A biological definition of neuronal α-synuclein disease: towards an integrated staging system for research

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See **Comment** pages 129 and 133

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Parkinson's disease and dementia with Lewy bodies are currently defined by their clinical features, with α-synuclein pathology as the gold standard to establish the definitive diagnosis. We propose that, given biomarker advances enabling accurate detection of pathological α-synuclein (ie, misfolded and aggregated) in CSF using the seed amplification assay, it is time to redefine Parkinson's disease and dementia with Lewy bodies as neuronal α-synuclein disease rather than as clinical syndromes. This major shift from a clinical to a biological definition of Parkinson's disease and dementia with Lewy bodies takes advantage of the availability of tools to assess the gold standard for diagnosis of neuronal α-synuclein (n-αsyn) in human beings during life. Neuronal α-synuclein disease is defined by the presence of pathological n-αsyn species detected in vivo (S; the first biological anchor) regardless of the presence of any specific clinical syndrome. On the basis of this definition, we propose that individuals with pathological n-αsyn aggregates are at risk for dopaminergic neuronal dysfunction (D; the second biological anchor). Our biological definition establishes a staging system, the neuronal α-synuclein disease integrated staging system (NSD-ISS), rooted in the biological anchors (S and D) and the degree of functional impairment caused by clinical signs or symptoms. Stages 0–1 occur without signs or symptoms and are defined by the presence of pathogenic variants in the *SNCA* gene (stage 0), S alone (stage 1A), or S and D (stage 1B). The presence of clinical manifestations marks the transition to stage 2 and beyond. Stage 2 is characterised by subtle signs or symptoms but without functional impairment. Stages 2B–6 require both S and D and stage-specific increases in functional impairment. A biological definition of neuronal α-synuclein disease and an NSD-ISS research framework are essential to enable interventional trials at early disease stages. The NSD-ISS will evolve to include the incorporation of data-driven definitions of stage-specific functional anchors and additional biomarkers as they emerge and are validated. Presently, the NSD-ISS is intended for research use only; its application in the clinical setting is premature and inappropriate.

Introduction

Parkinson's disease and dementia with Lewy bodies are currently defined by their clinical features, with detection of α-synuclein pathology used as the gold standard to establish a definitive diagnosis. Numerous clinical diagnostic criteria have been proposed over decades and widely used to classify individuals with Parkinson's disease and dementia with Lewy bodies. Clinical staging, such as the Hoehn and Yahr scale, has been developed and used to describe disease severity. Our concerns about these clinical definitions and staging are two-fold. First, the clinical syndromes and clinical progression are heterogenous, with overlap among disorders. Second, converging biomarker, clinical, epidemiological, and neuropathological data show that pathology begins long before any symptoms or signs, but clinical criteria cannot define Parkinson's disease or dementia with Lewy bodies during this prolonged period of neurodegeneration.

These concerns could be addressed by use of biomarkers that measure misfolded, predominantly neuronal α-synuclein (n-αsyn), the neuropathological hallmark of Parkinson's disease and dementia with Lewy bodies (panel 1). Until recently, n-αsyn could only be reliably measured post mortem. In 2016, a seed amplification assay[1] was developed, which could detect n-αsyn in vivo with high accuracy. Its rapid, rigorous optimisation and validation[2–6] has been a landmark advancement for the field. We propose that, given our ability to detect n-αsyn using this seed amplification assay, it is time to redefine Parkinson's disease and dementia with Lewy bodies on the basis of biology rather than clinical features. We recognise that a biological definition for Parkinson's disease and dementia with Lewy bodies is a major shift, but we believe that reflects the availability of tools to establish the gold standard diagnosis during life.

We suggest that a biological definition can combine Parkinson's disease and dementia with Lewy bodies under the term neuronal α-synuclein disease, on the basis of in vivo detection of n-αsyn (S). We further propose that individuals with n-αsyn are at high risk for developing dopaminergic neuronal dysfunction (D), a second key biological anchor for neuronal α-synuclein disease. Defining neuronal α-synuclein disease by its biology is crucial to further understand pathophysiology, to enable biology-specific therapeutic development[7] and therapeutic intervention before symptom onset to potentially prevent or halt progression,[8] and to identify biologically defined groups.[9]

Two centuries after Parkinson's disease was first described,[10] and three decades since the term dementia with Lewy bodies was proposed,[11] the knowledge and tools

are now available to allow the redefinition of these entities on the basis of biology and conceptualisation of a staging system rooted in biology. We propose an integrated biological and clinical staging system for neuronal α-synuclein disease that begins when it is still asymptomatic, and continues through the development of increasing functional impairment. The key rationale for a staging system is to accelerate therapeutic development in all disease stages, by including in research studies participants without symptoms on the basis of their biomarker profiles, as well as those in later stages, anchored by clinical features. Our approach of defining the disease on the basis of biology and biomarkers builds on similar efforts in other neurodegenerative diseases, including Alzheimer's disease[12,13] and Huntington's disease.[14]

In this Position Paper, we present the definition of neuronal α-synuclein disease and our concept for the neuronal α-synuclein disease integrated staging system (NSD-ISS), providing examples of how this proposed biological definition and staging system will advance the field. We also propose that a conceptual framework for neuronal α-synuclein disease staging is crucial to accelerate drug development, just as Alzheimer's disease staging has accelerated drug development. This inaugural version of the NSD-ISS is intended for research use only; its application in the clinical setting is premature and inappropriate. We urge the research community to work together to provide the data to test this concept fully. We also highlight key outstanding questions and opportunities for the NSD-ISS to facilitate further investigation, which in turn will inform future iterations of the staging system.

Panel 1: **Glossary of terms**

Neuronal α-synuclein (n-αsyn)
Disease-defining form of α-synuclein: pathological (ie, misfolded and aggregated), predominantly neuronal α-synuclein

Neuronal α-synuclein disease
Disease defined by presence of n-αsyn and dopaminergic dysfunction, independent of presence of clinical signs and symptoms

S anchor for neuronal α-synuclein disease (S)
Indicates presence (S+) or absence (S–) of n-αsyn as measured by any validated biomarker of n-αsyn pathology

D anchor for neuronal α-synuclein disease (D)
Indicates presence (D+) or absence (D–) of dopaminergic dysfunction as measured by any validated biomarker of dopaminergic dysfunction

Genetic status (G)
Indicates presence (G+) or absence (G–) of relevant pathogenic variants

α-synuclein seed amplification assay
An assay that leverages the self-replicating properties of misfolded α-synuclein by means of fragmentation and elongation cycles

α-synucleinopathies
A group of neurodegenerative diseases marked by histopathological evidence of pathological aggregates of misfolded α-synuclein

Development process

Details on the process for the development of our definition and the NSD-ISS are provided in the appendix (p 1). Briefly, in 2022, in the context of broad consensus among a range of stakeholders in research of neurodegenerative disease that a biological definition and a staging of α-synucleinopathies were crucial to advancing therapeutic development,[15] a working group was assembled under the auspices of The Michael J Fox Foundation for Parkinson's Research. This working group included international neuroscience and clinical experts, industry sponsors, non-profit organisations, regulatory authorities, and representatives of the patient community. Focusing on an approach grounded in existing data, the objectives were to develop a biological definition and a framework that delineates disease stages to accelerate targeted therapeutics, and to identify key gaps in knowledge. Following a series of virtual meetings, a face-to-face conference was held from Jan 25 to Jan 26, 2023. Following this conference and a series of weekly virtual meetings, seven international non-profit organisations, including The Michael J Fox Foundation, supported a face-to-face roundtable and subsequent virtual summit. These events were held in April, 2023, with diverse stakeholders, including an expanded group of neuroscience and clinical experts in α-synucleinopathies, patient community members, public–private partnership groups, representatives from industry and regulatory agencies, and additional patient advocacy groups. These events led to several key revisions to the NSD-ISS. The draft Position Paper was posted on The Michael J Fox Foundation for Parkinson's Research website between June 21, 2023, and July 19, 2023, for public comment, and key feedback was then incorporated.

Proposed unifying terminology

Neuronal α-synucleinopathies, defined by accumulation of disease-specific[16–18] pathological α-synuclein predominantly in neuronal cell bodies and neurites (Lewy bodies and Lewy neurites), can be asymptomatic or can manifest clinically with parkinsonism, cognitive impairment, and an array of other motor and non-motor manifestations. Based on the sequence and progression of clinical signs or symptoms, individuals have been designated with varying terms,[19–26] such as incidental Lewy body disease,[27] preclinical (without clinical features), premotor, pure autonomic failure, idiopathic rapid eye movement-sleep behaviour disorder, prodromal (early

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See **Online** for appendix

signs or symptoms not yet fulfilling clinical diagnostic criteria), or as having a possible or probable clinical diagnosis of Parkinson's disease, Parkinson's disease dementia, or dementia with Lewy bodies. We propose neuronal α-synuclein disease as a new unifying term defined by biology to encompass all α-synucleinopathies with n-αsyn—ie, predominantly neuronal deposition of misfolded pathological α-synuclein.

Definition of neuronal α-synuclein disease

Neuronal α-synuclein disease is defined by the presence of n-αsyn (S) and stage-dependent evidence of dopaminergic neuronal dysfunction (D). Additionally, presence of fully penetrant pathogenic variants in the *SNCA* gene (G) is sufficient for the diagnosis of neuronal α-synuclein disease. The current measures used to determine an individual's S or D status are categorical (positive or negative), but are anticipated to become quantitative as the field evolves. Central tenets of our definition of neuronal α-synuclein disease are: the disease is defined biologically on the basis of objective in-vivo biomarkers; the disease can be diagnosed in the absence of clinical manifestations; and clinical manifestations in the absence of biomarkers are not sufficient to diagnose the disease.

The biological anchors of the NSD-ISS

S anchor: n-αsyn

The presence of n-αsyn (S+) is the defining feature of neuronal α-synuclein disease and is key to the NSD-ISS framework. Over a century ago, Lewy bodies were identified as the pathological hallmark of disorders now encompassed in the definition of neuronal α-synuclein disease.[28] Landmark discoveries included the identification of the Ala53Thr *SNCA* variant as a cause for Parkinson's disease and determination that α-synuclein was the core constituent of Lewy bodies and Lewy neurites.[29] The key role of n-αsyn pathology is well established based on extensive pathological, molecular, and genetic evidence in animal models and in humans.[30]

Any rigorously validated biomarker of n-αsyn can be used to assess for neuronal α-synuclein disease. Efforts to identify and measure pathological α-synuclein in vivo have been underway for over two decades. Several measures of n-αsyn have been investigated and show promising results.[31,32] However, at present, only a CSF α-synuclein seed amplification assay has undergone robust validation. The assay has been validated with consistent results in two different studies conducted at multiple independent laboratories using well characterised samples,[33,34] and showed high accuracy when tested in a double-blind way in multiple, independent cohorts.[2–4,6] Thus, this CSF α-synuclein seed amplification assay meets the level of evidence required to reliably diagnose neuronal α-synuclein disease. This assay is positive in more than 95% of autopsy-confirmed cases of Parkinson's disease or dementia with Lewy bodies,[5,35] and identifies individuals with clinical signs or symptoms of Parkinson's disease and dementia with Lewy bodies with high accuracy.[2–4,6] The seed amplification assay also detects n-αsyn in individuals with idiopathic rapid eye movement sleep behaviour disorder, olfactory or autonomic dysfunction, and genetic risk who are most likely to progress to clinically defined disease.[2,36–38] Importantly, a positive CSF α-synuclein seed amplification assay in individuals[39] who do not have cognitive impairment and in individuals with isolated hyposmia[40] was associated with progression to clinically defined α-synucleinopathies within 4–6 years. Critically, this assay can distinguish n-αsyn from other α-synuclein forms, specifically those associated with the predominantly glial pathology of multiple system atrophy.[41,42] Standard operating procedures and best practices for biospecimen handling[43] are crucial for the accurate application of α-synuclein seed amplification assay. Currently, the most widely applied assay[2,44] uses maximal fluorescence emitted during aggregation to define positivity for n-αsyn and distinguish neuronal α-synuclein disease from healthy individuals and those with multiple system atrophy.

Several other measures of n-αsyn are being studied, and it is expected that other reliable n-asyn biomarkers will emerge. These biomarkers include seed amplification assays in other matrices, such as blood and peripheral tissue.[3,31,45–47] Other measures of n-αsyn also hold promise. Immunohistochemical detection of phosphorylated n-αsyn in skin biopsies has high accuracy for distinguishing neuronal α-synuclein disease from healthy controls[48,49] and clinically diagnosed Parkinson's disease from multiple system atrophy.[46,50] Furthermore, disease-specific post-translational modifications of α-synuclein and exosome-derived α-synuclein biomarkers are also being studied.[31] The NSD-ISS research framework enables incorporation of any emerging measures alongside, or instead of, the seed amplification assay to determine the presence of n-αsyn (S) once they have been rigorously replicated and validated.

A major goal is to develop quantitative measures of n-αsyn. Intensive efforts are also underway to develop imaging tracers for topographical in vivo detection of n-αsyn.[51,52] Neuronal α-synuclein disease is associated with a widespread distribution of n-αsyn aggregation both in the peripheral nervous system and CNS.[31] Whether pathological changes occur first in the periphery or concurrent to the CNS is unknown. The NSD-ISS framework can incorporate both peripheral and additional central biomarkers of n-αsyn pathology once such biomarkers are validated.

D anchor: dopaminergic neuron dysfunction

The degeneration of substantia nigra dopaminergic neurons (D) is a core pathological feature and the second key anchor of neuronal α-synuclein disease. Evidence of dopaminergic neuronal dysfunction and degeneration itself is not specific to neuronal α-synuclein disease but,

when combined with a biomarker of n-αsyn, is central to the definition of the disease.

The loss of midbrain dopaminergic neurons was identified as a key pathological marker in Parkinson's disease about 75 years ago and, soon after, symptomatic benefit from dopamine replacement was shown.[53] Extensive evidence shows that dopaminergic dysfunction is present in an overwhelming majority of S+ individuals with not only predominantly motor signs or symptoms, but also cognitive or other non-motor signs or symptoms of neuronal α-synuclein disease.[2,54–58]

Molecular imaging of the dopamine system has been widely used to detect dopamine dysfunction. Dopaminergic imaging with fluorodopa, tracers for the dopamine transporter, or vesicular monoamine transporter effectively indicate striatal changes in dopaminergic regions, showing the asymmetric, rostral–caudal striatal loss.[59,60] Furthermore, dopamine transporter binding correlates with neuronal density[61] and nigral cell counts[62] in the brains of individuals with neurodegenerative disorders. Importantly, more than 88% of people with dementia with Lewy bodies diagnosed on the basis of clinical diagnostic criteria or on neuropathology have abnormal measures in dopamine transporter SPECT.[54–56]

Dopamine transporter loss has been shown to occur before functional impairment, and individuals without functional impairment with dopamine transporter deficit are likely to develop functional impairment within 3–5 years. For example, reduced dopamine transporter binding in people with olfactory dysfunction or idiopathic rapid eye movement sleep behaviour disorder is associated with motor and cognitive progression.[63–67] Similarly, individuals with motor signs or symptoms without dopamine transporter deficit are unlikely to have n-αsyn and to progress to severe functional impairment.[2,68,69]

Currently, SPECT imaging using ioflupane (I^{123}) is the most widely used tracer to assess dopamine transporter binding, both in research and clinical practice. A quantitative dopamine transporter SPECT biomarker, the specific binding ratio in the lowest putamen adjusted for age and sex, is used to categorise individuals with dopamine transporter deficit (D+) or without dopamine transporter deficit (D–). Standardised dopamine transporter acquisition and analysis are essential. Several analysis protocols are used for dopamine transporter measurement. A goal will be to harmonise these outcomes to provide a unified standard. Data from several studies, including the Parkinson Progression Markers Initiative[70] and recent clinical trials,[71] are available to establish this quantitative standard.

There are also limited but evolving data showing that several PET tracers targeting dopamine transporters or vesicular monoamine transporters effectively detect dopaminergic dysfunction.[60,72,73] These PET tracers might be an alternative to ioflupane imaging. All PET and SPECT dopamine tracer data can be harmonised to a single quantitative scale, similar to the centiloid scale for amyloid imaging,[74] thereby enabling the incorporation of quantitative measures of dopamine transporter binding into future iterations of the NSD-ISS. Several other promising imaging modalities detect dysfunction in the dopaminergic system in vivo, such as neuromelanin-sensitive MRI.[72,73] The NSD-ISS research framework enables incorporation of any emerging measures of dopaminergic dysfunction in addition to or instead of dopamine transporter loss, once they have been rigorously replicated and validated.

Importantly, evidence suggests that n-αsyn can be detected by seed amplification assay before dopamine dysfunction is detectable by imaging.[2,40,75] Although most individuals develop detectable dopamine transporter loss before functional impairment,[63–67] signs or symptoms and functional impairment can occur in S+ individuals in the absence of dopamine transporter deficit. Additional data will clarify how frequently and under what conditions this impairment might occur. Furthermore, we acknowledge that presynaptic dopaminergic dysfunction is not specific for neuronal α-synuclein disease.[73]

Neuronal α-synuclein disease is a multisystem disease that might involve broad neuronal degeneration in the central, autonomic, and peripheral nervous system involving both dopaminergic and non-dopaminergic pathways.[76] The validation of imaging and other biomarkers that reflect neuronal α-synuclein disease-specific neurodegeneration will allow their incorporation into the NSD-ISS. Ultimately, we envision that a measure of neurodegeneration beyond dopaminergic dysfunction will be an anchor in the staging system.

G: genetic status

Genetic variants can either cause or increase risk for neuronal α-synuclein disease. Fully penetrant pathogenic variants in *SNCA*,[77] the gene that encodes α-synuclein, are disease-defining in the NSD-ISS. Individuals with these rare variants have a high certainty of developing n-αsyn pathology. Other genetic variants (G) identify individuals who might have increased age-dependent risk, but these individuals do not have neuronal α-synuclein disease unless they show evidence of n-αsyn (S+).

Genetics play a pivotal part in understanding neuronal α-synuclein disease biology, disease subtyping, and guiding therapeutic development. Pathogenic variants in numerous genes are associated with neuronal α-synuclein disease.[78–80] Approximately 10–15% of people with clinically diagnosed Parkinson's disease carry pathogenic variants, most commonly in *GBA1* and *LRRK2*.[81] Pathogenic variants in *GBA1* have also been identified in individuals with a clinical diagnosis of dementia with Lewy bodies.[79] These variants confer varied risk that is variant-dependent and increases with age.[82] Some less common genetic variants have high penetrance, such as biallelic pathogenic variants in *VPS13C, VPS35, PARK7, PINK-1,* and *PRKN*.[78] Furthermore, over 90 single nucleotide polymorphisms have been combined into a genetic risk score that is

associated with increased risk of clinical Parkinson's disease.[83] Given the low or variable penetrance of many genetic traits associated with neuronal α-synuclein disease, and that many individuals with these variants do not develop evidence for n-αsyn, the NSD-ISS does not consider genotype (aside from fully penetrant pathogenic variants in *SNCA*) sufficient to define the disease. However, understanding of the genetics of neuronal α-synuclein disease is important, and we expect the incorporation of genetics into the NSD-ISS to evolve.

Most individuals with risk variants who develop dopaminergic loss and functional impairment also have n-αsyn pathology and meet criteria for neuronal α-synuclein disease. However, a subset of individuals, including some individuals with pathogenic *LRRK2* variants or the majority of those with pathogenic *PRKN* variants, have evidence of dopaminergic dysfunction (D+), but do not have evidence of n-αsyn[2–4,84–86] (S- D+ G+). In the absence of n-αsyn at a given time of assessment, these individuals do not have detectable neuronal α-synuclein disease and must be defined and staged separately.

Overview of the NSD-ISS

Neuronal α-synuclein disease is a continuum, but discrete stages are required to provide a research framework for therapeutic development from the earliest stages, when pathological changes are identifiable but there are no clinical manifestations or functional consequences, to advanced disease. We propose an integrated staging system anchored on the disease biology (table 1). The biological definition of neuronal α-synuclein disease is key to enable staging based on biomarkers in

		Neuronal α-synuclein biomarker (S)	Dopamine dysfunction biomarker (D)	Clinical signs and symptoms attributable to neuronal α-synuclein disease	Functional impairment attributable to neuronal α-synuclein disease
Genetic risk					
R^{L}	(G) Genetic risk variants–low age-adjusted risk	Absent	Absent	No clinical signs or symptoms	No functional impairment
R^{H}	(G) Genetic risk variants–high age-adjusted risk	Absent	Absent	No clinical signs or symptoms	No functional impairment
Stage definition					
0	Fully penetrant *SNCA* variant (G+)	S–	D–	No clinical signs or symptoms	No functional impairment
1A	Characteristic pathological changes, but no evidence of clinical signs or symptoms	S+	D–	No clinical signs or symptoms	No functional impairment
1B	Characteristic pathological changes plus dopaminergic dysfunction, but no evidence of clinical signs or symptoms	S+	D+	No clinical signs or symptoms	No functional impairment
2A	Characteristic pathological changes and subtle detectable clinical signs and symptoms, but no functional impairment	S+	D–	Subtle clinical signs or symptoms that can be motor or non-motor: hyposmia, RBD, cognitive impairment, constipation, dysautonomia, depression, and anxiety	No functional impairment
2B	Characteristic pathological changes plus dopaminergic dysfunction and subtle detectable clinical signs and symptoms, but no functional impairment	S+	D+	Subtle clinical signs or symptoms that can be motor or non-motor: hyposmia, RBD, cognitive impairment, constipation, dysautonomia, depression, and anxiety	No functional impairment
3	Characteristic pathological changes plus dopaminergic dysfunction and clinical signs and symptoms causing slight functional impairment	S+	D+	Motor and non-motor signs and symptoms defined by a slight degree of functional impairment	Slight: functional impairment with minimal impact on activities of daily living
4	Characteristic pathological changes plus dopaminergic dysfunction and clinical signs and symptoms causing mild functional impairment	S+	D+	Motor and non-motor signs and symptoms defined by a mild degree of functional impairment	Mild: functional impairment severe enough to cause some impairment in activities of faily living, but those related to personal care are intact, such as bathing, dressing, walking, using the toilet, and eating
5	Characteristic pathological changes plus dopaminergic dysfunction and clinical signs and symptoms causing moderate functional impairment	S+	D+	Motor and non-motor signs and symptoms defined by a moderate degree of functional impairment	Moderate: functional impairment severe enough to require assistance with activities of daily living
6	Characteristic pathological changes plus dopaminergic dysfunction and clinical signs and symptoms causing severe functional impairment	S+	D+	Motor and non-motor signs and symptoms defined by a severe degree of functional impairment	Severe: functional impairment severe enough to depend on others for activities of daily living

The classification of the categories R^{L} and R^{H} for neuronal α-synuclein disease is based on genetic risk factors, including known pathogenic variants, and age. The penetrance of genetic risk factors is variable across age groups. Therefore, the R^{L} and R^{H} designations will be redefined even for the same variant. Furthermore, as new genetic risk factors are discovered, the criteria for the genetic risk groups will be updated. These genetic risk categories are not part of the neuronal α-synuclein disease integrated staging system (NSD-ISS) and are listed here to facilitate identification of individuals who might be at risk for neuronal α-synuclein disease, given the importance of genetics in the understanding of neuronal α-synuclein disease biology and future targeted therapeutics. D+=presence of neuronal dysfunction. D–=absence of neuronal dysfunction. RBD=rapid eye movement sleep behaviour disorder. R^{H}=high risk for neuronal α-synuclein disease. R^{L}=low risk for neuronal α-synuclein disease. S+=presence of neuronal α-synuclein. S–=absence of neuronal α-synuclein.

Table 1: **The proposed neuronal α-synuclein disease integrated staging system**

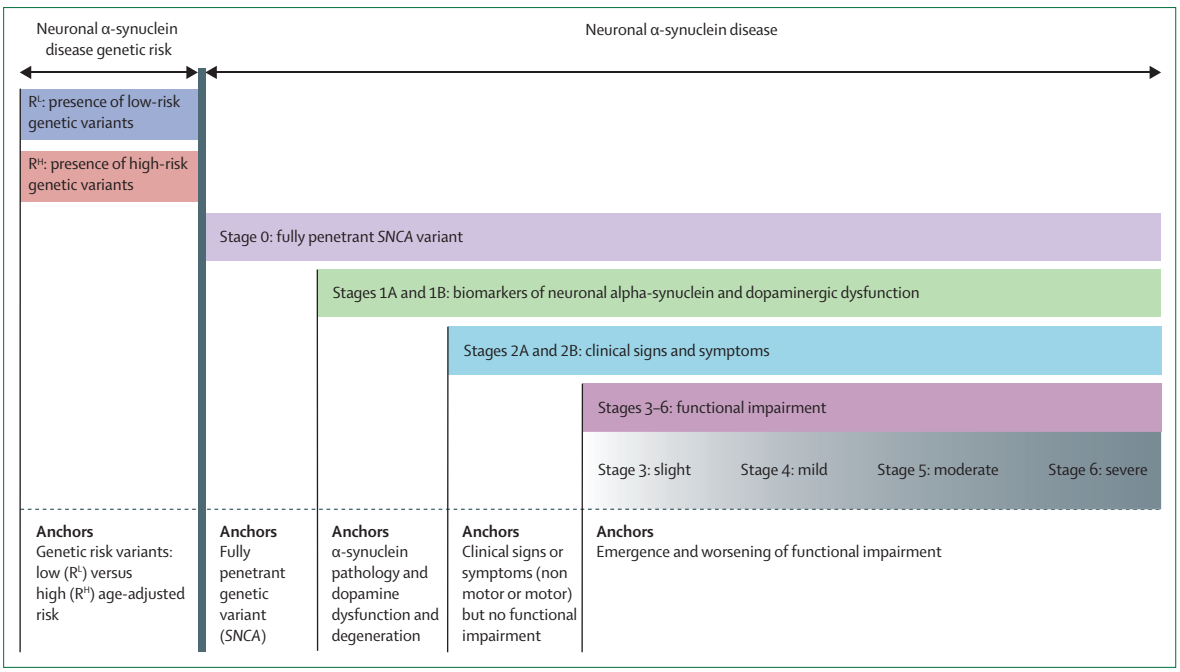

Figure 1: **Cumulative framework of the neuronal α-synuclein disease integrated staging system**

stages 1 and 2. Stages 3–6 are defined by integrating biomarkers with clinical signs or symptoms and specific anchors for their functional effect (figure 1). Although the NSD-ISS stages are sequential, differences in rates of progression might limit practical observation of early stages or sequential progression through subsequent stages in some individuals.

Individuals with pathogenic variants associated with neuronal α-synuclein disease risk, but who do not have evidence for n-αsyn, are categorised as low or high genetic risk (R^L or R^H respectively). These categories are referenced here to provide a framework within which to conduct research and clinical trials. However, as these individuals do not have neuronal α-synuclein disease, they are not assigned a stage.

Stages of the NSD-ISS

Stage 0 is defined by the presence of fully penetrant pathogenic variants in genes established to manifest with neuronal α-synuclein disease pathology. At present, fully penetrant pathogenic variants in *SNCA* are the only known genetic cause of neuronal α-synuclein disease that meet this criterion and therefore included in stage 0. These cases are very rare but important for understanding neuronal α-synuclein disease biology and targeting therapeutic development to prevent progression to, and beyond, stage 1. If other pathogenic variants that are fully penetrant for neuronal α-synuclein disease pathology are identified, they can be added to the definition of stage 0. Pathogenic variants in other genes do not define stages but are included along with S and D status in every stage.

Stage 1 and beyond require detection of n-αsyn (S+). Stage 1A includes individuals with biomarker evidence of n-asyn (S+), without evidence of dopaminergic dysfunction (D–), and no relevant signs or symptoms. Given the rarity of *SCNA* pathogenic variants, neuronal α-synuclein disease will start at stage 1 for most individuals. Stage 1B includes individuals with biomarker evidence of n-αsyn (S+) and dopaminergic dysfunction (D+), but no relevant signs or symptoms or functional impairment. We have separated stages 1A and 1B on the basis of the hypothesis that n-αsyn pathology precedes onset of dopaminergic dysfunction. Limited but accumulating data support this hypothesis,[2,40] but more evidence is required.

Stage 2 is defined by the presence of subtle clinical signs or symptoms without functional impairment. Clinical signs or symptoms can be motor or non-motor. Non-motor signs or symptoms include olfactory dysfunction, dysautonomia (orthostatic hypotension or heart rate abnormalities), constipation, neuropsychiatric symptoms (depression or anxiety), mild cognitive impairment, and disorders of sleep and wakefulness (rapid eye movement sleep behaviour disorder or excessive daytime sleepiness). Some non-motor symptoms, such as anxiety or constipation, might be non-specific, resulting from processes unrelated to n-αsyn pathology that are common in ageing. The lack of specificity of these clinical features is mitigated by the requirement for biomarkers of n-αsyn in these individuals, but we recognise that there is some uncertainty in the spectrum of the clinical features advancing individuals from neuronal α-synuclein disease stage 1 to 2, which requires investigation in future studies.

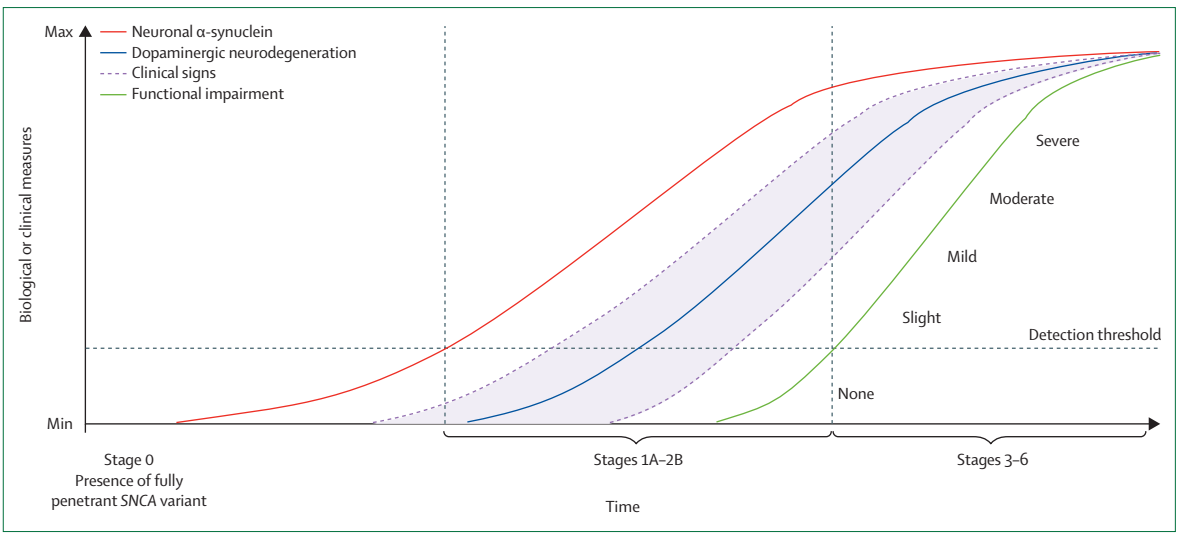

Figure 2: **Hypothetical model of dynamic biomarkers of the neuronal α-synuclein disease-integrated staging system (NSD-ISS)**
Shapes and slopes of the curves and their temporal relationship are qualitative and hypothetical.

	S anchor for NSD (S)	D anchor for NSD (D)	Genetic status (G)
Dopaminergic dysfunction with motor or cognitive functional impairment with predominantly glial asyn (ie, MSA)	S–	D+	NA
Dopaminergic dysfunction with motor or cognitive functional impairment without n-αsyn but with known biology (ie, PSP or CBD)	S–	D+	NA
Genetic variants with dopaminergic dysfunction but without evidence of n-αsyn	S–	D+	G+
Dopaminergic dysfunction with motor or cognitive functional impairment without n-αsyn and without known genetic variant (ie, unknown biology)	S–	D+	G–
Motor or cognitive functional impairment but without n-αsyn, dopaminergic dysfunction, known biology, or relevant genetic variants	S–	D–	G–

αsyn=α-synuclein. CBD=corticobasal degeneration. D+=presence of neuronal dysfunction. D–=absence of neuronal dysfunction. G+=presence of fully penetrant *SNCA* variant. G–=absence of fully penetrant *SNCA* variant. MSA=multiple system atrophy. n-asyn=neuronal α-synuclein. NA=not applicable. NSD=neuronal α-synuclein disease. PSP=progressive supranuclear palsy. S+=presence of neuronal α-synuclein. S–=absence of neuronal α-synuclein.

Table 2: **Biological or clinical categories that are not neuronal α-synuclein disease**

Similar to stage 1, stage 2 is subdivided into stages 2A and 2B on the basis of the presence of biomarkers. Therapeutics that slow or prevent individuals with evidence of n-αsyn pathology from developing dopaminergic dysfunction could be tested in individuals who are progressing from stage 1 to 2.

Stage 2B and beyond require the presence of biomarkers of both n-αsyn (S+) and dopaminergic dysfunction (D+). Most individuals with n-αsyn will have concurrent dopaminergic dysfunction and motor, cognitive, or other non-motor functional impairment.[57,63–67] However, additional evidence is required to determine the frequency to which functional impairment might occur in people with n-αsyn pathology before dopaminergic dysfunction. Current data suggest that this scenario is uncommon, but additional data could warrant modification of the requirement for both (S+) and (D+) to advance from stage 2A to stage 3. NSD-ISS provides a research framework to systematically address these questions.

In stages 3–6, the severity of functional impairment defines each progressive stage. Functional impairment can be driven by motor, cognitive, or other non-motor clinical signs or symptoms. Although this staging system is grounded on the neuronal α-synuclein disease biological framework, establishing the degree of functional impairment using a data-driven approach is necessary for therapeutic development and other applications of the NSD-ISS. We have conceptualised functional impairment qualitatively as progressing along the continuum of slight, mild, moderate, and severe, and provide categorical descriptors of this progression (table 1).

Most individuals with newly diagnosed Parkinson's disease, as defined by clinical diagnostic criteria,[22] will be stage 3, but some without functional impairment will be stage 2B. This staging based on biology and functional impairment is a major strength of the proposed framework, particularly to guide selection of participants for targeted drug development. Notably, those individuals with a cognitive syndrome and neuronal α-synuclein disease-defining biology will fit in the NSD-ISS based on anchors of cognitive functional impairment.

Although operational definitions of anchors for functional impairment for stages 3–6 are beyond the scope of this Position Paper, they are crucial for future versions of the NSD-ISS. We envision that the field will soon align on these definitions as data emerge. Examples of these anchors will be provided in a separate report to begin a data-driven discussion to develop consensus. Specifically, data derived from motor, non-motor, and cognitive functional rating scales assessments (ie, ability to perform activities of daily living) in prospective cohort studies and clinical trials will be used to define thresholds

for stages 3–6, similar to the Huntington's disease Integrated Staging System.[14] The Movement Disorders Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS)[87] Parts I and II are widely used to measure functional impairment and can be applied as a starting point. However, MDS-UPDRS has limited sensitivity to detect changes in function in early disease stages and new scales and approaches need to be developed.[88]

Progression of neuronal α-synuclein disease stages

Neuronal α-synuclein disease is a continuum, and an individual in a given stage is presumed to have passed through all preceding stages, beginning with stage 1A (figure 2). This presumption is supported by data from prospective observational studies,[2,40,63–67] although additional data from individuals in the earliest stages of neuronal α-synuclein disease are still needed. For example, an individual in stage 3 is presumed to have transitioned through stage 1 (1A, then 1B) and then stage 2. However, the transition through each of these stages might not be observed, depending on the timing of assessment. The NSD-ISS framework will enable the studies required to investigate timing for progression from each stage to the next and the key additional biological determinants that might influence the rate of progression.

Progression from stage 1 to stage 6 might not occur in all individuals with neuronal α-synuclein disease, but if it does occur, it might not be linear. It is probable that a substantial proportion of individuals in stage 1A—who are S+ but are asymptomatic—will not develop signs or symptoms and, therefore, might remain in stage 1A for life. As with other neurodegenerative diseases, including Alzheimer's disease[12,13] and Huntington's disease,[14] a biological definition of neuronal α-synuclein disease enables detection of asymptomatic disease, which is crucial for the development and testing of therapies that might prevent the progression of neuronal α-synuclein disease biology before any clinically meaningful consequences arise. We recognise that there might be important psychosocial and economic consequences to such early identification of neurodegenerative diseases that require further study. The NSD-ISS research framework will enable systematic evaluation to improve the process of informing research participants of their results.

Panel 2: Individuals who do not have neuronal α-synuclein disease

S– D+ G–: multiple system atrophy

Neuronal α-synuclein disease does not include multiple system atrophy. Multiple system atrophy is an α-synucleinopathy marked by predominantly glial α-synuclein accumulation.[30,92] Several lines of evidence support the notion that there are different α-synuclein strains in multiple system atrophy and neuronal α-synuclein disease.[41,92,93] For example, cryogenic electron microscopy studies have shown different conformations of α-synuclein filaments derived from brains of individuals with multiple system atrophy.[18] Advances in the most widely applied CSF α-synuclein seed amplification assay enable the distinction between neuronal α-synuclein (n-αsyn) and glial-predominant α-synuclein forms associated with multiple system atrophy, based on different maximum fluorescence emitted during amplification.[41,42,44,45]

S– D+ G–: other known biologies

Individuals with dopaminergic dysfunction who do not have neuronal α-synuclein disease might have other known biologies (table 2). Examples include progressive supranuclear palsy and corticobasal degeneration caused by tau-related or TDP-43-related neurodegeneration.[94]

S– D+ G+

Individuals with genetic variants (G+), such as in *LRRK2* or *PRKN*, with evidence of dopaminergic dysfunction (D+) and parkinsonism, but without evidence of n-αsyn (S–), whether assessed by CSF α-synuclein seed amplification assay or on neuropathological examination[2–4,84–86,95,96] do not have neuronal α-synuclein disease (table 2). Elucidating the pathology in these individuals is a research priority. This biological heterogeneity is only evident when the disease is defined by its biology, and highlights the value of a biological rather than a clinical disease definition. Understanding the biology of S– D+ G+ will inform and improve clinical trial design. The neuronal α-synuclein disease-integrated staging system (NSD-ISS) provides the framework for determining whether a given therapeutic strategy is appropriate for individuals with neurodegeneration or at risk of it, determined on the basis of knowledge of the mechanism of action and inclusion of biomarker-defined groups in study cohorts. For example, *LRRK2*-positive, S– participants might be included in *LRRK2*-targeted therapeutic studies independent of their S status,[97] but would not be candidates for n-αsyn-targeting therapeutic studies.

S– D+ G– with unknown biology

Among individuals with clinically diagnosed sporadic Parkinson's disease and with evidence of dopaminergic dysfunction, about 7% do not have n-αsyn, relevant genetic variants, or alternative known biology[2] (S– D+ G–; table 2). Although the CSF α-synuclein seed amplification assay as well as neuropathological studies[98] indicate that these individuals are truly n-αsyn negative, additional studies in larger population-based cohorts are needed to confirm this status. These individuals do not meet the biological definition for neuronal α-synuclein disease. Further studies will elucidate the relevant biologies underling the neurodegenerative process in these individuals. Importantly, these individuals should not be enrolled into α-synuclein-targeting therapeutic trials, highlighting the importance of an accurate biological definition.

Neuronal α-synuclein disease-associated clinical syndromes

The core principle of the NSD-ISS is that neuronal α-synuclein disease is defined by biology. Yet, a disease based on a single biology might have protean clinical manifestations. Individuals with neuronal α-synuclein disease might have a range of clinical syndromes, including a motor syndrome (ie, Parkinson's syndrome based on a biological definition), cognitive syndromes (ie, dementia with Lewy bodies or Parkinson's dementia), neuropsychiatric syndromes (ie, anxiety or depression), a sleep disorder (ie, rapid eye movement-sleep behaviour disorder), and other non-motor syndromes (ie, autonomic or hyposmia; appendix p 2). In most cases these syndromes will overlap, and contributions from motor and non-motor features will produce a cumulative effect on functional impairment. Clinical presentations arising from neuronal α-synuclein disease include n-αsyn-driven motor parkinsonism and cognitive impairment—currently diagnosed as Parkinson's disease, Parkinson's disease dementia, or dementia with Lewy bodies based on clinical diagnostic criteria.[22–24] Other well described syndromes

Panel 3: **Outstanding research questions**

- Although the CSF α-synuclein seed amplification assay is a validated biomarker of neuronal α-synuclein (n-αsyn), it requires CSF collection, and the assay is currently available in a small number of qualified laboratories. Thus, more feasible and scalable measures for n-αsyn are required.
- Additional data on n-αsyn are needed in diverse cohorts representative of the general population, in a greater number of disease populations, including larger cohorts of research participants with a clinical diagnosis of dementia with Lewy bodies, and in the real-world setting. This data acquisition will be enabled by scalable and feasible n-αsyn assessment.
- The S (presence of neuronal α-synuclein) and D (presence of dopaminergic dysfunction) domains are currently categorical. There is a crucial need for quantitative biomarkers to measure disease onset, progression, and response to therapy.
- Development of biomarkers that are minimally invasive and cost-effective will facilitate inclusive and representative population screening.
- The timeline of progression along the axis of biological staging is unknown. The prevalence of n-αsyn in asymptomatic older adults is age-dependent and is estimated at 5–12%.[2,6,27,39,99] These individuals have neuronal α-synuclein disease. Studies are needed to better understand the epidemiology of these stage 1A individuals, including the incidence of and rate of progression to D+, and incident functional impairment. Such data will be essential to enable therapeutic development for prevention of disability.
- Understanding the biology of research participants with clinically diagnosed Parkinson's disease or dementia with Lewy bodies who do not have neuronal α-synuclein disease (S– D+ G+ individuals and S– D+ G– individuals) is a high priority.
- As reliable biomarkers emerge that reflect molecular changes of underlying neurodegeneration (ie, mitochondrial, lysosomal, inflammatory, and other pathways[30]) that are neuronal α-synuclein disease-specific, additional biological anchors will be introduced to refine the staging system.
- Neuronal α-synuclein disease is a multisystem disease that involves neurodegeneration in other neurotransmitter systems besides dopamine.[76] With validation of biomarkers that reflect pathology in these systems will come the opportunities to incorporate them.
- Defining specific functional anchors across stages 3–6 was outside of the scope of this Position Paper and is underway. Several observational cohort studies, including the Parkinson Progression Markers Initiative,[70] the Dementia with Lewy Bodies Consortium,[100] and clinical trials[71] offer crucial data that will allow validation of functional anchors.
- Current understanding of the clinical features of neuronal α-synuclein disease, especially in its earliest stages, is largely based on findings from prospective cohort studies of clinically diagnosed individuals recruited according to genetic risk or presence of non-motor features.[19,20] With the biological definition of neuronal α-synuclein disease comes the opportunity to study biomarker-defined cohorts and observe the evolution of non-motor and motor features to establish the specificity for underlying biology. As additional data emerge, stage 2 of the neuronal α-synuclein disease-integrated staging system might be modified to incorporate the relative weights of different clinical features according to their specificity for an underlying cause.
- A key challenge for the neuronal α-synuclein disease-integrated staging system will be the assessment of the degree of contribution of multiple co-pathologies on functional impairment (particularly cognitive impairment). Acquiring Alzheimer's disease and other neurodegenerative biomarkers might become a routine component of neuronal α-synuclein disease staging.

include rapid eye movement-sleep behaviour disorder[89] and dysautonomia, including pure autonomic failure;[90] neuropsychiatric symptoms might predominate as well.[19,21] Although the NSD-ISS provides a unifying biological definition and staging, recognition of clinical syndromes is important to guide symptomatic management, family support, and education.

Another important implication of the biologically based framework of the NSD-ISS is that a clinical diagnosis of prodromal Parkinson's disease, Parkinson's disease, Parkinson's disease dementia, or dementia with Lewy bodies is neither sufficient nor necessary for a neuronal α-synuclein disease diagnosis. The NSD-ISS unifies what is currently defined as prodromal Parkinson's disease and dementia with Lewy bodies[19–21] and related disorders along the same continuum of progression of the neuronal α-synuclein disease neurodegenerative process (figure 1). The current distinction of prodromal versus clinically diagnosed Parkinson's disease or dementia with Lewy bodies is arbitrary, lacks standardised criteria for transition, and creates barriers in therapeutic development. Terminology such as phenoconversion lacks operational definition and is faulted by subjectivity. Enrolling individuals with neuronal α-synuclein disease in stages 1 and 2 (previously termed prodromal cohorts) into trials testing experimental therapeutics targeting specific molecular pathways is of high interest.[7,8] Success of these clinical trials depends on identifying participants with a unifying underlying disease biology and establishing the framework for defining progression. A biological definition and integrated staging system aims to accomplish both goals.

Incorporating other pathologies into the NSD-ISS framework

Many individuals have mixed pathology and comorbid diseases in addition to neuronal α-synuclein disease. A key challenge for the NSD-ISS will be to assess the relative effect of clinical signs or symptoms, particularly cognitive function, on functional impairment in individuals with multiple underlying pathophysiological processes and variable clinical syndromes. The NSD-ISS enables the investigation of the biological mechanisms resulting in functional impairment and the incorporation of biomarkers of Alzheimer's disease and other conditions into the neuronal α-synuclein disease staging.

Individuals who do not have neuronal α-synuclein disease

Based on extensive data from multiple cohorts,[2–4,6] the biological definition of neuronal α-synuclein disease applies to the majority (>90%) of individuals diagnosed with Parkinson's disease or dementia with Lewy bodies as per current clinical diagnostic criteria. By defining the disease based on biology, and specifically by the presence of n-αsyn, application of the NSD-ISS might result in the identification of individuals with parkinsonism and

evidence of dopaminergic dysfunction (D+)[2] who are n-αsyn negative (S–). These individuals do not have neuronal α-synuclein disease, regardless of their clinical syndrome, even in the presence of evidence of dopaminergic dysfunction or pathogenic genetic variants, and staging by NSD-ISS does not apply to them (table 2). Although determining the cause of parkinsonism in such individuals is critical, it is beyond the scope of this Position Paper; S– status does not inform alternative diagnoses but highlights specific examples of relevance to therapeutic development and the need for further research (panel 2)

Conclusions and future directions

Although evidence strongly support the biological definition for neuronal α-synuclein disease and the NSD-ISS, we recognise that there are knowledge gaps and that our understanding of neuronal α-synuclein disease biology and staging will evolve. These gaps, in turn, define key research priorities for the field. Importantly, the NSD-ISS provides a framework within which to answer key outstanding research questions, which will inform future iterations of the staging system (panel 3).

This first iteration of the NSD-ISS is intended to provide a research framework to accelerate therapeutic development, similar to the evolution of disease definition and staging of Alzheimer's disease.[12,13] At present, application of the NSD-ISS in the clinical setting is premature, and it is inappropriate to use the NSD-ISS clinically before sufficient data are available to enable understanding of stage-dependent disease progression. The goal is eventually achieving a clinically useful staging system to aid in early, accurate diagnosis, and to guide treatment.

During the process of development of the NSD-ISS (appendix p 1), there was broad consensus from key stakeholders[15] that its adoption would improve therapeutic development at all disease stages, from before onset of signs or symptoms through mild to severe functional impairment. Identifying individuals on the basis of biological characteristics enables a new approach to developing therapies targeting relevant biology that will pave the way for precision medicine in the treatment of neuronal α-synuclein disease.[8,91]

The NSD-ISS, with a consistent and uniformly understood definition of the study cohort at each stage, provides a framework for clinical trial design and evaluation by key constituencies, including pharmaceutical drug developers, regulators, academic experts, and clinical trial participants. It also enables development of stage-dependent outcomes to allow assessment within a stage and to define changes between stages[91] (eg, outcomes could reflect change from stage 2B to stage 3 or from stage 1 to stage 2). In turn, the availability of stage-appropriate endpoints can facilitate therapeutic development, including symptomatic therapies for individuals in late stages of the disease. Importantly, it also ensures that individuals who do not have n-αsyn pathology are not enrolled into n-αsyn-targeting therapeutic trials.

An advantage of the NSD-ISS will be to reduce heterogeneity in clinical trials by requiring biological consistency within the study cohort, rather than identifying study participants on the basis of clinical criteria for Parkinson's disease and dementia with Lewy bodies, which introduces heterogeneity. Moreover, the NSD-ISS provides a framework for designing studies to answer several crucial outstanding questions related to the epidemiology of neuronal α-synuclein disease, including the prevalence of asymptomatic n-αsyn in the general population (ie, prevalence of stage 1), incidence of n-αsyn positivity in different populations, and temporal progression across stages, including from S+ D– to S+ D+.

The NSD-ISS will enhance trial design, provide a consistent definition for the study cohort at each stage, and enable selection of trial endpoints. The NSD-ISS will evolve as new data and biomarkers emerge. Presently, the NSD-ISS is intended for research use only; its application in the clinical setting is premature and inappropriate.

Contributors

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