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Do Parkinson's Disease clinical subtypes really exist?

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Abstract

Introduction. Parkinson's Disease (PD) is a highly heterogeneous entity in terms of clinical manifestations, progression, and treatment response. This variability has given rise to the hypothesis that different clinical subtypes of the disease exist.

State of the art. To date, several clinical subtypes have been described, mostly based on different clinical features, and sometimes with the support of biomarkers, either fluid, neuroimaging, or neurophysiological. The most homogeneous subtypes detected are a 'benign subtype', characterised by younger age at onset, mild non-motor symptoms, and a slower rate of disease progression, and a 'malignant subtype', which features an older age at onset, a higher burden of non-motor symptoms, and faster disease progression.

Clinical implications. Despite extensive research, none of the subtypes identified so far seem to be biologically supported, so clinical subtyping does not elucidate PD aetiology and does not allow for the prediction of prognosis or treatment response. This study was aimed to review the literature on this topic and to examine the studies on PD subtyping. We also reviewed the proposed biomarkers for a biological classification of PD, and outlined the role of genetics and pathology within this context.

Future directions. In light of the recent proposal of a biological classification of PD, which might overcome the limits of the clinical diagnosis, PD subtyping should hopefully shepherd researchers towards a biological approach, also aided by recent advances in the field of biomarkers.

Keywords: Parkinson's Disease, biomarkers, diagnostic criteria, alpha-synuclein

Introduction

Clinical diagnostic criteria for Parkinson's Disease (PD) have been implemented and validated over time to improve the diagnostic accuracy of the disorder [1]. Nevertheless, the diagnosis remains challenging given that its clinical features can overlap with those of other neurodegenerative conditions, and reliable tests or biomarkers are lacking. Consequently, clinical diagnostic accuracy is still suboptimal [2]. Clinicopathological series have reported an overall diagnostic accuracy at an initial or early stage of 58% [3]. One of the main reasons for the complexity of PD is the significant clinical heterogeneity of the disease in terms of clinical features, rate of progression, and treatment response. This variability suggests the possible existence of different clinical subtypes, which differ not only in terms of phenotype, but also possibly in terms of underlying disease mechanisms [4]. In addition, the discovery of genetic forms of the disease, which can differ from idiopathic PD in several clinical features, has encouraged research into a biological classification of sub-entities within the PD spectrum [5].

Research on PD subtypes has the potential to clarify the pathophysiology and natural history of the disease and thus eventually to lead to therapeutic development. Accordingly, in 2014, the National Institutes of Health defined subtype identification as one of the three main clinical research priorities in PD [6]. Several classification systems have been proposed so far. Two extreme phenotypes of the spectrum were originally suggested in the early 1990s: 'benign' and 'malignant' PD.

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These two phenotypes correlate with different demographic, clinical, and habits/occupational factors.

The former subtype is associated with a younger age at onset, asymmetric clinical presentation in one limb, regular physical exercise, and active smoking. The benign phenotype also correlates with higher dopaminergic dose than malignant PD, more frequent wearing-off, and dyskinesia [7]. Conversely, the malignant phenotype is characterised by more prominent freezing of gait, postural abnormalities, hallucinations, depression, and autonomic dysfunction. Another popular classification, which partly overlaps with the previous one, has identified the 'tremor-dominant' versus the 'postural instability and gait difficulty (PIGD)-dominant' subtypes [8]. PIGD patients have been shown to have not only greater postural and gait difficulties, but also more severe bradykinesia. In addition, they have greater occupational disability, cognitive impairment, apathy, depression, and impairment in activities of daily living when compared to the tremor-dominant subjects. Tremor-dominant patients have been shown to display more severe tremor at rest, and also action-postural tremor, but an overall milder disease course [8].

PD subtyping is supposed to allow the prediction of disease progression, in terms of the analysis of time to reach a given 'disease milestone', namely any clinically relevant endpoint expressing a major disease-related event [9]. This method of tracking disease progression, ultimately, might be able to estimate response to treatment for possible future upcoming personalised management strategies [10].

The main challenge here is that clinical subtyping does not reflect the underlying biology of the disease process, and so biological subtyping would be more effective in finding possible therapeutic strategies within the context of personalised medicine. For this reason, recently, opinion leaders have started working on a proposal for a more precise biological classification of PD and other synucleinopathies [11]. Notwithstanding this, there is at present no consensus regarding a subtyping method for PD, neither for research nor for clinical practice.

The aim of this review was to interrogate the literature on disease subtyping in PD, and to examine hypothesis-driven, as well data-driven, studies on this topic. We have also reviewed the proposed biomarkers for a biological classification of PD and outlined the role of genetics and pathology in this context. We conclude this review with our 'take-home' message derived from reviewing the existing literature, and make recommendations for the next steps in researching the clinical and biological classification of PD.

State of the art

Phenomenologically identified subtypes

Clinical subtypes represent the primary classification system used in everyday clinical practice worldwide. Recent studies have shown how clinical subtypes may have distinct genetic underpinnings (see also our section 'Genetics' below for further details) [12, 13].

Benign tremulous parkinsonism

A clinical entity known as 'benign tremulous parkinsonism' has been identified for many years [14, 15]. Patients with this phenotype typically show:

1. Resting tremor as the first or among the first signs, with this being the most prominent symptom throughout the course of the disease
2. Other aspects of parkinsonism (i.e., rigidity, bradykinesia, stooped posture, difficulty turning in bed, sialorrhea, hypomimia) that remain mild
3. Absence of gait disturbance, except for reduced arm swing or mild stooping
4. Mild progression after 8–10 years, apart from tremor
5. Absence of disability apart from tremor (i.e., gait and balance remain unimpaired).

This subtype was well described in 2006 in a series of 116 patients seen at the Mayo Clinic over the course of a decade [16]. The authors reported 16 patients with a diagnosis of benign tremulous parkinsonism. Their tremor was often not very responsive to levodopa therapy, which was in fact unnecessary in a number of cases. Most patients had immediate family members with a diagnosis of tremor or PD. The neuropathology of benign tremulous parkinsonism is unknown. Striatal dopaminergic imaging studies however have shown similarities with classic idiopathic PD [16]. Patients with this clinical entity are seen in every busy PD clinic.

PD dementia

Dementia is common in patients with PD, possibly appearing in more than half of cases. In 2007, the MDS (Movement Disorder Society) Task Force proposed clinical diagnostic criteria for PD and dementia (PDD) [17]. PDD presents typically an insidious onset and a slowly progressive impairment in attention, executive, visuospatial functions and memory, with relatively preserved core language functions. Behavioural symptoms including hallucinations, delusions, apathy, and mood changes are frequent. Dementia in PD is more frequently associated with the PIGD motor phenotype. Imaging studies have demonstrated atrophy and hypometabolism, more prominent in the temporal and posterior areas. The main pathological correlate is Lewy body-type degeneration in the cerebral cortex and limbic structures, often with overlapping pathology that probably influences the timing and severity of the clinical picture. However, there is no 'gold standard' for the diagnosis *in vivo* [17]. Dementia with Lewy Body (DLB) is one of the most common types of degenerative dementia, second to Alzheimer's Disease (AD) [18]. In addition to dementia, distinctive clinical features include visual hallucinations, parkinsonism, cognitive fluctuations, dysautonomia, sleep disorders, and neuroleptic sensitivity. The pathological hallmark is the presence of eosinophilic intracytoplasmic

inclusions called Lewy bodies (LB) that contain aggregated alpha-synuclein (α-syn). LB are typically present in the deep cortical layers throughout the brain, especially in anterior frontal and temporal lobes, cingulate gyrus, and insula [19]. PDD and DLB share several clinical features, genetics, and neuropathology.

This has led to a debate as to whether DLB and PDD are the same disease, or represent different expressions of an LB disease spectrum, or are distinct disorders [20]. According to current criteria, PDD is diagnosed when cognitive decline develops in the setting of well-established PD [17], specifically when motor symptoms precede dementia by 12 months or more (the so-called 'one year rule'), whereas DLB is diagnosed when dementia occurs before or within one year after the onset of parkinsonism [19, 21]. There is a need to more clearly distinguish between these syndromes and to understand the neuropathological processes leading to each one.

At present, PDD and DLB are considered as the second of the three possible phenotypes described above, i.e., as sub/phenotypes or two ends of the LB disease spectrum, because there is a neuropathological continuum from PD to PDD and on to DLB [20, 22].

Some authors have advocated for the use of the term 'Lewy body disorders' [23], wherein the concept of Lewy body disorders would include DLB, Lewy body PD, rapid eye movement sleep behavioural disorder (REM SBD), and pure autonomic failure. Despite clinical differences, the common occurrence of Lewy pathology suggests that all these conditions might be treated with similar therapeutic approaches.

Overall, a proposed classification could be based on protein pathological deposition (i.e., synucleinopathies including PD, DLB, REM SBD, pure autonomic failure, and multiple system atrophy — MSA), the type of cellular inclusions (i.e., Lewy body disorders including PD, DLB, REM SBD, and pure autonomic failure), and the clinicopathological phenotype (i.e., motor-predominant Lewy body disorder including PD) [24].

PD axial dystonia

Dystonia, or a more general hyperactivity of paraspinal and non-paraspinal muscles, appears to be the most common cause for these peculiar forms of axial disability in PD based on findings from electromyographic investigations [25].

This hypothesis is supported by three main findings:

1. The existence of drug-induced camptocormia or Pisa syndrome
2. The (rare) existence of sensory tricks to alleviate some postural abnormalities
3. Evidence of misalignment improvement by botulinum toxin type-A or lidocaine administration in some patients [25].

In addition to the described trunk abnormalities, cervical muscles may also be involved. Antecollis is a forward flexion of the head and neck which can be mild as part of the stooped posture of PD. Severe antecollis can be associated with disproportionate flexion of the head and neck compared to the posture of the limbs and trunk. Antecollis is much more common in MSA than in PD, with a prevalence of 42.1% vs. 5.8% [26]. Also Pisa syndrome is much more frequent (42% vs. 2.5%) in the MSA parkinsonian subtype (MSA-P) than in PD [27].

Camptocormia is an abnormal flexion of the thoracolumbar spine during standing and walking that reduces in a recumbent position. There is little epidemiological data on this phenomenon. Tiple and colleagues assessed camptocormia in PD in a single-centre survey, finding a prevalence of 6.9%. This symptom was observed in patients with more severe PD, as clinically assessed by both Hoehn–Yahr (H&Y) staging and the Unified Parkinson's Disease Rating Scale (UPDRS) part III (motor part), longer levodopa treatment duration and greater levodopa daily dose, and the presence of dementia as per the DSM-IV definition. As a risk factor, the authors interestingly identified previous vertebral surgery [28]. Lateral deviation of the trunk which resolves on lying down, also known as Pisa syndrome, may be also observed in PD, often associated with camptocormia. Schäbitz and colleagues aimed to investigate the aetiopathogenesis of camptocormia in PD. In four PD patients with camptocormia, paraspinal muscles were studied by electromyography (EMG) and axial computerised tomography (CT) or by magnetic resonance imaging (MRI) scans and muscle biopsy. EMG or imaging studies suggested a circumscribed myopathy of the paraspinal muscles that was then confirmed by biopsy. None of the patients had evidence for systemic neuromuscular disease on clinical or laboratory testing.

According to these findings, in PD patients with pronounced forward flexion of the trunk, myopathy confined to the neck or erector spinae muscles must be considered, probably in a minority of patients, in addition to an imbalance of the central motor drive to the ventral or dorsal trunk musculature leading to trunk dystonia and a primary vertebrogenic disease such as ankylosing spondylitis [29].

PD non-motor or pauci-motor subtypes

PD is characterised not only by its motor aspects, but also by numerous non-motor symptoms (NMS) that include cognitive impairment, behavioural changes, sleep disturbances, autonomic dysfunction, pain and fatigue [30]. NMS are very common in individuals with PD. In two studies, at least one NMS was reported by almost 100% of patients [31, 32]. NMS also may be the presenting clinical feature of PD in more than one in five subjects [33]. NMS are now also recognised to be among the most robust prodromal signs of PD [34].

In particular, PD patients present multiple NMS, rather than an individual isolated NMS. Moreover, subgroups of PD patients tend to present with a combination of NMS, which can be identified as NMS clusters [35]. Sauerbier and colleagues have hypothesised several non-motor subtypes of PD, in relation to the spread of pathology. Specifically, the 'Park cognitive' and the 'Park apathy' subtypes are related to

Table 1. Overview of proposed Parkinson's Disease clinical subtypes

Clinical subtype	Main clinical features
Benign tremulous parkinsonism	— Resting tremor as first or among first signs, and that remains most prominent symptom throughout disease course — Other aspects of parkinsonism remain mild — Absence of gait disturbance except for reduced arm swing or mild stooping — Mild progression after 8 years, apart for tremor — Absence of disability besides tremor
PD-dementia	— Cognitive decline develops in setting of well-established PD — Insidious onset and slowly progressive impairment in attention, executive, visuospatial functions and memory, with relatively preserved core language functions — Behavioural symptoms including hallucinations, delusions, apathy, and mood changes
PD-axial dystonia	— Antecollis: forward flexion of head and neck — Camptocormia: abnormal flexion of thoracolumbar spine during standing and walking that reduces in recumbent position — Pisa syndrome: lateral deviation of trunk which resolves on lying down
PD non-motor or pauci-motor subtypes	— Predominance of non-motor features (e.g. apathy, fatigue, pain, autonomic dysfunction) over motor symptoms

PD — Parkinson's Disease

the neocortical route; the 'Park fatigue' and the 'Park pain' subtypes are related to the olfactory to limbic route; and the 'Park sleep' and the 'Park autonomic' subtypes are related to the brainstem route.

Non-motor subtyping has relevance for clinical practice, because it can influence therapeutic approaches, as well as research, as a specific phenotype may be included or excluded from a clinical trial [35].

Clinical subtypes are not limited to classic PD but are also used in other parkinsonian forms. A recent study [36] evaluated 24 patients with post-COVID-19 parkinsonism, with a mean onset age of 58 years after a mean of 30 days from the COVID-19 onset. Akinetic-rigid (n = 11) and mixed (n = 6) subtypes were the most common. Asymmetry was present in 13/15 patients. Brain MRI was unremarkable in 11/19, whereas dopaminergic system imaging was abnormal in 8/8 patients. Responsiveness to dopaminergic treatment was observed in 12/15 patients. The main features of the clinical subtypes are set out in Table 1.

Hypothesis-driven and data-driven studies on subtypes

Studies on PD subtypes have mainly employed two methods: a hypothesis-driven approach, or a data-driven method. Hypothesis-driven studies have identified subtypes starting from an *a priori* hypothesis, using a single classification variable, such as age at onset or tremor. The majority of these studies have considered classical motor features, detecting subtypes with PD as tremor versus akinetic-rigid predominance, or tremor-dominant versus PIGD-dominant [37].

Conversely, the data-driven method, a hypothesis-free approach, uses advanced biostatistical methods such as unsupervised clustering to standardise phenotypic variables, while a clustering algorithm categorises patients into subtypes on the basis of these variables. These models have often included motor and non-motor variables such as cognitive impairment, sleep disorders, autonomic dysfunction, and psychotic symptoms [38].

Hypothesis–driven studies

In a seminal study, Jankovic and colleagues performed a baseline analysis of the DATATOP cohort [39], that comprised 800 *de novo* PD patients. The criteria for the different groupings were defined before the data analysis and were based on previously reported possible subtypes and on the collective clinical experience of the investigators. The authors defined *a priori:* early onset versus late onset phenotype; benign versus malignant status; and tremor-dominant versus PIGD-dominant subtypes. Early-onset PD patients showed a slower progression of disease and better cognitive performance than late-onset PD subjects. Bradykinesia and PIGD were more common at onset in patients with a rapid rate of disease progression ('malignant PD' defined as duration of symptoms ≤ l year and mean H&Y stage of 2.5) compared to those with a slower progression ('benign PD'; duration of symptoms > 4 years). Comparisons of tremor-dominant PD type to PIGD-dominant type provided support for the existence of clinical subtypes. The PIGD group reported significantly greater subjective intellectual, motor, and occupational impairment than the tremor-dominant group.

Data-driven studies

Graham and Sagar, in the first data-driven study, identified three subtypes of PD: 'motor-only', 'motor and cognitive', and 'rapid progression'. The motor only subtype was characterised by motor symptom progression in the absence of cognitive decline. The motor and cognitive subtype exhibited the same rate of motor symptom progression but presented global

Table 2. Biomarkers in Parkinson's Disease

Biomarker	Advantages	Disadvantages
α -synuclein species (immunoassays)	CSF o-α-syn and p-α-syn: Increased levels in PD compared to HC and neurological controls Remarkable discriminatory ability, with some overlap	o-α-syn and p-α-syn: Increased levels were not found among people with iRBD Few studies, still a lack of validation in independent laboratories Tot α-syn: This biomarker alone should not be considered for diagnosis of PD Not applicable to blood: important content of α-synuclein in red blood cells with risk for erythrocyte contamination
Pro-aggregating forms of α-syn (SAA)	High sensitivity and specificity for diagnosis in CSF High diagnostic performance also in prodromal cases (e.g. iRBD) Applicable also to easily accessible matrices (e.g. olfactory mucosa)	Qualitative binary response (positive/negative) Technical issues still to be resolved to achieve reproducibility of results
Alzheimer's Disease biomarkers	Lower CSF Aβ42 levels robustly prognostic regarding development of cognitive decline in PD	Data on t-tau and p-tau are not as consistent as those about Aβ42 regarding their prognostic value in PD CSF sample: invasive procedure
Neurofilament light chain	May help to discriminate between PD and other neurodegenerative disorders Useful to differentiate PD vs atypical parkinsonism Levels in PD patients rise over time and with age, and correlate with clinical measures of PD severity Potential biomarker of cognitive decline in PD Measurable both in CSF and blood	Lack of standardised methods for NfL measurement both in CSF and blood Cut-off values need to be established
Neuroinflammatory biomarkers	A more proinflammatory profile in early disease seems to correlate with cognitive decline and faster motor progression, whereas a more anti-inflammatory profile may be associated with better cognitive function and more stable motor function	Findings need to be confirmed in larger studies
Neurophysiological biomarkers	TMS: diffuse malignant subtype had increased cortical excitability and reduced plasticity compared to mild motor-predominant subtype Specific changes in cortico-cortical and corticothalamic coupling observable in surface EEG recording during resting state; associated with loss of dopaminergic neurons in PD	Future longitudinal clinical and neurophysiological assessments of these findings are needed to test reliability of results over time
Ultrasound imaging biomarkers	Preliminary findings suggest atrophy of vagus nerve in PD which can be detected by ultrasound examination Non-invasive procedure	Several confounding factors Reliability of technique needs to be confirmed

SAA — seed amplification assay; NfL — neurofilament light chain; PD — Parkinson's Disease; HC — healthy controls; iRBD — idiopathic REM behaviour disorder; CSF — cerebrospinal fluid; o-α-syn — oligomeric alpha-synuclein; p-α-syn — phosphorylated alpha-synuclein; AB42 — amyloid beta 42; t-Tau — total Tau; p-Tau — phosphorylated Tau; TMS — transcranial magnetic stimulation; EEG — electroencephalogram

cognitive impairment as assessed by the Blessed Dementia Scale Information–Memory–Concentration Test, which provides a global measure of cognitive function. The rapid progression subtype presented an older age at disease onset plus rapidly progressive motor and intellectual disability [40].

Van Rooden and colleagues later identified PD subtypes by a data-driven approach applied to a broad spectrum of motor and non-motor features [41]. Data on symptoms was collected in 802 patients in two European-prevalent cohorts, the PROfiling PARKinson's disease cohort (PROPARK) [42] and *the Estudio Longitudinal de pacientes con Enfermedad de Parkinson* cohort (ELEP) [43]. The subtypes were subsequently characterised by clinical and demographic variables. Four PD cluster subtypes were detected. Cluster 1 (49% of cases) was characterised by mild symptoms, relatively young age at presentation with younger age at onset, and lower intake of and shorter exposure to levodopa than the other groups. Cluster 2 (13%) presented severe and frequent motor complications, moderately severe sleep problems and depressive symptoms. The disease duration was longer, and they had higher intake of and longer exposure to dopaminergic medication compared to patients in the other clusters. Patients in this subtype were comparatively young and had the youngest age at onset. Cluster 3 (30%) showed intermediate severity in non-dopaminergic domains, while motor complications were mild and less frequent than the other subtypes. Patients were relatively

old and had a higher age at onset. Cluster 4 (8%) included patients severely affected in most domains, although tremor was relatively mild. Motor complications were prominent, but less severe than in Cluster 2 [41].

Erro and colleagues in another study reported the findings of cluster analysis performed by assessing both motor and nonmotor symptoms in a large cohort of newly diagnosed drug-naïve PD patients [44]. Four groups of patients were identified:

1. Benign pure motor
2. Benign mixed motor-non-motor
3. Non-motor dominant
4. Motor dominant.

These findings suggest the existence of two benign subtypes (one with prevalent motor impairment and one with prevalent non-motor involvement), and two more severe subtypes of PD (one with dominant motor features and one with prevalent non-motor features) [44]. Furthermore, the authors evaluated whether dopaminergic dysfunction, as assessed by a 123[I]-FP-CIT SPECT scan, could explain, at least partly, the observed difference between the clusters. 123[I]-FP-CIT binding values paralleled the differing burdens of motor disability among the three clusters, but not the non-motor symptoms, except for depression. According to the authors, these findings indicated that the non-motor symptoms complex is only partly driven by dopaminergic dysfunction.

Using data from the Parkinson's Progression Markers Initiative (PPMI), Fereshtehnejad and colleagues classified different subgroups through cluster analysis of a dataset at baseline including clinical features, neuroimaging, biospecimen and genetic data [45]. Four-hundred and twenty-one *de novo* drug-naïve patients were analysed. The PPMI population was followed longitudinally for a mean of 32.8 ± 9.3 months. They described three subtypes of PD patients: 'diffuse malignant', 'mild motor-predominant', and 'intermediate'. The diffuse malignant subtype showed the most severe motor and non-motor manifestations (the highest baseline MDS-UPDRS total score, the most pronounced cognitive impairment, the presence of psychiatric features and sleep problems, and olfactory and autonomic dysfunctions at baseline). The mild motor-predominant subtype exhibited the lowest severity of motor and non-motor features. The intermediate subtype had characteristics midway between the other two. Regarding biomarkers, people with diffuse malignant PD had the lowest level of cerebrospinal fluid (CSF) amyloid-β (Aβ42) and Aβ42/total-tau ratio. Data from deformation-based magnetic resonance imaging morphometry demonstrated that a PD-specific brain network had more atrophy in the diffuse malignant subtype, and the least atrophy in the mild motor-predominant subtype. Patients with diffuse malignant PD showed the fastest progression rate (global composite outcome), with more significant impairment in cognition and in dopamine functional neuroimaging [46].

Another study investigated clinical subtypes of PD using comprehensive clinical (motor and non-motor features) data retrieved from the PPMI database. Two PD subtypes were described, the 'severe motor-non-motor subtype' (SMNS) and the 'mild motor-non-motor subtype' (MMNS). SMNS experienced symptoms onset at an older age and manifested more intense motor and non-motor symptoms than MMNS, who experienced symptoms onset at a younger age and manifested milder PD symptoms. SPECT imaging supported clinical findings such as that the SMNS subtype showed lower binding values than the mild motor-non-motor subtype, indicating more significant neural damage at the nigral pathway. In addition, SMNS and MMNS showed distinct motor and cognitive functioning progression trends. Such differences between SMNS and MMNS in both motor and cognitive remained stable throughout the three years of follow-up [47]. Based on baseline data from the randomised EXPANd (EXercise in PArkinson's disease and Neuroplasticity) controlled trial [48], Albrecht and colleagues tried to identify PD subtypes using multimodal, unsupervised clustering based on clinical, cognitive, motor, and neuroimaging data. They recognised three PD subtypes: a motor-cognitive subtype characterised by extensive changes in brain structure and function as well as impairment in motor and cognitive functions; a cognitive dominant subtype mainly impaired in cognitive abilities that showed frontoparietal structural and functional alterations; and a motor dominant subtype impaired in motor variables without major brain alterations [49].

Overall, the most homogeneous subtype identified by data-driven studies is a subtype with a poor prognosis, often called a diffuse–malignant subtype, characterised by a broad pattern of non-motor and motor features and an unfavourable prognosis.

The main features of this subtype are:

1. Older age at onset
2. Prevalent non-motor manifestations from the earliest stages, particularly RBD, dysautonomia and cognitive impairment
3. Faster progression to milestones of disease progression i.e., dementia, requirement for gait assistance, institutionalisation, and death [46, 50, 51].

Cluster analyses have also described an opposite phenotype with younger age at onset, a lower grade of non-motor involvement, more tremor predominance, slower progression, and a more favourable prognosis as regards cognitive and motor aspects [41, 46, 52].

In summary, the hypothesis-driven subtyping system proposed by Jankovic and colleagues has some limitations. Firstly, subjects were highly selected participants in a clinical trial, so the cohort may be not representative of all PD patients in the general population. Secondly, because of the large number of subjects, the power may be so great that minor, and perhaps clinically insignificant, differences were detected. Finally, since all the patients were in the early stages of their disease, some may have not yet differentiated into one of the defined (e.g. tremor-dominant or PIGD-dominant) categories. The analysis

was also based on clinical data collected at a single time point (cross-sectionally) and therefore progression of disease could only be estimated [8].

Data-driven studies have some weaknesses too. Firstly, the validity of clustering depends on the quality of the data analysed. The various databases consider different variables, leading to an inconsistency of results. A second issue is selection bias. In particular, most studies have specific criteria to include and exclude, and so potentially under-represented subtypes may be missed. Clustering studies compare patients at different stages of the disease; therefore, the clusters might represent distinct subtypes as well as different phases of the disease. Finally, clustering studies describe variability only at a group level, without considering individual-level differences [37].

Biomarkers-based subtypes

Identifying PD subtypes based on biomarkers alone is still challenging because even today the diagnosis of PD remains largely clinical. Therefore, biomarkers have predominantly been evaluated for their correlation with clinical manifestations or with previously defined clinical subtypes of PD. In the following paragraphs, we summarise the role of wet, neurophysiological, and neuroimaging markers in supporting the subtyping of PD.

Fluid biomarkers

Alpha-synuclein

Alpha-synuclein (α-syn) can be measured in CSF by means of immunoassays such as ELISA, electrochemiluminescence, and seed amplification assay (SAA) [53]. Different species of α-syn (total, phosphorylated, oligomeric and misfolded α-syn) have been investigated by immunoassays. The concentration of CSF total (t-α-syn) was found to be significantly lower in *de novo* PD patients with the non-tremor-dominant phenotype compared to the tremor-dominant one [54]. Various studies have reported lower levels of oligomeric-α-syn in PD, while others have found an association of even higher levels with cognitive impairment (PDD and DLB) [55, 56]. CSF phosphorylated (p-α-syn) concentrations have been correlated with PD severity [57], but not in more advanced stages of the disease [58]. The application of the immunoassay techniques is limited by the high risk of blood contamination. Indeed, red blood cells (RBC) are the overwhelming (> 99%) source of α-syn in blood, and their abundance and fragility can lead to a notable increase of α-syn in serum or plasma even after a low RBC contamination [59].

SAAs have been proposed for the diagnosis of PD [60]. CSF α-syn--SAAs have a proven high diagnostic performance for PD, with 86–96% sensitivity and 97–100% specificity at baseline [61]. Numerous studies have reported the successful detection of α-syn aggregates in CSF of prodromal cases of PD or DLB, including idiopathic RBD (iRBD), mild cognitive impairment (MCI), and pure autonomic failure [62–65]. Alpha-syn-SAA has been also applied to other matrices. In skin biopsies, α-syn SAAs have exhibited an accuracy similar to that of CSF in differentiating patients with PD and DLB from controls [66, 67]. In olfactory mucosa, PD and DLB were also distinguished from controls, although with a lower sensitivity [68]. Also, biopsies from submandibular glands were able to differentiate PD and DLB from controls with 100% sensitivity and 94% specificity [69], although this technique is somewhat invasive. Regarding saliva, SAAs have provided good results in discriminating PD and MSA from controls (PD: sensitivity 76% and specificity 94.4%; MSA: sensitivity 61.1% and specificity 94.4%) [70].

However, one of the main challenges is variability in assay protocols and experimental conditions, which can lead to inconsistencies in results and prevent the reproducibility of findings across different studies [71].

At present, α-syn SAAs mainly provide a qualitative binary (positive/negative) response. A challenge for the future will be to provide a quantitative measure of the α-syn present in the biological sample, and to assess if this correlates with the stage of the disease to see if it can be used to monitor treatment efficacy [72]. Note that α-syn SAA also results positive in subjects with a clinical diagnosis of PSP and corticobasal syndrome (CBS) [73], highlighting the crucial role of concomitant pathology.

Alzheimer's Disease biomarkers

The biomarker-based definition of Alzheimer's Disease (AD) validated in 2018 relies on the simultaneous assessment of markers of amyloidosis, tauopathy, and neurodegeneration, in the so-called A/T/(N) system [74]. These criteria were further updated in 2024 [75]. Considering the frequent coexistence of AD pathology in PD brains [76, 77], several studies have investigated the possible role of AD classic hallmarks as biomarkers of PD subtypes. Lower CSF Aβ42 levels have a robust prognostic value regarding the development of cognitive decline in PD. Decreased CSF Aβ42 levels have been associated with a higher rate of Mini-Mental State Examination (MMSE) test and Montreal Cognitive Assessment (MoCA) decline, supporting its role as an independent predictive factor for cognitive impairment [78]. Data from the PPMI cohort [79] indicated that PD patients with cognitive decline after 2 years of follow-up had significantly lower baseline CSF Aβ42 levels than those with normal cognitive function. PD patients with CSF evidence of amyloidosis (lower levels of CSF Aβ-42) were significantly older, had reduced cognitive performance and a higher frequency of *APOE4* alleles, and displayed reduced levels of all CSF measures (total-tau, phosphorylated-tau and α-syn) compared to PD patients without CSF evidence of amyloidosis [80]. Moreover, they exhibited significantly reduced grey matter in orbitofrontal and anterior cingulate regions.

Therefore, the authors suggested that cerebral amyloidosis in early PD patients may define a distinct PD phenotype, perhaps due to a synergic deleterious interaction between amyloid and α-syn. Accordingly, Fereshtehnejad and colleagues, exploiting data from the above-mentioned PPMI cohort, found that those patients with the diffuse malignant PD subtype, who had the fastest cognitive decline, showed an AD-like CSF profile with low Aβ42 and Aβ42/t-tau ratio [46]. Data on t-tau and p-tau are not as consistent as those about Aβ42 regarding their prognostic value in PD. Longitudinal studies showed that CSF t-tau levels measured at baseline were not predictive of cognitive decline in PD [81]. One longitudinal study found a significant correlation between p-tau and the rate of cognitive decline, as well as a faster motor progression [82, 83]. In another longitudinal study, higher p-tau and p-tau/Aβ42 predicted subsequent decline on cognitive tasks involving both memory and executive functions [83].

Neurofilament light chain

There is growing evidence indicating CSF and plasma neurofilament light chain (NfL) as a sensitive and specific biomarker that may help to discriminate between PD and other neurodegenerative disorders i.e., MSA, PSP, CBS, and frontotemporal dementia [84]. In particular, CSF levels of NfL have been found to be substantially increased in MSA and PSP compared to PD [85, 86]. A longitudinal increase in NfL serum concentration has been observed also in PD patients compared to controls. Serum NfL levels in PD patients rise over time and with age, and correlate with clinical measures of PD severity [87]. Considering age-dependent normal ranges, plasma NfL may represent a biomarker of cognitive decline in PD [88]. Indeed, CSF NfL levels at baseline correlate with the mean change per year in the Dementia Rating Scale scores [89]. Moreover, they predict the risk of conversion into PDD over the following 5–9 years, and the prediction accuracy is better when combined with other biomarkers such as CSF Aβ42 [90]. However, a standardised method for the measurement of NfL is lacking, and cut-off values have not been clearly determined so far [91, 92].

Neuroinflammatory biomarkers

Growing evidence indicates the involvement of neuroinflammation in the pathogenesis of PD [93]. In one positron emission tomography (PET) study on PD patients, evidence of activated microglia was found in the pons, basal ganglia, and frontal and temporal cortical regions [94]. Microglial activation has been found to correlate positively with the severity of motor symptoms [95]. YKL-40, a molecule expressed in astrocytes and microglia, both implied in the inflammatory processes [96], was found to rise over time in PD in tandem with faster cognitive decline [82]. A panel of four inflammatory proteins (IL-12B, CSF-1, CXCL11, and OPG) was able to discriminate between PD and healthy controls. The expression levels of five inflammation-associated proteins (CCL23, CCL25, TNFRSF9, TGF-alpha, and VEGFA) increased over time in PD. Raised levels of CCL23 (CC chemokine ligand 23) in PD patients were associated with worse cognitive performance, more severe motor impairment, and *APOE4* allele carriers. CCL23 might be a predictive biomarker for faster disease progression in PD [97]. Serum levels of TNF-a, IL1-b, IL-2 and IL-10 were also found to be higher in PD compared to controls. A more proinflammatory profile in early disease correlated with cognitive decline and faster motor progression, whereas a more anti-inflammatory profile was associated with better cognitive function and more stable motor function [98]. Accordingly, a proinflammatory biomarker profile (reduced apolipoprotein A1 [*ApoA1*] and raised CRP) was found to be significantly associated with the severe motor and the nonmotor disease phenotypes [99]. Various studies have also demonstrated that higher serum levels of triglycerides (TG) and *ApoA1* are significantly associated with PD-MCI and their levels are independent risk factors for developing MCI in PD patients [100].

Neurophysiological biomarkers

Neural plasticity refers to the capacity of the nervous system to modify itself, functionally and structurally, in response to experience and/or injury. Using transcranial magnetic stimulation (TMS), researchers found that the diffuse malignant subtype had increased cortical excitability and reduced plasticity (tested through a TMS paradigm named intermittent theta burst stimulation - iTBS) compared to the mild motor-predominant subtype. In addition, kinematic analysis of motor performance demonstrated that the diffuse malignant subtype was significantly 'slower' than the mild motor-predominant subtype [101].

One study tested whether the features of TMS-based neurophysiological measures taken off-medication were associated with dopaminergic medication-induced clinical effects. Motor cortex excitability [short-latency intracortical inhibition (SICI), intracortical facilitation (ICF), short-latency afferent inhibition (SAI), and input-output (IO) curve], and plasticity-related neurophysiological measures were assessed in 23 PD patients OFF-medication. SICI significantly correlated with changes in lateralised MDS-UPDRS motor and bradykinesia sub-scores, suggesting that patients with stronger basal intracortical inhibition benefit more from dopaminergic treatment than do patients with weaker intracortical inhibition. Also, ICF significantly negatively correlated with levodopa equivalent daily dose, suggesting that patients with stronger intracortical facilitation require less dopaminergic medication to achieve an optimal therapeutic benefit. The authors suggested that the variability of pathophysiological phenotypes was related to intracortical inhibitory and facilitatory mechanisms determining clinical response to dopaminergic medication [102]. Another study classified PD patients into three phenotypes with distinct electrophysiological profiles. These clusters were characterised by different levels of alterations in the somato-motor network (Δ and β band), the frontotemporal network (α2 band), and the

Table 3. Opportunities and challenges on clinical application of Parkinson's Disease subtypes

Opportunities	Challenges
Genetic profiles may differ	Clinical diagnostic criteria to fulfill are the same
Age at onset is extremely variable	Standard MRI is normal in most patients
Disease trajectories differ	123[I]-FP-CIT SPECT is altered in most cases
Life expectancy changes	Some degree of dopaminergic response is found in all cases
Need for levodopa is variable	Does not reflect disease biology

MRI — magnetic resonance imaging; 123[I]-FP-CIT SPECT — 123I-labelled N-(3-fluoropropyl)-2beta-carbomethoxy-3beta-(4-iodophenyl)nortropane (FP-CIT) single-photon emission computed tomography (Dopamine Transporter Scan)

default mode network (α1 band), which correlate with clinical profiles and disease courses. These clusters were sub-grouped into either moderate (only-motor) or mild-to-severe (diffuse) disease. EEG features might predict cognitive evolution of PD patients from baseline [103].

Ultrasound imaging biomarkers

According to Braak's hypothesis, the vagus nerve (VN) is a doorway to the central nervous system for α-syn pathology [104]. Despite recent criticism of this hypothesis, there are experimental findings which support the vulnerability of the VN. In animal models of the disease, misfolded α-syn spreads through the VN to the brainstem, as well as in the opposite direction [105]. In humans, studies on vagotomy have demonstrated that vagotomy was not associated with PD risk, but there was a suggestion of lower risk among patients with truncal, but not selective, vagotomy [106].

Current data suggests the presence of atrophy of the vagus nerve in PD patients, which can be assessed by ultrasound examination [105]. On a transverse scan, VN presents as a hypoechogenic structure within the cervical sheath, with an average cross-sectional area of 2.4 mm^2 for healthy controls and a 16% reduction observed in PD patients. VN size has been correlated with motor burden, but not with disease duration. This suggests that non-severely affected patients might not present a significant reduction in VN cross-sectional area (CSA). Moreover, there is an association with heart parasympathetic performance.

Perhaps combining heart rate variability (HRV) with VN ultrasound (imaging of the parasympathetic system) and cardiac 123I-metaiodobenzylguanidine scintigraphy (123I-MIBG; a biomarker of sympathetic denervation) might help to recognise a subgroup of patients developing autonomic failure, related to a more malignant disease subtype.

However, there are some factors which interfere with the reliability of this technique. Firstly, differences in age, sex, body mass, comorbid conditions, and the side being measured can lead to high interpersonal variability of VN diameter. This might contribute to nonsignificant results in some studies. Contradictory conclusions have been found also in the context of gastrointestinal disturbances. Another possible confounder is the presence of systemic diseases that may affect the nerve structure, such as diabetes, chronic inflammatory demyelinating polyneuropathy, and amyotrophic lateral sclerosis. Furthermore, if nerve degradation is continuous and progressive, as can be supposed, it may justify some part of the variation in VN area across studies. Finally, in subjects receiving levodopa, nerve damage may be also due to increased homocysteine levels and its neural toxicity [105]. Advantages and disadvantages of the mentioned biomarkers in PD are set out in Table 3.

Roles of genetics, mixed pathology, trigger factors

Genetics

Several genes, including *SNCA*, *LRRK2*, *PRKN, ATP13A2,* and *PINK1* and many others, have been associated with monogenic forms of PD [107]. *GBA* and other more recent genetic loci have been associated with an increased risk for developing PD [108]. Each genetic variant may lead to a different pathogenic pathway and be vulnerable to specific molecular targets, but whether the clinical features and treatment response of PD differ among molecular subtypes is still unknown [109, 110]. PD patient carriers of *GBA* variants present a shorter but more severe prodromal phase compared to PD patients without these mutations [111]. *GBA* variants are also more common among people with RBD than among the general PD population. Among patients with iRBD, those with *GBA* mutations are indistinguishable from those without, but the rate of conversion to LB disorders is increased and may be faster among severe *GBA* variant carriers [112]. Severe GBA variants are associated with more rapid disease progression, an increased risk of dementia, and faster cognitive decline compared to mild *GBA* variants [113, 114]. Regarding the motor aspects, GBA variants predict a more rapid progression of motor symptoms in patients with PD, with a greater effect on PIGD than tremor [114]. Furthermore, among PD subjects carrying *GBA1* variants, male sex has an additive value in increasing the risk of cognitive decline in PD [115]. Conversely, *LRRK2* variants, especially the G2019S variant, correlate with milder non-motor symptoms [116]. The G2019S mutation in the *LRRK2* gene has been associated with the PIGD subtype [117, 118].

Hyposmia and RBD are not prevalent features in prodromal *LRRK2* PD. The mean age at onset in patients with *PRKN* variants is younger compared to people with idiopathic PD,

and they are more likely to have symmetric involvement and dystonia at onset; they also have hyperreflexia at onset or later, normal olfaction, a low rate of cognitive decline, a good response to levodopa therapy, and (with lower limbs prominent) levodopa-induced dyskinesias during treatment [119]. Notably, patients with *LRRK2*, *PRKN*, and *PINK1* may or may not have LB pathology at post mortem examination [120–122].

Patients with *SNCA* variants have a poor prognosis, including a poor response to levodopa, a higher risk of dementia, psychiatric disorders, pyramidal signs, and rapid progression [123–125]. In particular, *SNCA* rs6826785 noncarriers have been significantly associated with PD-MCI [100]. A study demonstrated that the variant rs356182GG genotype near *SNCA* provides molecular definition for a clinically important endophenotype associated with more tremor-predominant motor phenomenology, slower rates of motor progression, and decreased brain expression of *SNCA* [126]. A recent retrospective study has investigated time-to-postural instability and other disease-specific milestones in monogenic PD, showing that progression-free survival from postural instability (e.g. falls) at 10 years after disease onset was longest in *ATP13A2* (97%) and shortest in *SNCA* (50%). In between these two extremes were *PRKN* (88%), *PINK1* (87%), and *LRRK2* (81%), similarly to idiopathic PD (72%). Interestingly, young age at onset in *PINK1*, and female sex in *LRRK2*, were associated with a decreased risk of postural instability [127].

The genetic architecture of PD subtypes was also analysed recently, not only the particular monogenic mutations [12]. A number of genetic variants seem to influence the clinical manifestations of the disease, the rate of progression, and the prognosis. For example, *APOE4* allele and other polymorphisms in other genes are related to accelerated cognitive impairment; variants in *COMT*, *DRD1*, *DRD2*, *DRD3*, and *DDC* correlate with the probability of impulse control disorder; CRHR1, *IP6K2*, and *PRSS3* polymorphisms are linked with more severe axial symptoms following deep brain stimulation. The influence of each variant alone appears negligible, but, when combined, they allow us to predict the clinical presentations or adverse effects to a treatment [12].

Mixed pathology

The classification of neurodegenerative disorders is classically based on neuropathological hallmarks. However, it is becoming increasingly evident that the pathology is not always 'pure', and that there is often a composite picture, wherein coexistence of α-synucleinopathy, tau-pathology, and amyloid-β pathology is frequently observed [76, 77]. PD patients who develop significant cognitive decline are classified as PDD. This subgroup has also a distinct pathological correlate, that is the 'typical' LB pathology associated with the presence of amyloid-β deposits in the limbic system [128]. Limbic and neocortical LB pathology has been claimed to be the main determinant of the development of cognitive impairment in previous studies, but this assumption has not always been confirmed [99]. Compta and colleagues have demonstrated that a combined high burden of all three (LB, amyloid-β, and tau) pathologies was the most robust neuropathological correlate of patients with PDD. In particular, higher cortical amyloid-β scores were associated with a faster progression to dementia [129]. Amyloid-β accumulation is believed to promote α-syn seeding and spreading in mouse models [130]. Therefore, co-existent amyloid-β pathology in PD and DLB could drive subtypes in which dementia presents early. Furthermore, the presence of vascular alterations contributes to the complexity of the pathological features [131].

In living subjects, a proxy of vascular pathology can be the presence of white matter hyperintensities (WMHs), namely neuroimaging biomarkers characterised by signal enhancement of the T2-weighted sequence in magnetic resonance imaging [132]. WMHs can result from blood-brain barrier damage; or chronic ischaemia, which is caused by injury to the microvascular structure; and/or brain hypoperfusion, due to the dysfunction of cerebrovascular autoregulation [133]. WMHs have been associated with cognitive decline in the general population [134]. Whether WMHs are correlated with cognitive impairment in PD is still debated. WMH burden could be a neuroimaging marker for PD-MCI conversion to PDD [135]. WMHs, but not vascular risk factors, have been found to raise the risk of developing PD-MCI [136]. In contrast, another study did not identify global or localised WMH load as a predictive marker of cognitive decline in *de novo* PD patients [137]. A metanalysis compared the association of WMH burden in patients with PD-MCI versus those with normal cognition (PD-NC) and in patients with PDD versus those without dementia (PD-ND). Results showed that WMH burden might be correlated with cognitive impairment in patients with PDD. Moreover, the localisation of WMHs presented specific effects on cognitive function. Specifically, deep white matter hyperintensity (DWMHs) and periventricular hyperintensity (PVHs) negatively influenced cognitive abilities in PDD. WMH locations correlated with domain-specific cognitive dysfunction in PD patients, including executive, attention, memory, speed learning, and visuospatial function [138]. A more recent metanalysis showed that increased WMH burden was associated with worse global cognitive function, as well as worse motor performance, in people with PD [139].

Trigger factors

The complex interaction between genetic and environmental factors might play a role in determining susceptibility to PD, and may contribute to the clinical heterogeneity of the disease. Despite many efforts to clarify the causes of neuronal death in the *substantia nigra pars compacta* and to detect potential triggers, the exact PD aetiology is still unknown. There is increasing evidence for the interplay between nervous and immune systems [140]. This interaction seems to underlie neuroinflammation which is a common feature of many neurodegenerative disorders [141] and may have multiple causes, such as the impairment

of the regulation of immune responses associated with ageing, infectious agents, exotoxins (e.g., pesticides), or deposition of insoluble protein fibrils (e.g., α-syn) [142].

It has been postulated that pathological aggregation and propagation of α-syn might first occur in the brain or the autonomic and enteric system [104, 143]. These observations have driven the hypothesis that PD may be classified into two subtypes: a 'body-first' (or gut-first) and a 'brain-first' subtype [144]. In the former, α-syn pathology is believed to originate in the autonomic and enteric nervous system and to spread into the CNS via the vagus nerve (VN) and sympathetic connectome; in the latter, α-syn pathology is believed to start in the brain itself, most often in the limbic system, and to descend through the brainstem and into the periphery. The former is closely associated with RBD during the prodromal phase and is characterised by marked autonomic damage before involvement of the dopaminergic system. In contrast, the latter phenotype does not present RBD during the prodromal phase and is characterised by nigrostriatal dopaminergic dysfunction prior to involvement of the autonomic peripheral nervous system. The existence of these subtypes is supported by *in vivo* imaging studies of RBD-positive and RBD-negative patient groups and by histological evidence [145].

Ultrasound measurement of the VN has been proposed as a helpful technique to track the route of propagation of neurodegeneration [105, 106] (Tab. 2). A recent study has shown that the VN CSA, specifically the right VN, exhibited a statistical correlation with the body-first PD subtype ($p < 0.001$) and some components of PD-related assessment scales [146].

However, the body-first and brain-first subtypes should not be considered as a definitive classification of PD, but rather as a hypothesis on clinicopathological phenotypes that explains a large degree of the disease variance. Other important factors, such as genetic predisposition and variable selective neuronal vulnerability, probably contribute to the clinical variability and the different progression patterns [147]. Furthermore, the brain-first/body-first hypothesis has been tested only in a single cohort of patients with PD, and thus requires further confirmation [38]. A significant body of evidence suggests how PD could be considered as an 'umbrella' term used to describe a progressive, chronic neurodegenerative syndrome with multiple features in which the degree of neurodegeneration and disease progression differ across subjects [9, 148].

Hence, PD should not be considered a unique disease entity, but rather a heterogeneous group of disorders that, while related by common neurodegeneration, exhibit different genetic, biological, and molecular abnormalities with different natural history [110, 148]. This interpretation may explain why PD aetiology is still unknown, as there could be many PD aetiologies.

Is alpha-synuclein accumulation and seeding the culprit?

The abovementioned pathology-based theories of α-syn or amyloid-β toxicity caused by their accumulation and possible seeding have been recently criticised for many reasons [148, 149]. Firstly, the assumption has been disputed that, as *SNCA* multiplication overexpresses α-synuclein, it must be toxic; indeed, a study demonstrated that high *SNCA* expression was associated with better motor and cognitive outcomes than cases with low *SNCA* expression [150]. Although most studies have reported no changes in behaviour or cell count in young mice knock-out for α-syn, the output is different when ageing, the most important risk factor for PD, is incorporated into the models. Upon knocking down α-syn in aged rats [151] or aged non-human primates [152], nigrostriatal degeneration and behavioural changes have been reported. Furthermore, it has been suggested that the spreading of alpha-syn pathology is not an active mechanism (replication in a prion-like manner), but a passive phenomenon (nucleation). The theory of α-syn oligomers toxicity has thus been questioned, given that some studies found no evidence for toxicity of these species [153]. Finally, we must remember that the result of α-syn SAA in the laboratory does not elucidate the pathogenesis, staging, or biology of PD in humans.

As a result, it has been suggested that the accumulation of aggregated α-syn is not the cause of the disease but is instead the consequence of an upstream biomolecular neurodegenerative pathway causing the depletion of the normal soluble protein (thus becoming insoluble and aggregated). Moreover, misfolded proteins might be sequestered into LB as a protective mechanism to promote the maintenance of neuronal and synaptic function despite coexistent and actively disrupting molecular abnormalities [148, 149].

Likewise, a recent meta-analysis has shown how in AD an increase and not a reduction of amyloid-β can improve cognitive function, thus supporting a fundamental role of soluble amyloid-β in AD (and, possibly, in turn, also of α-syn in PD) [154].

Conclusions and future directions

The impact of identifying PD clinical subtypes on our understanding of PD pathogenesis or clinical treatment remains unclear, with limited application in research or clinical practice (Tab. 3). In particular, subtype stability over time and its prognostic value are largely unknown.

The feasibility of subtyping as part of routine clinical practice is uncertain because of:

1. The significant extra time required to assign individuals to subtypes using multi-domain data, beyond that allocated to routine clinic visits
2. The lack of an accepted algorithm to classify individual patients.

The clinical diagnosis and classification of PD has limitations, not only given the low accuracy [2], but also because the cardinal motor features do not become evident until 60–80% of nigral dopaminergic neurons have been lost [155], making early diagnosis highly challenging.

Recently, a biological classification and staging system of PD has been proposed. According to this proposal, PD should be defined on the presence of aggregated α-syn in tissue samples or CSF (S), evidence of underlying neurodegeneration (N) defined by neuroimaging, and documentation of pathogenic gene variants (G) that cause or strongly predispose to PD. These three components are linked to a clinical component (C), defined by a single high-specific clinical feature or by several lower-specific clinical signs and symptoms.

Even though the clinical manifestations of PD reflect the stage of the disease and its heterogeneity, in this biological perspective they are not considered defining features of the disease [11]. The classification in clinical subtypes has a limited role in terms of a biological classification of PD, as clinical variability does not represent underlying biological or pathophysiological differences between individuals. Therefore, future subtyping of PD will also need to move towards a biological basis, in order to identify subtypes more consistently from a pathophysiological and biochemical-molecular perspective.

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