A biological classification of Parkinson's disease: the SynNeurGe research diagnostic criteria

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With the hope that disease-modifying treatments could target the molecular basis of Parkinson's disease, even before the onset of symptoms, we propose a biologically based classification. Our classification acknowledges the complexity and heterogeneity of the disease by use of a three-component system (SynNeurGe): presence or absence of pathological α-synuclein (S) in tissues or CSF; evidence of underlying neurodegeneration (N) defined by neuroimaging procedures; and documentation of pathogenic gene variants (G) that cause or strongly predispose to Parkinson's disease. These three components are linked to a clinical component (C), defined either by a single high-specificity clinical feature or by multiple lower-specificity clinical features. The use of a biological classification will enable advances in both basic and clinical research, and move the field closer to the precision medicine required to develop disease-modifying therapies. We emphasise the initial application of these criteria exclusively for research. We acknowledge its ethical implications, its limitations, and the need for prospective validation in future studies.

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Introduction

A rapidly growing body of evidence provides insights into the molecular pathogenesis of Parkinson's disease, allowing the opportunity to develop disease-modifying therapies. This evidence shows that Parkinson's disease—to date, thought of as a clinicopathological entity[1]—might have various genetic or environmental causes that initiate the disease along different, only partly overlapping pathways.[2–6] Neuropathological findings have highlighted the fundamental role of Lewy pathology (ie, Lewy bodies and Lewy neurites) and its major molecular component (misfolded species of the protein α-synuclein), which we refer to as Parkinson's type synucleinopathy.[7,8] The neuropathological evidence has helped to clarify the differences between Parkinson's disease and other synucleinopathies, such as multiple system atrophy, but has also challenged the traditional boundaries between Parkinson's disease and dementia with Lewy bodies.[9,10] Neuropathological evidence has also shown that Lewy pathology is neither sufficient nor necessary for a diagnosis of clinically defined Parkinson's disease, as some patients with clinical and genetic Parkinson's disease do not have these neuropathological features.[11]

Fluid, tissue, and imaging biomarkers now allow for objective identification of genetic risk, pathological processes, and neurodegeneration, even before overt clinical symptoms have appeared. However, despite these advances, the current diagnostic criteria for Parkinson's disease are almost exclusively based on the identification of clinical features, and have been so for more than a century.[1,10,12] Furthermore, the cardinal motor features do not become evident until some 60–80% of nigral dopaminergic neurons are lost.[13,14] Furthermore, there is no single neurobiologically based disease construct. A biological approach to the classification and diagnosis of Parkinson's disease could serve as the basis for objective preclinical and clinical diagnosis and staging, and for accurate subdivision of Parkinson's disease according to pathogenic mechanisms. A biological diagnosis could also advance research in multiple fields, such as epidemiology, biomarker discovery, and precision medicine, including development of disease-modifying therapies. A main reason why disease-modifying therapies have not been established to date might be the exclusive reliance on clinical diagnosis without adequate biological stratification.

In this Personal View, we propose a biological classification of Parkinson's disease that considers the presense or abscense of pathological α-synuclein (S) in tissues or body fluids, the presence of characteristic features of neurodegeneration (N), and genetic contributions (G). We propose the term SynNeurGe (pronounced phonetically as synergy) for this composite, to highlight the relationships and interactions between its three principal components. The establishment of a biological definition of Parkinson's disease recognises that the biological processes that eventually lead to the development of the cardinal clinical features of Parkinson's disease are present long before the onset of these features, and that it is now possible to detect biological changes much earlier than was previously feasible. We propose this classification and criteria for research purposes exclusively, rather than as diagnostic criteria for clinical practice.

Proposed components of a biological classification of Parkinson's disease

Although most cases of Parkinson's disease are considered sporadic, genetic factors (eg, evidenced by polygenic risk scores) contribute to the development of the disease and monogenic causes account for a minority of cases. Genetic or epigenetic mechanisms are presumably among the most upstream biological factors underlying the disease, but these are still poorly defined for most patients with sporadic Parkinson's disease with Lewy pathology. We have therefore chosen to highlight synuclein status as the first component in our biological

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See Online for appendix

Panel 1: **The new Parkinson's disease concept**

We propose a biological classification of Parkinson's disease based on the presence or absence of pathological α-synuclein (S) in CSF or peripheral tissue, neuroimaging features defining the presence of neurodegeneration (N), and the presence of Parkinson's disease-specific pathogenic gene variants (G). Some of these genetic variants serve as the earliest upstream cause of Lewy pathology (ie, Parkinson's type synucleinopathy). The latter is believed to result in or be associated with Parkinson's disease-related neurodegeneration that eventually leads to clinical signs and symptoms in many functional domains. However, variations from this sequence are extremely common, such as the absence of Parkinson's disease-specific pathogenic gene variants in most cases of Parkinson's disease, or pathological changes lacking synucleinopathy in a minority of patients with a genetic cause or predisposition. Moreover, the pattern of Parkinson's disease-associated neurodegeneration (and its clinical correlates) can vary considerably between individuals. Therefore, we propose an overarching biological approach that encompasses this variability.

Although the clinical signs and symptoms associated with Parkinson's disease are part of a continuum that reflects the stage of the disease and its variability, when applying a biological construct, they are not considered defining features of the disease. The proposed biological classification encompasses and harmonises different concepts derived from a predominantly clinical perspective, including preclinical,[10] premotor, and prodromal Parkinson's disease,[12,15] non-motor syndromes (rapid eye movement sleep behaviour disorder[15] and postganglionic pure autonomic failure[16]), Parkinson's disease,[10,17,18] Parkinson's disease with dementia,[19] and dementia with Lewy bodies.[19–21]

classification. Panel 1 summarises this notion and other general concepts underlying our proposed biological classification of Parkinson's disease.

Synucleinopathy

The pathology of Parkinson's disease, with few exceptions, is defined by the presence of widespread aggregated α-synuclein in the form of Lewy bodies and Lewy neurites in the peripheral nervous system and CNS. It is widely believed that the deposition and spread of pathological forms of misfolded α-synuclein are key in the development and progression of the neurodegenerative process.[22] The development of biomarkers to establish the presence of Parkinson's type synucleinopathy in living patients has advanced rapidly in the past 5 years. On the basis of results from large cross-sectional[23–25] and longitudinal[26,27] studies, we recommend the designation of Parkinson's type synucleinopathy status as α-synuclein positive (S^+) if a pathological test specified in table 1 is confirmed. All other conditions are considered as α-synuclein negative (S^-). The list in table 1 might change as more sensitive and specific tests become available.

We propose that the demonstration of pathological α-synuclein species should be a defining molecular anchor of the Parkinson's disease classification (ie, an S^+ or S^- designation). Current criteria for the neuropathological diagnosis of sporadic Parkinson's disease require the presence of Lewy pathology.[28] Therefore, within our proposed biological classification, all individuals designated as having sporadic Parkinson's disease must be S^+. Asymptomatic S^+ individuals are classified as having Parkinson's type synucleinopathy, acknowledging that it is uncertain if these individuals will eventually develop clinical disease. Some patients with genetic forms of Parkinson's disease will be classified as S^- because they might lack α-synuclein aggregation (eg, particularly most carriers of a biallelic *PRKN* variant[29] and a proportion of patients with *LRRK2*-Parkinson's disease[30]). Thus, we propose that carriers of gene variants with sufficiently high penetrance should be classified as S^- forms of Parkinson's disease.

Multiple methods have evaluated the presence of pathological α-synuclein in vivo in biological fluids (ie, CSF, saliva, blood, and tears) and tissues (ie, skin, salivary glands, gastrointestinal tract, and olfactory mucosa; appendix pp 4–6). However, the evidence does not support the use of quantitative measurements of α-synuclein concentrations in biological fluids as a marker of a biological diagnosis.[31,32] Immunohistochemistry and immunohistofluorescence to assess the presence of pathological α-synuclein have been applied to multiple tissues. The data suggest that only skin biopsies, with specific methods (appendix pp 6–8), provide adequate diagnostic sensitivity and specificity to distinguish between patients with Parkinson's disease, people with rapid eye movement (REM)-sleep behaviour disorder as a presumed early clinical manifestation of Parkinson's disease, and healthy controls to be considered useful for a biological classification. The pattern and distribution of α-synuclein in biopsies should be taken into consideration to differentiate Parkinson's disease from multiple system atrophy (appendix pp 6, 22–23).

The development of α-synuclein seed amplification assays has revolutionised the widespread application of a biological diagnosis of Parkinson's disease[33,34] (appendix pp 8–11). α-synuclein positivity, detected by use of these assays, has been found in multiple biological samples, with the highest sensitivities in skin and CSF (0·92 [95% CI 0·87–0·95] and 0·90 [0·86–0·93], respectively).[35] Seed amplification assays might be positive in patients at very early stages of the pathological process (eg, people with REM-sleep behaviour disorder or pure autonomic failure).[26,27] These assays have also distinguished patients with Parkinson's disease from people with dopamine transporter scans without evidence of dopaminergic deficit (SWEDD)[36] and have corresponded with the expected underlying neuropathologies in patients with

	Biomarker status	Method of evaluation	Sensitivity*	Specificity*
S^+	Endorsed	α-synuclein seed amplification assays in CSF	High	High
S^+	Endorsed	α-synuclein seed amplification assays in skin	High	High
S^+	Endorsed	α-synuclein immunohistochemistry or immunohistofluorescence in skin	Moderate	High
S^+	Investigational	α-synuclein seed amplification assays in neuronal exosomes from plasma	Insufficient evidence	Insufficient evidence
S^+	Investigational	α-synuclein seed amplification assays in plasma or serum	Insufficient evidence	Insufficient evidence
S^+	Investigational	α-synuclein seed amplification assays in submandibular gland	Insufficient evidence	Insufficient evidence
Exclusion criterion ruling out S^+ (eg, non-Parkinson's disease synucleinopathy)	For S^+ testing unable to differentiate Parkinson's disease from multiple system atrophy†	Elevated neurofilament light chain	High for atypical parkinsonism (eg, multiple system atrophy)	High for multiple system atrophy but low for specific diagnoses (eg, also elevated in progressive supranuclear palsy, but these cases would be S^- in the absence of co-pathology)
Exclusion criterion ruling out S^+ (eg, non-Parkinson's disease synucleinopathy)	For S^+ testing unable to differentiate Parkinson's disease from multiple system atrophy†	Neuroimaging features of multiple system atrophy (eg, characteristic changes in the putamen, cerebellum, and pons)	Moderate	High

Endorsed means that we propose the biomarker for the operationalisation of the SynNeurGe criteria. Investigational means that the biomarker might be endorsed once more reliable data become available (appendix pp 2–23). S^+=α-synuclein positive. S^-=α-synuclein negative. *High sensitivity and specificity: >80%; moderate sensitivity and specificity: >70% and ≤80%; low sensitivity and specificity: ≤70%. †To date, although some seed amplification assays applied to the CSF and immunohistochemistry or immunohistofluorescence studies of the skin purport to be able to distinguish between Lewy pathology (ie, Parkinson's type synucleinopathy) and multiple system atrophy, further confirmatory evidence is needed and therefore additional exclusionary testing is recommended.

Table 1: **Proposed research criteria for Parkinson's type synucleinopathy**

genetic forms of Parkinson's disease. Some examples that can illustrate this point are provided by S^+ *GBA1*-associated Parkinson's disease, similar to people with sporadic Parkinson's disease (ie, positivity as high as 96%). People with *LRRK2* -associated Parkinson's disease have more variable results (68–78%), and patients with Parkinson's disease with biallelic pathogenic variants in autosomal recessively inherited genes, particularly *PRKN*, are largely S^-.[25,37] However, these detection methods have limitations, especially related to the differentiation of Parkinson's disease from multiple system atrophy (table 1; appendix pp 8–10, 22–23). Rapid advances are anticipated, particularly with the development of reliable blood-based seed amplification assays,[38,39] and the eventual shift from binary positive and negative diagnostic test results to methods of monitoring disease status and progression.

Many biological pathways are postulated to be involved in Parkinson's disease. Numerous studies have evaluated potential biomarkers for Parkinson's disease, including markers of neurodegeneration, neuroinflammation, protein aggregation, proteostasis network components (appendix pp 2–3, 12–13), and enteric dysfunction,[40] but none reliably distinguishes people with Parkinson's disease from healthy controls or from other neurodegenerative parkinsonian disorders. Given the biological heterogeneity, technological complexity, interlaboratory variability, and the need for cross-validation by different laboratories, these approaches are not ready for use as diagnostic biomarkers.[41,42] Thus, we recommend that the S^+ or S^- component of the biological classification of Parkinson's disease document the presence of Parkinson's type synucleinopathy by use of validated immunohistochemistry, immunohistofluorescence, or seed amplification assays in skin biopsies or seed amplification assays in CSF (table 1) while other tissues, fluids, and methods are still being investigated.

Neurodegeneration

In our proposed criteria, evidence of any of the findings listed in table 2 is sufficient to define neurodegeneration in biologically suspected Parkinson's disease (appendix pp 23–34).However, available methods have inadequate specificity to differentiate between people with Parkinson's disease and those with other neurodegenerative forms of parkinsonism, and they focus on a limited number of neuroanatomical systems, chiefly the nigrostriatal dopaminergic projection.

A principal confirmation of Parkinson's disease-associated neurodegeneration is dopaminergic denervation. Reduced striatal uptake (typically asymmetric and with a caudal to rostral pattern) can be detected by use of molecular imaging markers for the dopamine transporter (DAT), vesicular monoamine transporter 2 (VMAT2), or aromatic amino acid decarboxylase (F-dopa). Although the sensitivity of these methods is high, similar findings can be detected in patients with multiple system atrophy (including the rostral–caudal gradient) or progressive supranuclear palsy (which tends to affect the caudate and putamen equally).[43] Findings incompatible with Parkinson's disease—and more typical of other neurodegenerative parkinsonisms—include radioisotopic evidence of marked post-synaptic dopamine receptor loss (eg by use of [^{11}C]raclopride-PET or [^{123}I]iodobenzamide-SPECT).[44]

A second indirect indication of Parkinson's disease-associated neurodegeneration is altered glucose metabolism, evidenced by [18F]fluorodeoxyglucose PET. Although changes in glucose metabolic networks (known as Parkinson's disease-related pattern) reflect alterations in the activity of nigrostriatal–pallido–thalamo–cortical projections and are therefore only indirectly related to the loss of nigrostriatal dopaminergic neurons, these changes are so typical as to provide presumptive evidence of denervation to define Parkinson's disease. Similar changes can be detected in prodromal disease (ie, in those with REM-sleep behaviour disorder).[45] These alterations have also been reported in a small cohort of patients taking neuroleptics, which is therefore an important exclusionary criterion for this marker.[46] The specificity of FDG-PET Parkinson's disease related pattern within degenerative forms of parkinsonisms is high because atypical parkinsonisms, such as multiple system atrophy, progressive supranuclear palsy, or corticobasal syndrome are associated with different characteristic patterns.[47]

A third line of evidence indicating Parkinson's disease-associated neurodegeneration is cardiac sympathetic denervation. Reduced tracer uptake on meta-iodobenzylguanidine SPECT provides sufficient evidence of peripheral cardiac sympathetic denervation to define the presence of neurodegeneration in people with Parkinson's disease. This evidence can be seen in prodromal disease (in people with REM-sleep behaviour disorder or pure autonomic failure) but not in all patients with early stage Parkinson's disease.[48] The specificity of cardiac sympathetic imaging is high, but imperfect, as abnormalities in tracer uptake have been reported in patients with progressive supranuclear palsy and, especially, in patients with multiple system atrophy, and interpretation can be challenging.

Non-dopaminergic molecular imaging of other neurotransmitter systems, for example by use of PET tracers of CNS serotonin or noradrenaline transporters, or PET ligands of acetylcholine esterase to show peripheral cholinergic denervation are of interest, but not sufficiently validated yet to be the basis of the definition of Parkinson's disease-related neurodegeneration.[49–51]

Imaging of substantia nigra pathology with iron-sensitive MRI, free water, or neuromelanin are promising future markers of neurodegeneration but are still considered investigational (table 2).[43] In our classification, the Parkinson's disease-associated neurodegeneration status of a person is positive (N^+) if a pathological test specified in table 2 is confirmed. All other conditions are considered as N^-.

Genetics

Monogenic pathogenic variants predisposing to Parkinson's disease can be detected in up to 15% of patients[52] and in selected populations, such as Arab Berbers, this proportion can reach 40% of cases with

	Biomarker status	Examination	Interpretation	Sensitivity*	Specificity*
N^+	Endorsed	Dopaminergic PET or SPECT	Striatal dopaminergic deficit	High	Low
N^+	Endorsed	Metabolic FDG-PET	Parkinson's disease-related brain metabolic pattern	High	High
N^+	Endorsed	Cardiac meta-iodobenzylguanidine SPECT	Sympathetic cardiac denervation	Moderate to high	Moderate
N^+	Investigational	Neuromelanin MRI	Limited test–retest stability	Moderate to high	Low
N^+	Investigational	Iron-sensitive MRI	Sophisticated method restricted to specialised centres, might not directly prove neurodegeneration	Moderate to high	Low
N^+	Investigational	Substantia nigra free water MRI	Sophisticated method restricted to specialised centres, might not directly prove neurodegeneration	High	Moderate to high if applied to extranigral sites
N^+	Investigational	Structural MRI (T1) morphometry	Sophisticated method restricted to specialised centres	Low	Moderate to high
N^+	Investigational	Diffusion tensor imaging	Sophisticated method restricted to specialised centres	Low to moderate	High
N^+	Investigational	Multimodal MRI	Sophisticated method restricted to specialised centres	Moderate to high	High
Exclusion criterion ruling out N^+	Endorsed	Structural MRI	Findings characteristic of atypical parkinsonism—eg, progressive supranuclear palsy (midbrain and superior cerebellar peduncle atrophy), multiple system atrophy (pontine atrophy, hot cross bun sign, cerebellar atrophy, increased basal ganglia iron with putaminal rim), and corticobasal syndrome (parietal atrophy)	Moderate, stage dependent	High
Exclusion criterion ruling out N^+	Endorsed	FDG-PET	Progressive supranuclear palsy and multiple system atrophy have characteristic patterns that are distinct from Parkinson's disease	High	High

Endorsed means that we recommend the biomarker for the operationalisation of the SynNeurGe criteria. Investigational means that the biomarker might be endorsed once more reliable data become available (appendix pp 24–34). N^+=positive Parkinson's disease-associated neurodegeneration status. FDG=[18F]fluorodeoxyglucose. *High sensitivity and specificity: >80%; moderate sensitivity and specificity: >70% and ≤80%; low sensitivity and specificity: ≤70%.

Table 2: **Proposed research criteria for Parkinson's disease-associated neurodegeneration**

Parkinson's disease.[53,54] Confirmed types of monogenic Parkinson's disease include four dominantly inherited forms (*SNCA*, *LRRK2*, *VPS35*, and *CHCHD2*) and three recessively inherited forms (in *PRKN*, *PINK1*, and *PARK7*).[55] The likelihood of developing clinical Parkinson's disease in asymptomatic carriers of a pathogenic variant depends on the gene involved and, in the case of *SNCA* and *GBA1*,[56] on the specific variant. With respect to *GBA1*, only the variants that increase the risk of manifesting Parkinson's disease, and can thus be viewed as pathogenic variants acting in a dominant fashion with highly reduced (age-dependent) penetrance,[57] qualify for use in our proposed biological classification. Reduced penetrance—ie, the conditional probability of being affected by a disease given a particular genotype—is well documented in inherited disorders.[58] Detailed genotype and phenotype information on these conditions is available[59,60] from the International Parkinson and Movement Disorder Society (MDS) gene database except for information on *GBA1* and *CHCHD2* variants, whose investigation is in progress.

In our classification, we propose different categories of genetic pathogenic effects (table 3; appendix pp 35–37). The first category includes the most likley fully penetrant variants: *SNCA* triplications, *SNCA* missense variants, and biallelic *PRKN*, *PINK1*, and *PARK7* missense, nonsense, small indels, and copy number variants. The second category includes the genetic variants that confer a strong predisposition to Parkinson's disease but with incomplete penetrance, such as *SNCA* duplications and variants in *LRRK2*, *VPS35*, and *CHCHD2*. The third category includes the genetic variants that result in intermediate and lower predispositions, including pathogenic *GBA1* variants; *GCH1* monoallelic variants[61,68] and 22q11.2 deletion syndrome[67] might also fall into this category but are considered investigational to date.

A second aspect to consider regarding Parkinson's disease-specific genetic variants is the degree of predisposition for a Parkinson's type synucleinopathy (table 3). For example, variants in *SNCA*[62] or *GBA1*[57] appear to unequivocally predispose to Parkinson's type synucleinopathy. *LRRK2* monoallelic (or biallelic) variants predispose to Parkinson's type synucleinopathy in most cases, although neurodegeneration without synucleinopathy occurs in a substantial minority of cases.[61] Biallelic variants in *PRKN* predispose to a Parkinson's type synucleinopathy in approximately 20% of cases.[29] Only a few postmortem reports are available for people with variants in *PINK1*,[63,64] *PARK7*,[65] or *CHCHD2*,[66] and those with the 22q11.2 deletion syndrome.[67] Some of these variants are associated with Parkinson's type synucleinopathy, but not all, or with a low level of evidence. For variants in *VPS35* and *GCH1*, the predisposition for a Parkinson's type synucleinopathy is unknown.[61]

We recommend reporting the Parkinson's disease genetic status of an individual as positive if a fully penetrant genetic variant (G_F^+) or a variant with strong or

For more on the **Movement Disorder Society gene database** see www.mdsgene.org

	Biomarker status	Genetic variant	Pathogenic effect	Predisposition for
G_F^+	Endorsed	*SNCA* monoallelic triplication[61,62]	Fully penetrant	Parkinson's type synucleinopathy
G_F^+	Endorsed	*SNCA* monoallelic pathogenic single nucleotide variants[61,62]	Fully penetrant	Parkinson's type synucleinopathy
G_F^+	Endorsed	*PRKN* biallelic pathogenic variants[61]	Fully penetrant	Neurodegeneration without synucleinopathy in ~80% of cases and Parkinson's type synucleinopathy in ~20% of cases
G_F^+	Endorsed	*PINK1* biallelic pathogenic variants[61,63,64]	Fully penetrant	Parkinson's type synucleinopathy in a single case[63] and neurodegeneration without synucleinopathy in another[64]
G_F^+	Endorsed	*PARK7* biallelic pathogenic variants[61,65]	Fully penetrant	Parkinson's type synucleinopathy in the single case reported[65]
G_P^+	Endorsed	*SNCA* monoallelic duplication[61,62]	Strong predisposition	Parkinson's type synucleinopathy
G_P^+	Endorsed	*LRRK2* monoallelic (or biallelic) pathogenic variants[61]	Strong predisposition	Parkinson's type synucleinopathy in most cases; neurodegeneration without synucleinopathy in a minority of cases
G_P^+	Endorsed	*VPS35* monoallelic pathogenic variants[61]	Strong predisposition	Unknown
G_P^+	Endorsed	*CHCHD2* monoallelic pathogenic variants[61,66]	Strong predisposition	Unknown
G_P^+	Endorsed	*GBA1* monoallelic severely pathogenic variants[57,61]	Intermediate predisposition	Parkinson's type synucleinopathy
G^-	Investigational	*GCH1* monoallelic pathogenic variants[61]	Low or uncertain predisposition	Parkinson's type synucleinopathy in the single case published
G^-	Investigational	22q11.2 deletion syndrome[61,67]	Low or uncertain predisposition	Neurodegeneration without synucleinopathy in a third and Parkinson's type synucleinopathy in two-thirds of published cases

Endorsed means that we recommend the biomarker for the operationalisation of the SynNeurGe criteria. Investigational means that the biomarker might be endorsed once more reliable data become available (appendix pp 35–37). G_F^+=Presence of a fully penetrant pathogenic gene variant. G_P^+=Presence of a pathogenic gene variant with strong or intermediate predisposition for Parkinson's disease. G^-=Genetically indeterminate—ie, presence of a pathogenic gene variant with a low predisposition for Parkinson's disease, or evidence from polygenic risk scores, or absent or unknown genetic contributions.

Table 3: **Proposed research criteria for Parkinson's disease-specific pathogenic gene variants**

	Synucleinopathy	Neurodegeneration	Biological designation
Sporadic disease			
G^-	S^+	N^+	Sporadic Parkinson's disease
G^-	S^+	N^-	Sporadic Parkinson's type synucleinopathy
G^-	S^-	N^+	Non-Parkinson's disease neurodegeneration (or false-negative S test)
G^-	S^-	N^-	No evidence for Parkinson's disease
Genetic disease			
G_F^+	S^+ or S^-	N^+ or N^-	Genetic Parkinson's disease (eg, carriers of *SNCA* pathogenic variants)
G_P^+	S^+	N^+	Genetic Parkinson's disease (eg, carriers of *GBA1* pathogenic variants)
G_P^+	S^+	N^-	Genetic Parkinson's type synucleinopathy (eg, *GBA1*-Parkinson's type synucleinopathy)
G_P^+	S^-	N^+ (gene predisposing for either Parkinson's type synucleinopathy or non-synucleinopathy)	Genetic α-synuclein negative Parkinson's disease (eg, carriers of *LRRK2* or *PRKN* pathogenic variants)
G_P^+	S^-	N^+ (gene consistently predisposing for Parkinson's type synucleinopathy)	Non-Parkinson's disease neurodegeneration (or false-negative S-test)
G_P^+	S^-	N^-	Genetic predisposition for Parkinson's disease (eg, *GBA1* predisposition for Parkinson's disease)

G^-=Genetically indeterminate status (ie, presence of a pathogenic gene variant with a low predisposition for Parkinson's disease, or polygenic risk scores, or absent or unknown genetic contributions (appendix pp 35–37). S^+=Presence of Parkinson's type α-synucleinopathy. N^+=Presence of Parkinson's disease-associated neurodegeneration. N^-=Absence of Parkinson's disease-associated neurodegeneration. S^-=Absence of Parkinson's type α-synucleinopathy. G_F^+=Presence of a fully penetrant pathogenic gene variant. G_P^+=Presence of a pathogenic gene variant with strong or intermediate predisposition for Parkinson's disease.

Table 4: **Proposed biological research classifications in biomarker-positive individuals with sporadic or genetic disease**

intermediate predisposition (G_P^+) is confirmed (table 3). All other conditions (genetic variants or polygenic risk scores with a low predisposition for Parkinson's disease, or absent or unknown genetic contributions) are considered as genetically indeterminate (G^-).

The biological classification

The biological classifications of sporadic and genetic Parkinson's disease resulting from different combinations of biomarkers are listed in table 4. Any diagnostic interpretation must consider the possibility of false-negative findings in the S, N, and G categories due to current technical limitations. In our SynNeurGe classification, an isolated S^+ designation defines Parkinson's type synucleinopathy if N^+ is not yet present. S^+ is an essential prerequisite for a biological Parkinson's disease classification in G^- individuals (ie, patients with sporadic Parkinson's disease) but requires further evidence of N^+ (since there are no established biomarkers of neuronal dysfunction preceding neurodegeneration).

As indicated earlier, genetic causes of Parkinson's disease are variably associated with Parkinson's type synucleinopathy. For some people with genetic Parkinson's disease (eg, carriers of *SNCA* variants or triplications), S^+ is expected as the biological process becomes established but, in other people, S^+ might never occur (eg, in most carriers of *PRKN* variants). Therefore, G^+ individuals can be classified as having Parkinson's disease, even when they are S^-, if they carry a genetic variant that does not invariably predispose to a Parkinson's type synucleinopathy. N^+ generally indicates the transition from Parkinson's type synucleinopathy to biologically defined Parkinson's disease (or to genetic S^- Parkinson's disease in rare instances).

Because monogenic conditions can have long preclinical periods, starting as early as at birth or even conception, the field of hereditary neurodegenerative disease is adapting its classifications to consider the long preclinical period in someone with a highly penetrant genetic form as the earliest disease stage.[67] Therefore, in our classification, we recommend that carriers of fully penetrant variants designated as G_F^+ qualify, by definition, for a diagnosis of genetic Parkinson's disease (figure; table 4). Individuals with pathogenic gene variants with reduced penetrance would qualify as having genetic predisposition for Parkinson's disease, but require additional evidence of neurodegeneration to be classified as genetic Parkinson's disease. Individuals carrying gene variants with low predisposition for Parkinson's disease, or with polygenic risk scores, or with absent or unknown genetic status are considered as genetically indeterminate.

Conditions not compatible with a diagnosis of Parkinson's disease are also reported in table 4. A critical appraisal of these allocations is presented in the appendix (pp 38–40).

Clinical manifestations

S^+ or G^+ individuals must be further subclassified by their clinical status, regardless of their N status, since signs and symptoms might arise from neuronal dysfunction preceding neurodegeneration, or from undetected neurodegeneration. Once the biological definition has been made, potentially associated clinical signs and symptoms (C^+) can be documented to establish if they are attributable to that individual's Parkinson's disease. To this end, the

proposed clinical criteria below can be applied to any individual designated as S^+, N^+, or G^+.

The concept of a C^+ state

There are four considerations for defining the concept of a C^+ state (appendix pp 41–44). First, early clinical symptoms of Parkinson's disease are diverse, can fluctuate in severity, and are often predominantly non-motor, reflecting pathology outside the brain areas that currently define clinical Parkinson's disease on standard diagnostic criteria (ie, mainly the substantia nigra). Although non-motor features frequently precede motor features, there is no uniform order of appearance (precluding a specific unitary, initial non-motor, and then motor staging). Moreover, non-motor features and subtle motor features commonly coexist. Therefore, a clinical status designation should not rely upon the nature and the order of appearance of clinical features. Second, clinical symptoms differ in their specificity. In the context of biological Parkinson's disease, some signs and symptoms are almost pathognomonic (eg, core motor features, REM-sleep behaviour disorder, and neurogenic orthostatic hypotension). However, many symptoms are common in the general population and will remain non-specific, even after a diagnosis of biological Parkinson's disease. Third, many clinical features are also early phase markers of other synucleinopathies, including multiple system atrophy and dementia with Lewy bodies lacking motor features of Parkinson's disease. Although clinical clues can help distinguish these conditions (eg, normal olfaction suggesting multiple system atrophy and mild cognitive impairment suggesting dementia with Lewy bodies), it is not possible to reliably identify the disease at this early phase on the basis of clinical markers alone. Finally, the C^+ state should not be confused with a disease stage. Clinical markers of early Parkinson's disease include those with a long latency to full clinical Parkinson's disease (such as olfaction and autonomic dysfunction) and others that become overtly abnormal only proximate to a clinical diagnosis of Parkinson's disease (such as cognitive changes and motor exam).

The C^+ state includes all clinical stages of disease. Moreover, in our definition, there is no distinction between prodromal and defined disease stages. In the future, clinical status could also be stratified according to its effects on activities of daily living (eg, mild, moderate, and severe functional impairment). In summary, the core definition of a C^+ state implies that clinical signs or symptoms of Parkinson's disease have occurred because of the underlying biological process.

Methodology for the diagnosis of the C^+ state

We recommend the reporting of clinical status in a three-component system: asymptomatic individuals (C^-) and those with defined clinical features possibly (C_{poss}^+), or probably (C_{prob}^+) related to Parkinson's disease. Our criteria for the C^+ states are provided in panel 2. For each of these clinical features, it should be presumed that no other, more probable explanation exists for the sign or symptom (according to best clinical judgement). For example, if a person has subthreshold parkinsonism and is taking medications that can cause parkinsonism, or has urinary dysfunction probably explained by prostatism, the clinical feature should not be scored as present. Moreover, the development of the clinical feature should be consistent with early Parkinson's disease (eg, a static symptom with onset before age 30 years would generally be excluded). These criteria are to be applied to people with biological evidence of Parkinson's disease (ie, S^+, N^+, or G^+). If such evidence is not present, the International Parkinson and MDS criteria for prodromal Parkinson's disease should be used for individuals without parkinsonism[12,69] and the MDS criteria for clinical Parkinson's disease[10] used for those who have parkinsonism.

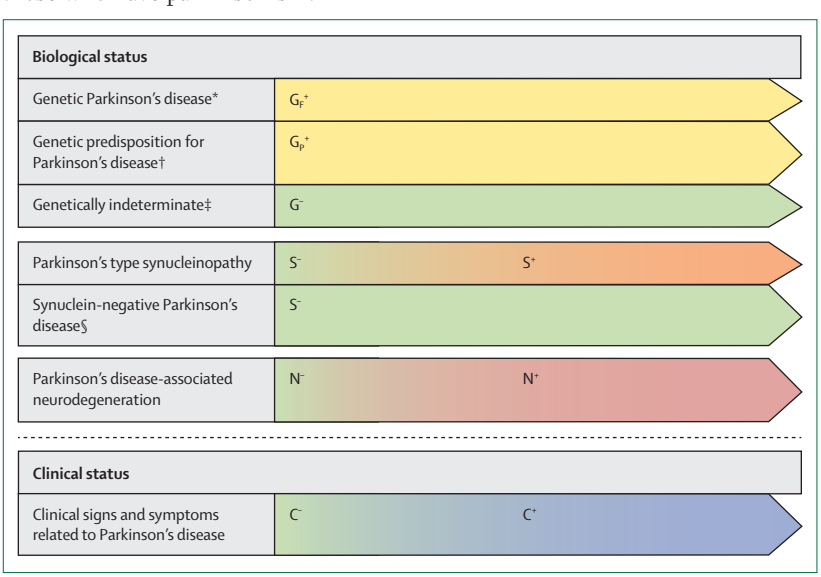

Figure: **Research framework of our biological classification of Parkinson's disease**
Temporal sequence and variability of the components contributing to the biological classification of Parkinson's disease. Green bars indicate a physiological condition and the other colours indicate pathological conditions. Colour gradients indicate that transitions of states are gradual. The temporal relationship between onset of S^+ and N^+ is not fully understood. Our framework does not imply any temporal alignment of the occurrence of the different C states in relation to the S, N, or G states, and that is emphasised by the horizontal dashed line. S^+=Presence of Parkinson's type α-synucleinopathy. S^-=Absence of Parkinson's type α-synucleinopathy. N^+=Presence of Parkinson's disease-associated neurodegeneration. N^-=Absence of Parkinson's disease-associated neurodegeneration. G_F^+=Presence of a fully penetrant pathogenic gene variant. G_p^+=Presence of a pathogenic gene variant with strong or intermediate predisposition for Parkinson's disease. G^-=Genetically indeterminate (ie, presence of a pathogenic gene variant or polygenic risk scores with a low predisposition for Parkinson's disease or absent or unknown genetic contributions). C^+=Presence of clinical symptoms or signs potentially associated with Parkinson's disease. C^-=Absence of clinical symptoms or signs potentially associated with Parkinson's disease. *Fully penetrant pathogenic gene variants qualify for a diagnosis of genetic Parkinson's disease on the basis of G^+ per se. †Pathogenic gene variants with strong or intermediate predisposition for Parkinson's disease qualify as genetic predisposition; a diagnosis of Parkinson's disease additionally requires N^+. ‡Pathogenic gene variants or polygenic risk scores with low predisposition for Parkinson's disease, or absent or unknown genetic contributions are considered genetically indeterminate; a diagnosis of Parkinson's disease additionally requires S^+ and N^+. §α-synuclein-negative Parkinson's disease can be diagnosed in people with pathogenic gene variants that do not consistently predispose for a Parkinson's type synucleinopathy (eg, a carrier of a pathogenic *LRRK2* variant with S^-, and N^+). S^+, N^+, or G^+ individuals must be further subclassified by their clinical status, regardless of their N status, since signs and symptoms might arise due to neuronal dysfunction, preceding overt neurodegeneration.

Panel 2: **Clinical manifestations in patients meeting criteria for a biological diagnosis of Parkinson's disease**

These clinical features are to be documented in individuals designated as G^+, S^+, or N^+ (by the criteria outlined in the text and tables 1, 2, and 3) using the following criteria. Unless otherwise noted, the definition of each feature from the Movement Disorder Society's prodromal Parkinson's disease criteria[12,69] applies. For each feature, it should be verified that there is no other, more probable explanation based on best clinical judgment and that the temporal evolution of the symptom is consistent with Parkinson's disease.

Clinical features possibly related to Parkinson's disease (C_{poss}^+)

- Option 1: if S^+ or N^{+*} then at least one feature from one of the following categories.
- Option 2: if isolated G^+ (S^- and N^-) then at least one feature from two of the following categories.

Motor features

A single cardinal manifestation of parkinsonism (ie, expert-examined bradykinesia, rigidity, or rest tremor); abnormal quantitative motor testing (>1 SD below age-adjusted normal motor speed)†.

Sensory features

Olfactory loss.

Autonomic features

Chronic constipation; urinary dysfunction; severe erectile dysfunction (onset <60 years); probable neurogenic orthostatic hypotension (ie, heart rate increase <0·5 bpm/mm Hg systolic blood pressure drop).[70]

Sleep

History of REM-sleep behaviour disorder (polysomnographic confirmation not necessary); excessive daytime somnolence.

Cognition

Mild cognitive impairment.

Clinical features probably related to Parkinson's disease (C_{prob}^+)

- Option 1: if S^+ or N^{+*} then at least one feature from at least two of the previous categories (clinical features possibly related to Parkinson's disease).
- Option 2: if isolated G^+ (S^- and N^-) then at least one feature from at least three of the previous categories (clinical features possibly related to Parkinson's disease).
- Option 3: if G^+, S^+, or N^+ then at least one of the following features: parkinsonism[10] (bradykinesia plus either rigidity or rest tremor); dementia; REM sleep behaviour disorder (polysomnography confirmed); neurogenic orthostatic hypotension (laboratory confirmed; ≥20/10 mm Hg blood pressure drop within 3 min of standing or head-up tilt test).[70]

G^+=positive Parkinson's disease genetic status, when a fully penetrant pathogenic variant or a pathogenic variant with strong or intermediate predisposition is confirmed. S^+=Presence of Parkinson's type α-synucleinopathy. N^+=Presence of Parkinson's disease-associated neurodegeneration (see table 2). S^-=Absence of Parkinson's type α-synucleinopathy. N^-=Absence of Parkinson's disease-associated neurodegeneration. bpm=beats per minute. REM=rapid eye movement. *N^+ would only be considered when combined with G^+ or S^+. †As with the assessment of clinical motor manifestations, no other more probable explanation for the test result (according to best clinical judgement) should be present (appendix pp 36–38).

Conclusions and future directions

We propose a biological classification of Parkinson's disease consisting of Parkinson's type synucleinopathy, Parkinson's disease-associated neurodegeneration, and Parkinson's disease specific genetic variants. Our approach is proposed exclusively for research purposes. Advances in the past 5 years, including the establishment of sensitive and specific in vivo biomarkers to detect the presence of α-synuclein pathology,[33–35] have placed the field in the crucial position of shifting from largely clinically based diagnostic criteria to an emphasis on the biological underpinnings of a disease that affects the peripheral nervous system and CNS decades before our clinical approaches permit diagnostic consideration. A biological classification of Parkinson's disease is mandatory for the next stage of basic and clinical research studies and will serve as a framework for future biomarker-based subclassification and staging systems that will allow implementation of precision medicine approaches to disease modification.

New criteria that incorporate biological components have been proposed for other neurodegenerative diseases, including Alzheimer's disease[71] and Huntington's disease,[72] and are contributing to clinical research advances. Our biological criteria of Parkinson's disease, with three binary classes (SynNeurGe), is similar but not identical to the amyloid, tau, and neurodegeneration (ATN) classification proposed for Alzheimer's disease.[71] As with the ATN system, which was instigated by the development of amyloid and especially tau biomarkers, the SynNeurGe criteria have been made possible by the development of tools to detect α-synuclein pathology in vivo. The ATN approach was proposed at an early stage in the validation process of tau imaging and has been developed further with the plan to incorporate new phospho-tau plasma markers.[73] Similarly, we believe that the validation of synuclein biomarkers is now sufficiently advanced to allow the development of a biological research criteria. Although it could be argued that, to date, the ATN classification has not resulted in the development of fully effective disease-modifying therapies for Alzheimer's disease, it has led to advances in our understanding of the pathobiology of Alzheimer's disease and is affecting drug development. We have carefully considered and proposed the criteria for each component of this SynNeurGe classification with the similar goal of supporting such broadly based research, beyond its application to disease-modifying clinical trials.

There are similarities and clear differences between the two approaches. For example, although the ATN classification does not specify clinical status, our proposed approach includes a clinical component layered onto the binary SynNeurGe components. Furthermore, the ATN system does not factor in temporal ordering, but our approach implies an order to the three components: S^+ and then N^+ in sporadic disease and G^+, then S^+ or S^-, and then N^+ in genetic subtypes. However, this sequence of events is only assumed and might not be accurate in all S^+ cases. Although our proposed criteria might suggest many complex combinations (details provided in tables 1, 2, and 3), it is actually a simple binary approach to the three components, as has been widely applied in the ATN system, with the clinical component added only to S^+, N^+, or G^+ cases. Acknowledging that about 15% of Parkinson's disease cases are monogenic,[52] we distinguish between

Panel 3: Differences between the SynNeurGe and the NSD-ISS criteria

SynNeurGe

A biological classification in which Parkinson's disease (ie, a genetic and sporadic disease) involves multifaceted, complex biological processes.

Terminology and scope

Parkinson's type synucleinopathy is defined by prevailing Lewy pathology (Lewy bodies and Lewy neurites).[76] The classification accepts genetic forms of Parkinson's disease without Parkinson's type synucleinopathy as can be assessed by current methods.

Purpose

Designed for all types of research studies, including epidemiology, genetics, neuroimaging, biomarkers, and clinical trials, not limited or restricted to a single method of defining synuclein or neurodegeneration status.

Method

An evidence-based and consensus-based approach done exclusively by academic experts in various aspects of Parkinson's disease pathogenesis, genetics, biomarkers, imaging, and clinical features.

Aim

A Parkinson's disease classification system to define subtypes within the broad biological spectrum of the disease.

Stages

Not formally proposed since prospective studies must first show the sequence of events in the proposed Parkinson's disease classification.

α-synuclein

Detected by CSF and skin seeding amplification assays, skin immunohistochemistry or immunohistofluorescence; multiple system atrophy can be differentiated by these assays and exclusion criteria (appendix pp 22–23). Individuals classified as $G^{-}S^{+}N^{-}$ are designated as having Parkinson's type synucleinopathy; considerably more research is required to determine implications.

Neurodegeneration

Detected by presynaptic dopaminergic imaging tracers; [^{18}F]fluorodeoxyglucose as a marker of Parkinson's disease-related metabolic pattern; meta-iodobenzylguanidine SPECT as a marker of peripheral autonomic involvement.

Genetics

Includes both genetic and sporadic Parkinson's disease, including fully penetrant pathogenic gene variants (G_{F}^{+}) and pathogenic gene variants with strong or intermediate predisposition (G_{P}^{+}) states; allows for α-synuclein negative (S^{-}) genetic subtypes.

Exclusion criteria

Specified for Parkinson's type synucleinopathy (S), Parkinson's disease-associated neurodegeneration (N), and Parkinson's disease-specific genetic variants (G).

Clinical features

Motor and non-motor clinical markers are clearly defined and designated as possibly or probably related to Parkinson's disease.

Neuronal α-synuclein disease integrated staging system (NSD-ISS)

Posits a biological definition restricted to α-synuclein pathology (ie, one disease caused by one biology).

Terminology and scope

The distinction between neuronal synuclein disease and Lewy body disease is unclear,[8] and does not account for astrocytic synuclein pathology in patients with Parkinson's disease or neuronal synuclein pathology in patients with multiple system atrophy.

Purpose

Designed primarily for targeted therapeutics predominantly in early stages of sporadic Parkinson's disease. This approach would not be inclusive of disease-modifying trials targeting some genetic causes of Parkinson's disease, such as in trials of *GBA1* activators, *LRRK2* kinase inhibitors, or *PRKN* activators. Furthermore, in S^{-} individuals, α-synuclein is assumed to have no role in their disease pathogenesis. They would therefore be excluded from all trials targeting this component.

Method

Consensus process satisfying the interests of multiple stakeholders.

Aim

A staging system to describe sequentially occurring events in neuronal synuclein disease.

Stages

Seven proposed stages (0–6) mixing diagnostic biomarker testing with functional impairment (biomarker testing defines earlier stages, and functional impairment defines later stages; no data available on progression from the earliest to the next stages (ie, from stage 1 to stage 2).

α-synuclein

Detected by use of CSF seed amplification assays only. The criteria postulate exclusion of multiple system atrophy by neuronal synuclein disease-specific seed amplification assay (which has not been fully validated to date). Individuals characterised as $S^{+}D^{-}G^{+}$ are designated as having a defined early state of disease (neuronal α-synuclein disease).

Neurodegeneration

Detected by use of dopamine transporter SPECT imaging only.

Genetics

The criteria exclude most genetic forms of Parkinson's disease and refer mostly to sporadic disease, and very rare *SNCA* variants.

Exclusion criteria

Not specified.

Clinical features

The criteria lists motor and non-motor features, but these features are not operationalised.

genetic and non-genetic forms and acknowledge a category of genetic Parkinson's disease in individuals who carry highly penetrant pathogenic gene variants (G_F^+) but don't have other biological criteria. Similar to the staging of Huntington's disease,[72] these cases might be classified as a stage 0 Parkinson's disease. Individuals with incompletely penetrant genetic predisposition (ie, carriers of variants in *LRRK2* or *GBA1*) could be compared with people at risk of Huntingdon's disease with 36–39 CAG repeats in the huntingtin gene.

Beyond these similarities, our approach differs from the biological classifications proposed for Alzheimer's disease[71] and Huntington's disease[72] particularly in that we propose an integrative biological approach with a causal spectrum ranging from purely sporadic (apart from polygenic risk) to purely genetic forms of the disease. We propose a C^+ state component, because the extensive background data used in the Huntington's disease and Alzheimer's disease staging systems (eg, sequential biomarkers, neuroimaging, clinical, and functional changes) are not yet available for Parkinson's disease. However, the prospective application of our biological classification would permit and enhance the generation of such data.

The incorporation of an S^- designation is essential to our criteria. Our system acknowledges that α-synuclein is not necessary for the development of clinical Parkinson's disease and is absent in a proportion of patients with selected genetic forms—particularly in carriers of *LRRK2* variants[61]—and in most patients with biallelic *PRKN* pathogenic variants.[29] However, most patients with *LRRK2* variants are S^+, and some patients with biallelic pathogenic *PRKN* variants show classic Lewy body pathology, as do most patients with clinical parkinsonism carrying *PRKN* heterozygous pathogenic variants. There is insufficient information about biallelic pathogenic *PINK1* and *PARK7* variants, although both have been reported to be associated with S^+ Lewy body pathology.[63–65] Given this knowledge, we believe that defining Parkinson's disease exclusively as a synucleinopathy misrepresents our understanding of the pathogenesis of Parkinson's disease, and the formal acknowledgment of S^- cases will advance our understanding of Parkinson's disease. We have therefore chosen the classification designation, rather than proposing a biological definition of Parkinson's disease, to underscore its biological heterogeneity. This approach makes no distinctions between prodromal and clinical stages, or between clinical Parkinson's disease and dementia with Lewy bodies. However, this approach should not be interpreted as an invalidation of accepted diagnostic criteria for these clinical states. The biological and clinical designations overlap and serve different purposes. The criteria for prodromal Parkinson's disease[12] and dementia with Lewy bodies[20] remain useful for the identification of patients in whom markers for S, N, and G cannot yet be detected, and for identifying patients with mild cognitive impairment or neuropsychiatric symptoms who have early stage dementia with Lewy bodies. The clinical criteria for Parkinson's disease[10] remain important in making accurate diagnoses of Parkinson's disease, as the cause of parkinsonism and the clinical criteria for dementia with Lewy bodies[20] remain important for identifying this disease as the underlying cause of dementia. Our biological criteria of Parkinson's disease recognise the unifying biological factors underlying both diseases.

Shortly after our proposal was published in preprint form,[74] a group working in affiliation with the Michael J Fox Foundation presented an alternative disease definition[75] (neuronal α-synuclein disease) and integrated staging system (NSD-ISS). There are similarities between the two proposals, but considerable differences too. In panel 3, we compare the SynNeurGe and NSD-ISS criteria.[77] Despite some similarities,

Panel 4: Limitations of the SynNeurGe criteria and ethical concerns

Although our biological classification of Parkinson's disease is proposed for the exclusive purposes of advancing research, the application of these criteria to asymptomatic individuals in a non-research setting is a scenario with important ethical concerns and implications,[78,79] particularly given the limited understanding of the natural history of individuals in the various biological categories that we propose and the inability to prevent progression of Parkinson's disease from its early stages. Prospective studies must validate the evolution of these biological categories and provide more reliable methods to predict the underlying biological processes in asymptomatic individuals. Many asymptomatic individuals fulfilling criteria for some biological designations might never develop signs and symptoms of Parkinson's disease. This circumstance would be similar to that of some amyloid-positive individuals in the ATN system. Future research made possible by this biological approach will advance the understanding of the factors that promote neurodegeneration or protect individuals from following this course. Important studies will include population-based risk screening, biomarker assessment, and longitudinal follow-up of sufficiently large cohorts for sufficiently long periods to understand the prognostic implications of Parkinson's type synucleinopathy in asymptomatic individuals. Such knowledge will be mandatory for the successful application of disease-modifying therapy at the very earliest disease stages. α-synuclein CSF seed amplification assays and skin immunohistochemistry evaluations and genetic testing are already being marketed to consumers, so the restriction of a biological classification of Parkinson's disease exclusively for research purposes emphasises the need to proactively limit the inappropriate use of these commercial tests. Proposing this biological classification for research purposes now is preferable to generating a belated reactive response to the widespread free market application of these tests.

important differences in the overall constructs and purposes of the two proposals must be emphasised. The SynNeurGe biological classification attempts to incorporate the complex multifaceted biological factors that underlie Parkinson's disease to support a broad range of future research approaches. However, in the NSD-ISS criteria, the biological definition of neuronal synuclein disease is restricted to sporadic patients who are positive in CSF seed amplification assays, and only includes rare *SNCA* genetic cases. This definition forms the basis of the NSD-ISS staging system, developed to accelerate therapeutics especially targeted at premotor stages. The NSD-ISS criteria present its biological categories as stages, whereas we refer to the proposed categories as states that do not imply a sequence of events. We deliberately refrained from proposing stages because we believe that longitudinal studies must first show the temporal evolution in the proposed classification scheme. Moreover, we consider that the available seed amplification assays, which are binary (positive or negative), do not have the robustness to follow disease progression. Therefore, we present a classification that can be used to define subtypes within the Parkinson's disease spectrum and can be broadly applied in research with the goal of establishing precision medicine for Parkinson's disease.

We believe that establishing a biological classification of Parkinson's disease will advance research on several fronts, including epidemiology, natural history, neuroimaging, clinical trials, the development of newer biomarkers, etc. However, we also acknowledge important limitations and concerns (panel 4).

The genetic component of our classification has major limitations. We expect continuous advances in our understanding of genetic (including polygenic risk scores and genomic data from global, rather than largely White populations) and environmental risk factors (including gene–environment interactions and epigenetic factors) and potential protective factors. These advances could be eventually incorporated into future iterations or revisions of this classification. No regulatory agencies, such as the US Food and Drug Administration, have formally approved the methods for defining the presence of pathological α-synuclein that we have endorsed. Therefore, further studies, including blinded and confirmatory analyses of samples derived from multiple centres, are required to evaluate the sensitivity of these methods for defining synuclein positivity and their relationship with peripheral nervous system and CNS pathology. We also expect further optimisation of S and N biomarkers that will improve the sensitivity and specificity of the endorsed testing. For example, we expect the development of successful S imaging tracers that can be easily incorporated into our criteria. We also expect that new tools will successfully identify disease mechanisms in subgroups of patients, allowing their incorporation into the biological scheme (eg, a markers of inflammation or mitochondrial dysfunction). Finally, other classification components could be combined with SynNeurGe designations when appropriate (eg, an additional ATN designation[71] or other biomarkers of dementia with Lewy bodies[20,21] in patients with cognitive impairment or a neuroimaging marker of cerebrovascular co-pathology). We emphasise that these research criteria are the first step in the crucial process of moving the field from a purely clinical towards a biological approach to Parkinson's disease.

Search strategy and selection criteria

GUH and AEL initiated the consensus process. After initial discussions on the overarching structure of the biological classification of Parkinson's disease, we established working groups on Parkinson's disease synucleinopathy (CHA, TFO, and AEL), Parkinson's disease-associated neurodegeneration (WP and AJS), Parkinson's disease-specific pathogenic gene variants (CK and GUH), and Parkinson's disease-associated clinical status (DB and RP). The working groups conducted the literature searches and reviewed the available evidence underpinning the use of their respective biological constructs and proposed and presented solutions for each component to the group in a series of virtual rounds (that took place between June, 2022, and July, 2023) for critical discussion, combined with follow-up emails until a unanimous consensus was reached on each component and its integrated interpretation. References were identified by searches of PubMed between Jan 1, 2000, and Jan 1, 2023, by use of the search terms: "Parkinson's disease AND neurobiology, neuropathology, neurodegeneration, MRI, PET, SPECT, genetic, mutation, OR synuclein". There were no language restrictions. We narrowed the selection by evaluating review articles published in the past 5 years discussing the biological basis of Parkinson's disease and evaluated all original research articles on the biological definition of Parkinson's disease by sequential analysis of titles, abstracts, and full manuscripts. The final reference list was generated on the basis of relevance to the topic of this Personal View.

Contributors

GUH designed and drafted the figures. All authors contributed to the study design, searched the literature, did data collection, analysis, and interpretation, and contributed to the writing of this Personal View. GUH and AEL contributed equally to the final revisions of the manuscript.

Declaration of interests

GUH reports participation in industry-sponsored research projects from AbbVie, Bial, Biogen, Biohaven, Novartis, Sanofi, Takeda, and UCB; served as a consultant for AbbVie, Alzprotect, Aprineua, Asceneuron, Bial, Biogen, Biohaven, Kyowa Kirin, Lundbeck, Novartis, Retrotope, Roche, Sanofi, and UCB; received honoraria for scientific presentations from AbbVie, Bayer Vital, Bial, Biogen, Bristol Myers Squibb, Kyowa Kirin, Roche, Teva, UCB, and Zambon; received publication royalties from Academic Press, Kohlhammer, and Thieme; and holds a patent on the Treatment of Synucleinopathies (US patent:

US 10,918,628 B2; European patent: EP 17 787 904·6–1109/3 525 788). CHA reports consultant fees from Cionic, CND Life Science, Jazz, Neurocrine, Precon Health, and XW Pharma. DB reports having served on advisory boards of UCB Pharma and ACImmune; received honoraria from Biogen, UCB Pharma, and Novartis; and her research was supported by UCB Pharma, the European Union, Novartis Pharma, and Lundbeck. CK is deputy editor of *Movement Disorders* and associate editor of *Annals of Neurology*; serves as a medical adviser to Centogene for genetic testing reports in the fields of movement disorders and dementia, excluding Parkinson's disease; serves as a medical advisor to Retromer Therapeutics; received honoraria for scientific presentations from Bial and Desitin; and does not hold any stocks or stock options with any companies that are connected to Parkinson's disease or to any of the topics in this Personal View; WP reports personal fees from AbbVie, AFFiRiS, AstraZeneca, Bial, Boston Scientific, Britannia, Intec, Ipsen, Lundbeck, NeuroDerm, Neurocrine, Denali Pharmaceuticals, Novartis, Orion Pharma, Prexton, Teva, UCB, and Zambon; royalties from Thieme, Wiley Blackwell, Oxford University Press, and Cambridge University Press. RP received personal fees as an advisor from Takeda, Roche, Biogen, AbbVie, Curasen, Lilly, Novartis, Eisai, Merck, and Vaxxinity; and received a stipend from the International Parkinson and Movement Disorder Society. AJS chairs a data safety monitoring board for Neurocrine; serves on a data safety monitoring board for AskBio; serves as an advisor to Capsidia; receives a stipend from the International Parkinson & Movement Disorder Society as editor-in-chief of *Movement Disorders*. AEL has served as an advisor for AbbVie, AFFiRis, Alector, Amylyx, Aprinoia, Biogen, BioAdvance, BlueRock, Biovie, Bristol MyersSquibb, CoA Therapeutics, Denali, Janssen, Jazz, Lilly, Novartis, Paladin, Pharma 2B, PsychoGenetics, Retrophin, Roche, Sun Pharma, and UCB; received honoraria from Sun Pharma, AbbVie and Sunovion; is serving as an expert witness in litigation related to paraquat and Parkinson's disease; received publishing royalties from Elsevier, Saunders, Wiley-Blackwell, Johns Hopkins Press, and Cambridge University Press; and co-shares a patent for diagnostic assays for movement disorders that includes alpha-synuclein seeding assay testing. TFO reports no competing interests.

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