



From Biological Detection to Clinical Decision-Making: Incorporating α -Synuclein Seed Amplification Assays in Parkinson's Diagnosis

Authors: Melanie J. Plastini,¹ *Luis Concha-Marambio¹

1. Amprion Inc., San Diego, California, USA

*Correspondence to luis@ampriondx.com

Disclosure: Concha-Marambio is an employee of Amprion Inc; holds stock options; and is a named inventor of patents related to the α -synuclein seed amplification assay, which have been assigned to Amprion Inc. Plastini is a full-time employee of Amprion Inc; and holds stock options.

Received: 02.07.26

Accepted: 17.07.26

Keywords: α -synuclein (α Syn), biomarkers, biological diagnosis, clinical implementation, Parkinson's disease (PD), precision medicine, seed amplification assay (SAA), synucleinopathy.

Citation: EMJ Neurol. 2026; <https://doi.org/10.33590/emjneuro/3QK65W9Z>



INTRODUCTION

Parkinson's disease (PD) remains largely a clinical diagnosis based on characteristic motor features and supportive clinical criteria. However, clinicopathological studies report diagnostic accuracies of 70–85%, with even lower accuracy in early disease and atypical parkinsonism. Critical to the development and implementation of precision disease-modifying therapies is the availability of biomarkers that reflect underlying biology rather than clinical phenotype.

Detection of misfolded α -synuclein (α Syn) in the cerebrospinal fluid (CSF) by seed amplification assay (SAA) is recognised as a promising diagnostic tool for neurodegenerative disorders. Studies have demonstrated high sensitivity and specificity for detecting underlying synuclein pathology, including validation in more than 600 neuropathologically confirmed cases, with similar performance in clinically diagnosed PD.¹ Accumulating evidence suggests that α Syn-SAA has the potential to reshape the diagnosis

of synucleinopathies by improving diagnostic confidence in selected clinical contexts. However, widespread clinical implementation requires a deeper understanding of how biomarker results should be interpreted across diverse patient populations.

BIOLOGICAL DIAGNOSIS AND CURRENT RESEARCH FRAMEWORKS

Unlike traditional biomarkers that capture downstream consequences of disease, α Syn-SAA amplifies and detects misfolded α Syn aggregates, the primary component of Lewy bodies and Lewy neurites that are a pathological feature of PD and related synucleinopathies. Multicenter studies have reported sensitivity exceeding 85–90% for clinically diagnosed PD, with high specificity among healthy controls and other neurodegenerative diseases.¹ Particularly impactful were the initial findings in the Parkinson's Progression Markers Initiative (PPMI) cohort,¹ which demonstrated α Syn-SAA positivity in

87.7% of PD participants and 86% of prodromal participants prior to evidence of dopaminergic deficit, suggesting that α Syn pathology, detectable by α Syn-SAA, may precede neurodegeneration detectable by conventional imaging. Recent advances in α Syn-SAA technology have demonstrated the ability to distinguish multiple system atrophy (MSA) from PD and other synucleinopathies, representing an important clinical advance given the rapid progression and poorer prognosis associated with MSA.²

These findings have resulted in enthusiasm for moving toward a biologically defined framework for PD,^{3,4} similar to the biomarker-based framework adopted in Alzheimer's disease (AD). Recent research criteria increasingly incorporate α Syn-SAA as evidence of underlying synucleinopathy. However, translating a biomarker from research settings into clinical care requires more than diagnostic accuracy alone. While emerging SAAs have demonstrated clear clinical utility in distinguishing MSA from other synucleinopathies, the broader challenge of clinical implementation lies not in whether a biomarker can detect active disease, but in establishing clinical use guidelines and how these assays can best inform patient care across a range of presentations.

REAL-WORLD COHORTS, DIVERSE POPULATIONS, AND ACCESSIBILITY

Most studies have focused on well-characterised research cohorts enriched for PD and related synucleinopathies. However, in routine neurology clinics, patients often present with overlapping symptoms, vascular disease, medication effects, or uncertain diagnoses. Moreover, increasing evidence suggests that synuclein pathology frequently coexists with other neurodegenerative diseases, including AD.⁵ As clinical adoption of α Syn-SAA expands, performance across broader patient populations, including individuals with nonspecific symptoms, atypical parkinsonism, and community-based cohorts, will further define the real-world utility of α Syn-SAA and refine evidence-

based clinical use guidelines. Although current testing relies on CSF, continued advances in blood and skin-based assays may further improve accessibility. Beyond the need for CSF, technical aspects of the assay require strong laboratory skills and close attention to detail. To ensure reproducible and reliable results, α Syn-SAA should be performed by trained professionals operating under an established quality management system using rigorously qualified SAA-competent materials sourced through standardised quality control processes. As for any *in vitro* diagnostic test, compliance with relevant regulatory standards is required for the use of α Syn-SAA as part of medical decision-making. In the USA, the test is currently offered to clinicians as a laboratory developed test, in compliance with Clinical Laboratory Improvement Amendments (CLIA) regulations, through a centralised commercial laboratory. In Europe, implementation must comply with the EU *In Vitro* Diagnostic Regulation (IVDR). This is also likely to occur initially through centralised reference laboratories operating under standardised workflows. In addition to scientific and regulatory considerations, clinical implementation is influenced by intellectual property and licensing frameworks. Many of the methodological advances that enable robust, analytical, and clinical validation are proprietary, meaning that commercial implementation may require access to licensed technologies in addition to regulatory approval. As assay methodologies and access become increasingly standardised, broader adoption across healthcare systems is anticipated.

NEGATIVE TEST RESULT IN SYMPTOMATIC INDIVIDUALS

Although α Syn-SAA demonstrates high specificity for PD, not all individuals with parkinsonism test positive. A negative result may reflect a non-synucleinopathy disorder, technical and biological variability, or lower positivity in specific genetic subtypes such as *LRRK2*-associated PD. A recent analysis of α Syn-SAA-negative participants in the PPMI cohort found that 14.3% underwent diagnostic revision during

follow-up, highlighting that a negative test can represent biological heterogeneity and disorders that mimic PD rather than a false negative.⁶ Importantly, more advanced SAA technologies can distinguish Type 1 synuclein seeds associated with PD and dementia with Lewy bodies from Type 2 synuclein seeds associated with MSA.² Earlier-generation assays were unable to detect Type 2 seeds and may have yielded negative results in symptomatic individuals. The new accuracy of this distinction has prompted recommendations for assay-specific result interpretation and clinical management. α Syn-SAA results should therefore be interpreted within the broader clinical context, alongside clinical examination and other available imaging and biomarker data. Defining the implications of biomarker-negative parkinsonism remains an important area for future research.

POSITIVE TEST RESULT IN INDIVIDUALS WITH NONSPECIFIC SYMPTOMS

Symptoms such as chronic constipation, mild cognitive impairment, or subtle motor complaints are common in the ageing population and are not specific to synucleinopathy. If such an individual tests positive for α Syn-SAA, does this indicate prodromal PD, incidental Lewy body disease, or merely increased future risk? This issue mirrors challenges previously encountered in AD, where amyloid positivity alone does not necessarily equate to symptomatic disease. Studies of prodromal populations suggest that α Syn-SAA positivity can precede motor symptom onset by years.^{7,8} Isolated rapid eye movement sleep behaviour disorder, in particular, has been associated with prodromal PD. The rate of phenoconversion in these cases is still being researched; however, in a 2025 PPMI analysis of 96 participants with prodromal PD, defined by RBD and/or hyposmia with mild dopamine-transporter imaging deficits, 23 phenoconverted over follow-up of up to 9.2 years: 21 to PD and two to dementia with Lewy bodies.⁸ α Syn-SAA-positive participants were significantly more likely to phenoconvert, and faster amplification

was associated with greater risk. However, the assay did not independently predict the timing of conversion for an individual. These findings support α Syn-SAA as a means of detecting underlying pathology and elevated phenoconversion risk and may support enrichment for prevention trials.

As testing becomes more widely available, clinicians will increasingly encounter biomarker-positive individuals who do not meet diagnostic criteria for PD or other synucleinopathies. Establishing evidence-based approaches for counselling, monitoring, and treatment management in these cases will be imperative, while underscoring the need to interpret positivity alongside clinical features, imaging, genetics, and other biomarkers.

POSITIVE TEST RESULT IN ASYMPTOMATIC INDIVIDUALS

Studies have shown that participants who test positive and are asymptomatic, cognitively unimpaired, and with no known underlying neurological disorders can progress to a clinical synucleinopathy over 10 years and report more synucleinopathy-related non-motor symptoms.^{9,10} This raises the possibility of identifying at-risk individuals before irreversible neurodegeneration occurs, an essential step toward preventive therapies. The detection of α Syn pathology in asymptomatic individuals may ultimately lead to the ability to diagnose and treat prior to the onset of clinical symptoms, as well as track disease progression and phenoconversion over time. However, without effective disease-modifying therapies, the ethical and psychological implications of disclosing biomarker positivity also warrant careful consideration. Longitudinal studies are still needed to determine conversion rates, timelines, and modifiers of disease progression among asymptomatic SAA-positive individuals.

FUTURE APPLICATIONS AND THE PATH FORWARD

α Syn-SAA represents a major advance in the field of neurodegenerative disorder biomarkers, particularly in the biological detection of neuronal synucleinopathy. Importantly, a positive α Syn-SAA should not be interpreted as synonymous with a biological diagnosis of PD, but rather as evidence of underlying α -synuclein pathology to improve diagnostic confidence in selected clinical contexts. Consistent with emerging biological frameworks, additional biomarkers reflecting nigrostriatal dysfunction, together with clinical evaluation, remain necessary

to fully characterise disease stage and phenotype. Nevertheless, widespread clinical implementation requires a deeper understanding of biomarker interpretation across the disease continuum. As the field makes advances and new iterations of frameworks for biologically defined neurodegenerative diseases, α Syn-SAA is poised to become an important component of the diagnostic toolkit. Yet, like all biomarkers, its greatest value is when integrated with clinical phenotype, imaging, and complementary biomarkers to guide patient care.

References

1. Siderowf A et al. Assessment of heterogeneity among participants in the Parkinson's Progression Markers Initiative cohort using α -synuclein seed amplification: a cross-sectional study. *Lancet Neurol.* 2023;22(5):407-17.
2. Ma Y et al. Sensitivity and specificity of a seed amplification assay for diagnosis of multiple system atrophy: a multicentre cohort study. *Lancet Neurol.* 2024;23(12):1225-37.
3. Höglinger GU et al. A biological classification of Parkinson's disease: the SynNeurGe research diagnostic criteria. *Lancet Neurol.* 2024;23(2):191-204.
4. Simuni T et al. A biological definition of neuronal α -synuclein disease: towards an integrated staging system for research. *Lancet Neurol.* 2024;23(2):178-90.
5. Tosun D et al. Association of CSF α -synuclein seed amplification assay positivity with disease progression and cognitive decline: a longitudinal Alzheimer's Disease Neuroimaging Initiative study. *Alzheimers Dement.* 2024;20(12):8444-60.
6. Brooker SM et al. Clinical and imaging characteristics of Parkinson's disease with negative alpha-synuclein seed amplification assay. *Mov Disord.* 2026;41(5):1114-27.
7. Concha-Marambio L et al. Accurate detection of α -synuclein seeds in cerebrospinal fluid from isolated rapid eye movement sleep behavior disorder and patients with Parkinson's disease in the DeNovo Parkinson (DeNoPa) cohort. *Mov Disord.* 2023;38(4):567-78.
8. Coughlin DG et al. α -Synuclein seed amplification assay amplification parameters and the risk of progression in prodromal Parkinson disease. *Neurology.* 2025;104(5):e210279.
9. Palmqvist S et al. Cognitive effects of Lewy body pathology in clinically unimpaired individuals. *Nat Med.* 2023;29(8):1971-8.
10. Winer JR et al. Effects of α -synuclein pathology on synaptic dysfunction and clinical outcomes in normal aging. *Alzheimers Dement.* 2026;22(5):e71455.