Dr. Bruno. Next slide, please.

Okay. Yes. So this question is directed towards Mr. Victor Nussbaum. So as a patient advocate, how does biomarker testing change a patient's quality of life, given that there is no current disease modifying treatment?

Mr. Nussbaum

All right, thank you for that question. I was initially diagnosed 4 1/2 years ago with Parkinson's by a non-movement specialist. And that was followed by a visit to a movement disorder specialist at Beth Israel in Boston, who wasn't quite sure that I had Parkinson's and ordered a DAT scan, which turned, the result was, no, I have a normal DAT scan. And she said, you know, I'm still not sure. I think you have essential tremor, I'm pretty sure of that. Her 30 years of experience said that and said, in either case, whether I had Parkinson's or essential tremor, she would tell me the same thing. Just go and exercise. Have a healthy diet, exercise, and she would not consider Levodopa or anything like that. And about, and she did tell me about a skin, a biopsy that I could take. And the word biopsy scared me a bit, and I said, well, just exercise. I've always been active. I'm an active, you know, a lifetime of tennis playing, three, four, five times a week. I'll just keep playing tennis.

And about a year later, my symptoms changed a bit. My posture changed. I was hesitating on the tennis court, not because I'm in my 60's, just didn't make any sense. And a friend of mine was in a clinical study as a normal, for the biopsy and I saw him and he said, it's nothing, just go and take it, and I took it and it was a positive.

You know, I have the misfolded alpha synuclein protein. I have Parkinson's. And that was about a year after the initial diagnosis. And that changed my approach to Parkinson's.

And, you know, it creates a community. It's a club that I wouldn't have chosen to belong to, the Parkinson's community, but belonging to it created an ability for me to advocate for Parkinson's research, for me to participate in a year-long study about the effects of monitoring me digitally. Going to DC with 350 other people to advocate for the National Parkinson's Plan and more Parkinson's research money.

Exercise programs, I developed a pickleball for Parkinson's program that's now morphing into a complete comprehensive in-person Parkinson's Wellness Center.

And that just changed, it all stems from a conclusive diagnosis. And my neurologist says, I'm not typical. I'm fortunate that most people look at me and say, you have Parkinson's? And my tremors are minor. I have the sleep thing. My right arm doesn't swing properly when I walk. But it's afforded me the ability to live fully with Parkinson's and everything from meditation to rock climbing to Parkinson's golf,

to, you know, getting that neuroplasticity going.

You know, pickleball is not the same as tennis. Rock climbing is not the same as golf. And getting those pathways going increases my quality of life and my approach to this.

So I'm hopeful that there is, I think there is a cure out there. We just don't know what it is. And I'm hopeful that the biomarker studies are getting us closer to that solution.

So I hope that helps.

Dr. Barre

Very helpful. I really appreciate hearing your perspective and interested in finding out more about pickleball, particularly when you started. Sounds great.

I think we can go on to the next slide, next question.

Right. Okay. So this is for Dr. O'Brien or directed at Dr. O'Brien, obviously, as with other questions, others can chime in if they'd like. So I think several panelists have already noted that CSF assays may be better validated than skin testing, but you'll require lumbar puncture and expertise. So I think with that context, you know, what barriers to test adoption do you anticipate, you know, with lumbar puncture being required, patients may pay aversion and limited availability of experienced practitioners. Skin biopsy is less invasive, but require specialized specimen processing? Should coverage be limited to certain facilities or regions, which, you know, of course could create access issues.

Dr. O'Brien

So again, similar to the Alzheimer's disease biomarkers, I think there's going to be a pretty standard pattern of dissemination where first you'll see specialty centers with cognitive and movement subspecialists using them and then it'll spread out to general neurology.

I don't know that lumbar puncture assays or even the skin biopsies are really going to make it out to primary care, maybe in more rural settings. But I think there's going to be an access issue for as long as there's a shortage of neurologic subspecialists.

I'm not so concerned about patient aversion to lumbar punctures. There's a lot of good data that with appropriate education and counseling, people are actually pretty accepting of those tests. Again, I think the main limitation is the availability of people who can perform them and that might necessitate travel to a specialty center that can do that. In our center, I mean, we are fairly well resourced, but we don't have a lot of people actually trained to do the skin biopsy. So that's been a limitation for us. We only have a couple of providers who do it, so I think you're going to see the same problem as you know, having providers available to do LPs. I wouldn't want the insurance coverage to be a barrier, which is something that we were seeing with the blood biomarkers and Alzheimer's disease currently. So I don't like the idea of limiting coverage to certain regions.

I do think we need more, just best practice guidelines saying like what patient populations are appropriate to use these tests in and potentially use that as a way to gauge whether coverage is appropriate. There's a lot of work being done now in terms of like tele neurology being able to close the access gap to, to seeing a specialist. So I think the test manufacturers could actually help out with that and offer something similar to, like what C2N does with remote blood collection, identifying providers in areas who can actually do the lumbar punctures or collect the skin biopsies. So I think there are ways to get past those barriers.

Dr. Barre

Thank you. Dr. Mattke, I see your hand raised.

Dr. Mattke

Yeah, I think Dr. O'Brien is exactly right. There's A shortage of the people who can do the specimen collection for both cases, but we don't want to aggravate that by limiting coverage, because that might preclude people who can do it, who may not necessarily have to be the ones to interpret the test results.

By the way, lumbar puncture, this aversion in the US is a cultural thing. In continental Europe, where I trained, there's just no issue. Even internal medicine docs do it quite routinely, and it

actually belongs into your catalog. So there's something with the Anglo-Saxon psyche that creates this aversion to lumbar puncture, which with this sort of tiny diagnostic needle shouldn't really be a big deal.

Dr. Barre

Thank you. Dr. Bruno.

Dr. Bruno

Yes, I just wanted to echo that in our center, we have different islands. So we talked to the general neurologist and they would refer us and we actually make the decision to do the skin biopsy or lumbar puncture. And actually it is done locally in their different islands so the patient doesn't have to travel but done by the local practitioner. So we're trying to minimize the travel, especially if they have movement disorder. And so the coverage, the coverage limitation would make it a little bit difficult in that kind of model.

Dr. Barre

Very helpful context. Thank you, Dr. Bruno. Okay. I don't see any other hands raised, so if we can move to the next. Perfect. Okay.

So this next one, I think we'll have this directed at Dr. VandeVrede, Dr. Okun, and subsequently Dr. Esper will give you each an opportunity to weigh in here.

So the question is, as long as disease modifying therapies remain unavailable for synucleinopathies, what other, and I know we've touched a little bit on this in terms of counseling and some other things, but what other patient relevant outcomes should be demonstrated to justify use of these biomarker tests? And asked in another way, what constitutes meaningful clinical utility in these biomarkers?

Dr. VandeVrede

I'll start this one. I'll say Mr. Nussbaum's, you know, comments I think are probably most relevant for the importance of an accurate clinical diagnosis. I don't think I need to go much further than that, what he said, but maybe just to emphasize that disease modifying therapies aren't required to still need an accurate diagnosis for a patient that in itself is important can actually build towards the trials that allow us to get to those disease modifying therapies. But I think this question is more about sort of intrinsic performance of test and diagnostic accuracy, I think is amongst the most important for the context of use that it's intended for, which is specified with inclusion of as many patients from representative populations as possible to increase your certainty that that performance is going to be, have external validity to it. But if the question is more about clinical utility outside of diagnostic confirmation, then there's a lot of a wealth of literature on this looking at things like diagnostic certainty in the clinician, disclosure effect in the patient, looking at subsequent management,

in terms of medications that are prescribed or avoided, the need for emergency room visits or additional hospitals, hospitalizations, all of these are sort of outcomes that can be looked at, but usually are best done, you know, in the real world setting, because it's hard to model that in the research world, but I think all of those can help support the, the clinical utility of it, but at the core of it, it's accurate diagnosis, I think.

Dr. Barre

Thank you and appreciate the call back to Mr. Nussbaum's comments.

Dr. Okun, and then subsequently Dr. Esper, please.

Dr. Okun

Yeah, yeah, I think, doctor, I think Mr. Nussbaum's comments are really important, and it's really to the credit of this group to have persons with disease speaking and leaning into this. So, I would just say that, in general, when we think about biomarkers, a biomarker doesn't have to lead directly to a cure or something at that level, you know, to have clinical value, but it should improve something that matters to people like Mr. Nussbaum. Okay. So I think when we think about this, I like the term meaningful utility, you know, and could that shorten a long diagnostic journey?

Could it reduce uncertainty for him? Could it avoid unnecessary or harmful testing or treatments? Could it identify clinically important co-pathology? Does it improve prognostic counseling? Does it guide your symptomatic treatment? Does it prompt you to try to be safer with the person? Does it help you and your caregiver, planning? And then, of course, can it connect them to an appropriate clinical trial? And you heard that from doctor, or from Mr. Nussbaum directly, that this was something that was important to him. So I would look for evidence that the testing has

some changes in real decisions and medications, referrals, follow-up intensity, rehab, counseling, health care utilization. And, you know, I wouldn't consider it sufficient that it simply shows that it can classify somebody with biologically, you know, disease with high accuracy. I think the person remains at the center of these decisions. And the test, in my mind, will earn its place in care when it helps us to make a better decision for all of the Mr. Nussbaums. And so that's where I would leave my comments on this.

Dr. Barre

Thank you Dr. Okun. Dr. Esper?

Dr. Esper

Yes, I wholeheartedly agree with the comments mentioned thus far. And as mentioned, this, the patients at the core here. So if these tests can change the patient's, you know, care journey, you know, then it has done its job. And I think that's what we need to consider, in the long term.

Dr. Barre

Thank you, Dr. Esper. I believe that concludes the questions that I have. Oh, Dr. Mattke.

Dr. Mattke

Yeah, just one remark on that. There's a precedent for that, the IDEAS Study that CMS used to determine whether amyloid PET should be covered also used that as an endpoint, what my 2 colleagues just mentioned, changes in management, not necessarily like survival and very hard clinical outcomes, but did it influence clinical decision making.

Dr. Barre

Thank you. Thank you for that reference.

So I believe that concludes the questions that I'm tasked with. So with that, I'm going to hand it over to my colleague, Dr. Bergman.

Dr. Berman

Thank you, Luke. First, I just want to comment on the CAC thus far. I've been extremely excited, interested, and educated by the responses. I will say as a simple country internist, those of us of my generation were trained in spinal taps as well as

skin biopsies. So if they come to the state of Florida, I'll be more than happy to do that for them. And I'm a general internist, so I think it's a generational thing, but I do appreciate the comment. And I do want to mention, Victor, your comments were enlightening and inspiring. And I appreciate you being here and sharing your advocacy and your story with us. So each one of you were emailed a link that will allow you to respond. Next slide, please. Respond to these key questions. Next slide.

There we go. You'll be asked to judge or scale or vote on a one to five basis.

Not sunsetting yet here, but I appreciate that slide. One being the least likely and five being most likely. So I'm going to read each of these questions and go use the link that you were provided to vote when I finished reading the question. That would be very nice and we appreciate it.

And not sure what's going on here for me. But anyway, at the end of the CAC, you will have the questions and the results provided. So, I'm not sure what happened there.

But the first question is: Based on the evidence, so far, I would consider a biomarker test for all patients suspected of having a synucleinopathy. So please vote.

One being least likely, 5 being most likely.

The next question is based on the evidence so far, I would consider a biomarker test only for.

Dr. Rajadhyaksha

Sorry, Dr. Bergman, one second. Dr. Esper, you have a question?

Dr. Berman

Ohh, I'm sorry.

Dr. Esper

Yeah, I know I saw it earlier today, but who sent the e-mail just so I can find it again?

Dr. Berman

Probably Jo Gilbertson.

Dr. Esper

Ok, thank you.

Dr. Berman

Yes, ma'am. Sorry I missed your hand.

Question #2.

First of all, did you find it Dr. Esper?

Dr. Esper

Yeah, yes, I found it. Thank you.

Dr. Berman

Okay, you're welcome. Next, based on evidence so far, this is question #2, I would consider a biomarker test only for patients whereas synucleinopathy cannot be ruled out.

Please vote.

Question #3.

Based on evidence so far, I would consider a biomarker test for patients with a suspected co-pathology.

Oh, please make sure that you vote for each one of these. It's very useful for us to kind of synthesize all the information and finalize our evidence gathering.

Question #4, based on the evidence provided, there is a demonstrated impact on clinical management and differentiating between various synucleinopathies.

That was Dr. Mattke's comment at the very close of the conversation.

Question #5. Based on evidence provided, there is an impact on outcomes in differentiating between various diseases.

So while you're finishing up, I want to again thank you for your time and your expertise and the very engaging conversation. And as an internist, I found this very enlightening and I appreciate everything. I'm going to turn it back over to Aparna, where she will give closing comments and closing instructions.

And again, appreciate your time and effort and expertise. Thank you.

Dr. Rajadhyaksha

Thank you again for all your valuable time. I know this was not easy between patients and other commitments. We do value expertise and truly this is this is not simple, right? We with not too many guidelines, but not too many, too much of, you know, straightforward utility just because of how complex this issue is.

Just trying, at 2 hours is not enough to get to the meat of this. And I think, where I get from this is how does it help in clinical decision making? What changes can we facilitate for our patients is going to be a true north as far as how we work through this policy.

And you know what benefits or value add we can add for, for our patients in the Medicare population. So, with that, our audio recording will be in will be online. We will have our bibliography, which we which we sent everybody also published.

If anyone attending or here has any other literature articles which you feel we should know about, which was not included, please do not hesitate to send it to us. We will include it in our evidence as we work through this policy. Our intention is to have a draft policy based on this information.

And that will be another opportunity for people to provide comments and provide literature on it. Till then, if you have anything, please don't hesitate to reach out. We thank you again. Have a good afternoon.

Dr. Esper

Thank you.

Jo Gilbertson

Thank you, everybody. This is Jo. Again, we want to thank the CAC panelists for information and discussion and take the time out of your day to be here and share your expertise. The MAC CMDs will take the information from today's meeting and will continue discussions. Please monitor the MAC websites and some of our listserv emails.

Thank you so much. Have a great rest.

Dr. Wong

Okay, bye.

Jo Gilbertson

Bye-bye.