Journal of Neural Transmission
https://doi.org/10.1007/s00702-026-03208-x

REVIEW

Disease modification in advanced Parkinson's disease: a review and roadmap for paving the way for next-generation interventions

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Received: 5 May 2026 / Accepted: 8 June 2026

Abstract
Parkinson's disease (PD) exhibits highly heterogeneous clinical trajectories, yet "advanced PD" (aPD) lacks a standardized definition. Current reliance on clinical milestones (e.g., motor fluctuations, cognitive decline) is limited by non-linear progression and the absence of objective measures. Although biomarkers like aggregated α-synuclein, MRI, and PET are under investigation, their correlation with clinical progression remains modest. Robust, reproducible endpoints are urgently needed to evaluate disease-modifying therapies across diverse phenotypes, accounting for genetic background, age of onset, co-pathologies, and motor/autonomic/cognitive domains. Given this complexity, single-target interventions are likely insufficient. We propose a multi-domain therapeutic framework for aPD that integrates: (A) simultaneous targeting of key pathological cascades, including α-synuclein aggregation, mitochondrial dysfunction, oxidative stress, proteostasis imbalance, neuroinflammation, and the gut–brain axis; (B) biology-driven patient stratification using emerging biomarkers to match subgroups with targeted interventions; and (C) systematic management of comorbidities and lifestyle factors, such as cardiovascular health and exercise, to enhance neuroresilience. Finally, advancing aPD care requires addressing systemic determinants, including global healthcare inequities, and prioritizing caregiver well-being. Mechanistically informed, patient-centered strategies that combine multi-target therapies with precision stratification and holistic support will be essential to modify disease progression and improve long-term outcomes.

Keywords Advanced Parkinson's disease · Deep brain stimulation · Disease modification · Biomarkers

Introduction

Parkinson's disease (PD) is a complex neurodegenerative disorder characterized by the presence of cardinal motor signs such as bradykinesia, and that may include rigidity, resting tremor, and postural instability. PD is also known for the present of a wide spectrum of non-motor symptoms, such as constipation, hyposmia, and REM sleep behavior disorder (Tanner and Ostrem 2024). The course of Parkinson's disease is characterised by a prolonged preclinical phase, followed by a prodromal stage which non-motor symptoms predominate, but during which subtle motor manifestations may already be detectable. Increasing evidence from longitudinal population-based cohorts and wearable sensor studies, including the HAAS cohort, Rotterdam Study, UK Biobank, and PREDICT-PD programme, indicates that subtle motor abnormalities, such as alterations in gait kinematics, motor variability, and upper-limb movement, can be detected years before clinical diagnosis (Bloem et al. 2021; Schalkamp et al. 2023; Simonet et al. 2021). This prodromal phase ultimately progresses to a clinically manifest stage characterised by the cardinal motor features of bradykinesia, rigidity, resting tremor, and postural instability. Advanced diagnostic workarounds with genetic assessment, and alpha-synuclein (aSyn)-focused assays that use amplification technologies, such as RT-QuIC or PMCA (known as

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Published online: 19 June 2026

seed amplification assays – SAA), to detect tiny amounts of pathogenic aSyn from tissues of liquid biomarkers (cerebrospinal fluid, blood) are established (Amaral-do-Nascimento et al. 2026). However, current versions of these assays provide only a binary positive/negative readout, albeit with a high sensitivity and specificity for PD. Therefore, prodromal phases of PD can now be detected permitting complement clinical assessment and introduction of these persons to clinical studies. The definition of advanced PD (aPD) is however missing. Generally, the course is progressive but the evolution of disease stages beginning with the clinical stage is highly challenging. Despite a wide variability, most PD patients will develop motor and non-motor complications including cognitive decline, vegetative dysfunction and loss of postural reflexes (García-Ruiz et al. 2012; Hely et al. 2008; Kim et al. 2020; Tanner and Ostrem 2024). The evolution is not necessarily linear, rapid exponential progression after years of stability in PD may occur (García-Ruiz et al. 2012).

Several variables may affect evolution including genetic background, age at onset, early axial motor symptoms and presence or absence tremor (Hely et al. 2008; García-Ruiz et al. 2012; Kim et al. 2020). Retrospective studies also revealed a subset of patients with rapid aggressive evolution and patients with slow progression (so called ¨benign¨ PD) (Merola et al. 2020).

The use of the term aPD is still debated, and no single consensus definition currently exists in the literature. Proposed criteria reflect different conceptual and practical purposes: *clinical milestone-based definitions* identify aPD by the emergence of specific features such as motor fluctuations, loss of postural reflexes, cognitive decline, and neuropsychiatric complications, as applied in landmark longitudinal cohorts; *treatment-based definitions* operationalise aPD as the stage at which patients require device-aided or infusion therapies due to inadequate control with conventional oral regimens, a pragmatic approach widely used in clinical practice guidelines; and *emerging biomarker-informed frameworks* seek to anchor disease staging to objective biological substrates, though these remain incompletely validated for advanced stages. Each of these definitions captures a partially overlapping but distinct patient population, and the choice of definition carries material consequences for trial design, endpoint selection, and the interpretation of epidemiological data. Throughout this review, we adopt a broad operational perspective that integrates clinical milestones with the underlying systems-level pathology, recognising that a unified, biologically grounded definition of aPD remains an urgent unmet need (Shulman et al. 2008; Becker et al. 2022; Brumm et al. 2023; Aslam et al. 2024). The objective measure of aPD is far from easy, non-parametric clinical scales (including *MDS-UPDRS* and Hoehn and Yahr staging scale) have evident limitations and progress in a non-linear fashion (Shulman et al. 2008; Aslam et al. 2024). Identifying a meaningful progression metric for aPD is, however, of a vast relevance since also this group of patients should be considered for clinical interventions that modify disease course and life quality (Brumm et al. 2023; Aslam et al. 2024). This review proposes an operational overview of aPD that discuss clinical variables with underlying systems-level pathology rationale that can pave the developments in the field in the next years. Disease modifying or neuroprotective treatments are in our view clear unmet goals for PD and the entire neurodegenerative field. Important first steps would be to operationalize the definition of aPD and better quantify the distinct clinical states during advanced disease stages. Then, we must test the efficacy of potential disease-modifying treatments. For this, we need reliable endpoints that can account for progression across the spectrum of clinical features (Brumm et al. 2023; Espay et al. 2025a, b).

For the transition to aPD, clinical triggers from motor (fluctuations, dyskinesia, loss of postural reflexes) and non-motor domains can be utilised (severe constipation, sleep apnea, significant weight, variability, cognitive decline, and neuropsychiatric symptoms such as hallucinations). Since axial symptoms and cognitive decline are critical milestones, metrics of these elements are rational measures to define aPD (Hely et al. 2008; Shulman et al. 2008; García-Ruiz et al. 2012; Kim et al. 2020; Merola et al. 2020; Becker et al. 2022; Brumm et al. 2023; Aslam et al. 2024).

At present, it seems that clinical milestones better describe aPD, while objective measures should be extensively studied and introduced into clinical practice (Brumm et al. 2023; Simuni et al. 2024, 2025; Reyes et al. 2025; Bernhardt et al. 2025; Espay et al. 2025a, b). Advanced MRI techniques such as diffusion-based microstructural imaging or neuromelanin-sensitive sequences the detect white and grey matter integrity changes, substantia nigra and cortex-based degeneration mirror disease stages and the cognitive–motor decline in aPD. Wearable sensor–derived gait and mobility metrics provide high-resolution, longitudinal measures of motor microstructure “in vivo” (e.g., stride variability, postural instability) that correlate with disease severity and progression, making them promising digital biomarkers to complement imaging-based microstructural markers in aPD. However It is important to note that there is a modest correlation of quantitative pathology quantification such as derived from aSyn SAA, imaging and clinical deterioration and such studies should follow in the coming years (Bernhardt et al. 2025).

For the moment, biomarkers have a role for diagnosis and classification of PD (Brumm et al. 2023; Simuni et al. 2024, 2025; Reyes et al. 2025; Bernhardt et al. 2025) but

the utility of biomarkers to track the evolution of aPD is not yet defined.

A further consideration that shapes the conceptual framing of this review is the asymmetry between biomarker development in early versus advanced PD. In early and prodromal disease, the field has made substantial progress. The Neuronal α-Synuclein Disease Integrated Staging System (NSD-ISS) integrates aSyn SAA positivity with dopaminergic imaging and functional milestones to provide a biologically grounded staging framework (Russo et al. 2025; Simuni et al. 2024), and plasma and CSF markers such as neurofilament light chain (NfL) and phosphorylated tau are increasingly validated as correlates of early neurodegeneration and cognitive trajectory (Buhmann et al. 2023; Pagonabarraga et al. 2022; Pedersen et al. 2024). By contrast, equivalent frameworks for advanced PD (aPD) remain underdeveloped, in part because the biological substrate, treatment burden, and clinical heterogeneity of advanced disease differ substantially from the earlier stages in which most biomarker research has been conducted.

This disparity raises a fundamental question that this review also seeks to address: should biomarkers ideally be applicable across the entire disease spectrum, or are they inherently stage-specific? We argue that the answer is likely both. Certain markers, most notably aSyn SAA positivity as a biological trait marker, may retain diagnostic and stratification utility across disease stages, although their quantitative dynamics in aPD require further characterisation (Siderowf et al. 2023; Vijiaratnam and Foltynie 2023). Others, however, appear to be stage-specific by nature. Local field potentials recorded from implanted DBS devices, digital gait and mobility metrics derived from wearable sensors, and markers of co-pathologies such as amyloid-β and phospho-tau may have particular relevance and validity in the context of established advanced disease (Hall et al. 2021; Janssen Daalen et al. 2024; Pilotto et al. 2024).

Recognising this distinction is consequential for clinical trial design. Endpoints and biomarkers validated in early PD cannot be assumed to be appropriate surrogates for disease progression in aPD, and the field requires dedicated validation efforts in this population (Dam et al. 2024; Russo et al. 2025; Vijiaratnam and Foltynie 2023). Accordingly, this review discusses disease definition and biomarker utility across the full disease spectrum while focusing specifically on the unmet needs and opportunities that are distinctive to advanced stages.

Quantification of clinical states and the role of the interference through advanced therapies

An operational way to define aPD is describing it as 'patients requiring *advanced* treatments' (Schneider et al. 2026). In these population, the traditional concept of disease modification becomes increasingly difficult to demonstrate, as substantial dopaminergic neuronal loss and widespread multisystem pathology are already present. The adoption of deep brain stimulation (DBS) for PD has steadily increased over the past decades and it is now an established treatment, along with other advanced options: L-dopa–carbidopa intestinal gel infusion (LCIG), continuous subcutaneous dopaminergic delivery, and MRI-guided focused ultrasound (see Table 1).

These treatments further complicate the assessment of any intervention modifying the trajectory of the disease. In fact, all these treatments are particularly effective in treating dopaminergic responsive problems, including the motor and non-motor fluctuations. Nevertheless, while these interventions are not proven to alter the molecular drivers of neurodegeneration, they can profoundly modulate pathological basal ganglia network activity, stabilize motor fluctuations, and reduce treatment-related complications. Furthermore, these approaches carry a number of indirect effects able to influence the trajectory of disability, delaying secondary complications, functional decline, and also give the chance of implement healthy habits, such as exercising (see below).

The possible protective effect of DBS has been long debated (Tinkhauser et al. 2020). F-dopa PET studies have shown a dopaminergic decline similar to non-DBS patients (Hilker et al. 2005). On the other hand, a randomized pilot study has provided evidence for tremor reduction

Table 1 Plasmatic biomarker and DBS

References	Aim	Biomarkers	Meaning
(Carrillo et al. 2024)	Discriminant	Acylcarnitine, Sphingolipids, fatty acid oxidation, steroids, leptin, TNFα, GFAP, BDNF, etc.	Different from HC, drug-naïve and patients on L-dopa
(Frank et al. 2025)	Discriminant	GFAP, NfL	Higher after surgery, especially in cognitive impaired pts (GFAP)
(Gong et al. 2023)	Predictor	Bleomycin hydrolase and Creatine kinase M-type	Downregulated in responders
(Zhou et al. 2022)*	Predictor	CRP, NfL, S100β	Higher in POD (CSF in particular)

*also CSF; POD: post-operative delirium

in treated patients after 1 week of stimulation discontinuation (NCT00282152) (Hacker et al. 2018). The long-term follow-up of the same cohort has not confirmed an effect on disease progression, as more DBS patients were subsequently reported to be dead (Hacker et al. 2023).

Whether continuous dopaminergic stimulation (or rather 'continuous dopaminergic *delivery*') is disease modifying is yet to be confirmed in human patients as it derives from animal models of the disease. The lack of fluctuations and the disappearance of dyskinesias has been wrongly interpreted as evidence of such effect, ignoring a few facts: (1) Peak-dose dyskinesias may improve; however, troublesome dyskinesias often persist in patients exhibiting a brittle response to levodopa (Figs. 1 and 2); (2) Challenging these patients with a supratherapeutic dose of L-dopa still elicits dyskinesias(Elia et al. 2012); (3) New dyskinetic phenotypes are seen over time (e.g. low-dose dyskinesias) (Marano et al. 2019).

What biomarkers for aPD?

Given the profound effects of advanced treatments on dopaminergic signs and complications of L-dopa treatments, a natural approach would be focusing on non-dopaminergic signs signifying the spread of neurodegeneration towards other brain regions. These include motor signs such as balance disorders, speech problems, freezing of gait etc., but also non-motor issues such as cognitive deficits. MDS-UPDRS part III is the gold standard for PD assessment, although it is biased towards appendicular and dopaminergic signs; not surprisingly such bias is not shown in part II assessing the disability resulting from the disease (Fig. 3). Thus, alternative study designs are needed (Fig. 4). Withdrawal trial to capture the underlying disease progression are not feasible for ethical reasons. Alternatively, measuring the effect of a standardized dose of L-dopa over time might provide insights into the tendency of the basal ganglia to produce dyskinesias, which is known to worsen over time (Fig. 1).

The recent introduction of sensing-capable devices has expanded our understand of brain physiology in PD and open the field to adaptive DBS (aDBS), now approved in a plethora of countries worldwide (Allert et al. 2018). Local field potentials (LFPs) are certainly reliable and feasible state biomarkers of different patients' conditions, from lead misplacement to motor fluctuations and quality/quantity of sleep (Balachandar et al. 2024). While the beta band (13–30 Hz) is the classic LFP of interest, newer studies have explored other frequencies, particularly the finely tuned gamma as a marker of overtreatment (Oehrn et al. 2024). The role of LFP as biomarker of disease modifying effect is still unexplored.

Other objective source of biomarkers for surgical prediction are network activity evaluated with functional MRI or PET modalities, as well as microstructural MRI (Loehrer et al. 2025; Unadkat et al. 2025). Lastly, fluid biomarkers are

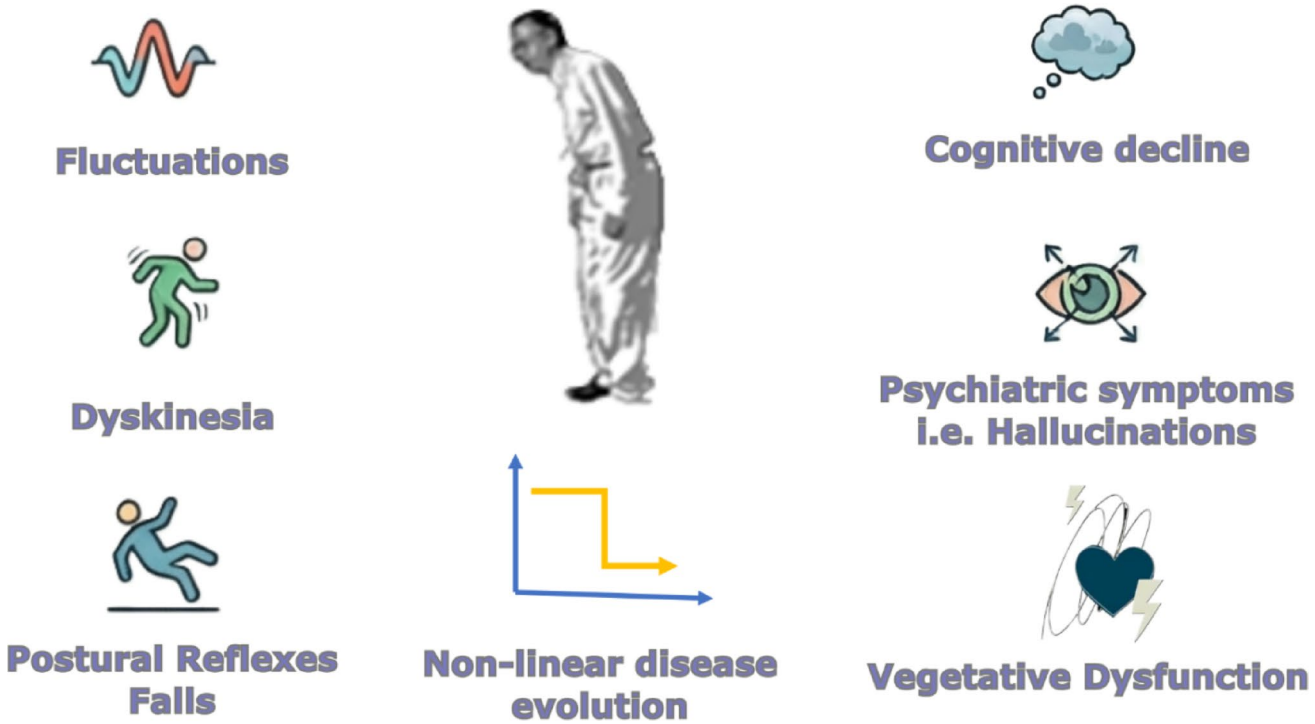

Fig. 1 Clinical milestones relevant for aPD definition

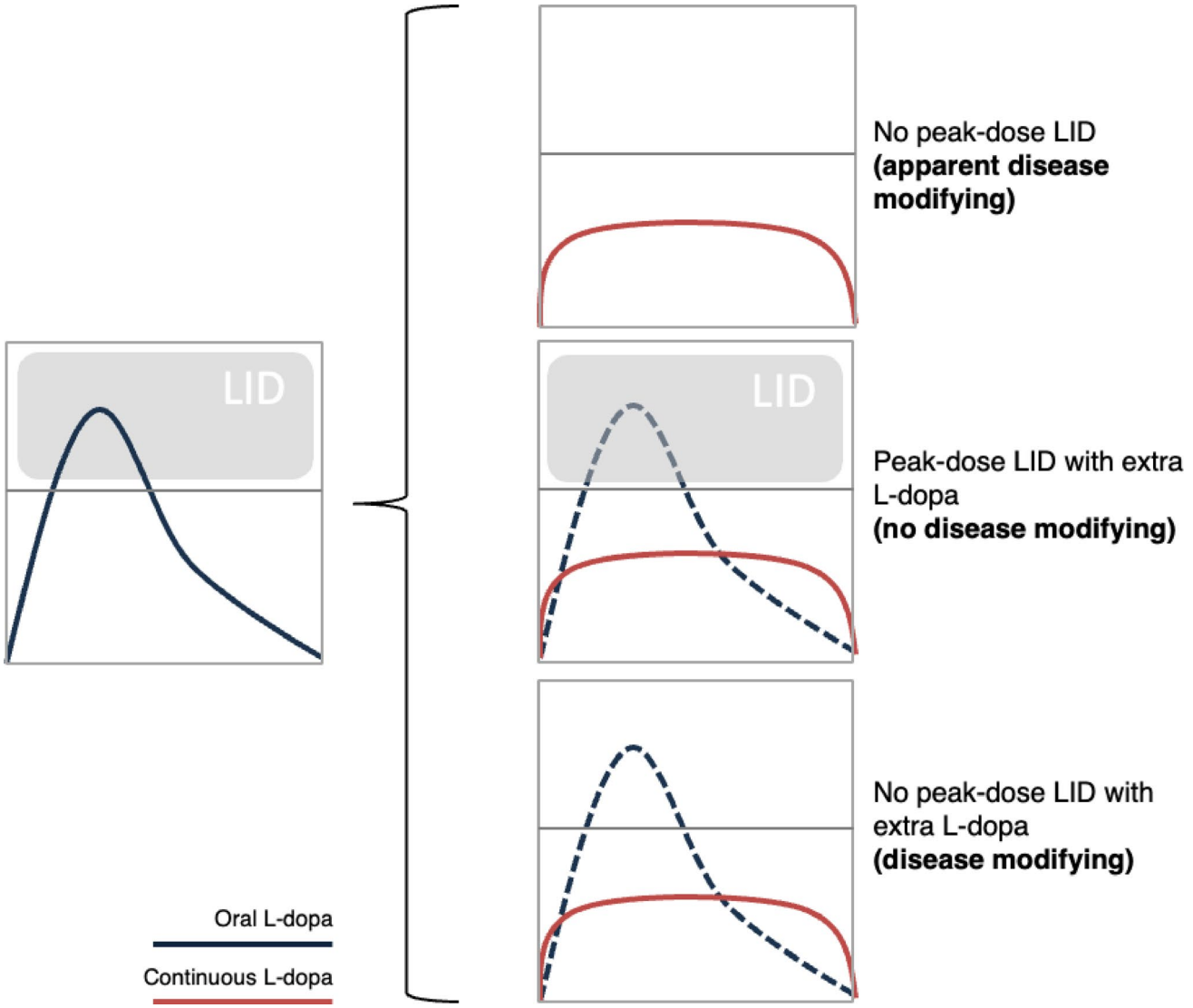

Fig. 2 Different scenarios when a patient with LID receives continuous dopaminergic delivery: LID reduce/disappear because the plasmatic concentration of L-dopa is kept under the threshold for LID (*top*), LID reappear if the patient is challenged with the same dose able to cause LID at baseline (*middle*, no disease modifying effect), LID do not appear (or do with a milder expression) when the patient is challenged with the same dose that was able to cause LID at baseline (*bottom*, disease modifying effect). *LID*L-dopa induced dyskinesias

slowly gaining traction, with several options entering center stage.

Emerging treatment modalities

Cell-based regenerative strategies represent an emerging frontier that is increasingly relevant even for patients with established neurodegeneration. Clinical trials of dopaminergic neuron transplantation derived from human induced pluripotent stem cells (iPSC) and embryonic stem cells (ESC) are now well underway, with several programs, including the CiRA/Sumitomo collaboration in Japan and the STEM-PD trial in Europe, demonstrating feasibility, safety, and early signals of engraftment and functional integration (Sawamoto et al. 2025; Kayhanian and Barker 2026). In the context of aPD, where substantial nigral neuronal loss has already occurred, cell replacement strategies offer a conceptually distinct approach from neuroprotection: rather than halting ongoing degeneration, they aim to restore dopaminergic circuitry by providing new neuronal substrate (Tabar et al. 2025). Key challenges remain, including optimizing cell survival, axonal integration, and functional connectivity within a pathological host environment that may continue to promote aSyn propagation to grafted cells, as observed in historical fetal transplant recipients (Kordower et al. 2008; Angot et al. 2012; Gima et al. 2024). Nevertheless, if these barriers can be overcome, iPSC- and ESC-derived transplantation could complement multi-target disease modification

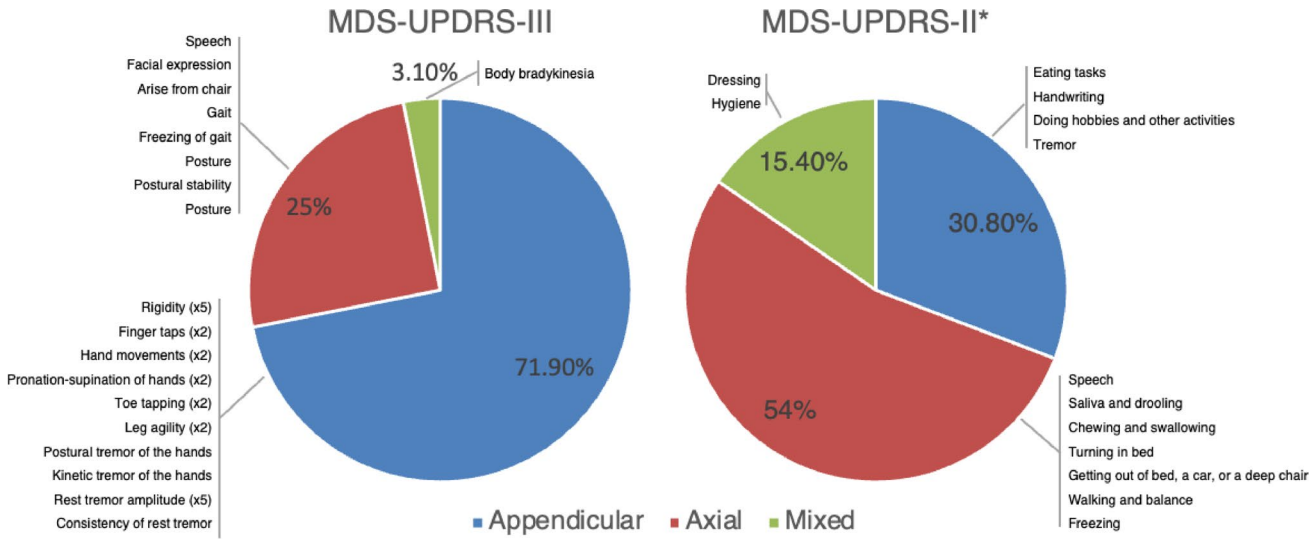

Fig. 3 MDS-UPDRS part III is the gold standard for PD assessment, although it is slightly biased towards appendicular and dopaminergic signs; while this bias is not seen in part II assessing the disability resulting from the disease. These pie charts depict the relative weight of appendicular, axial and mixed items on the total score. *only considering the motor items of the scale; *MDS-UPDRS* Movement Disorders Society Unified Parkinson Disease Rating Scale

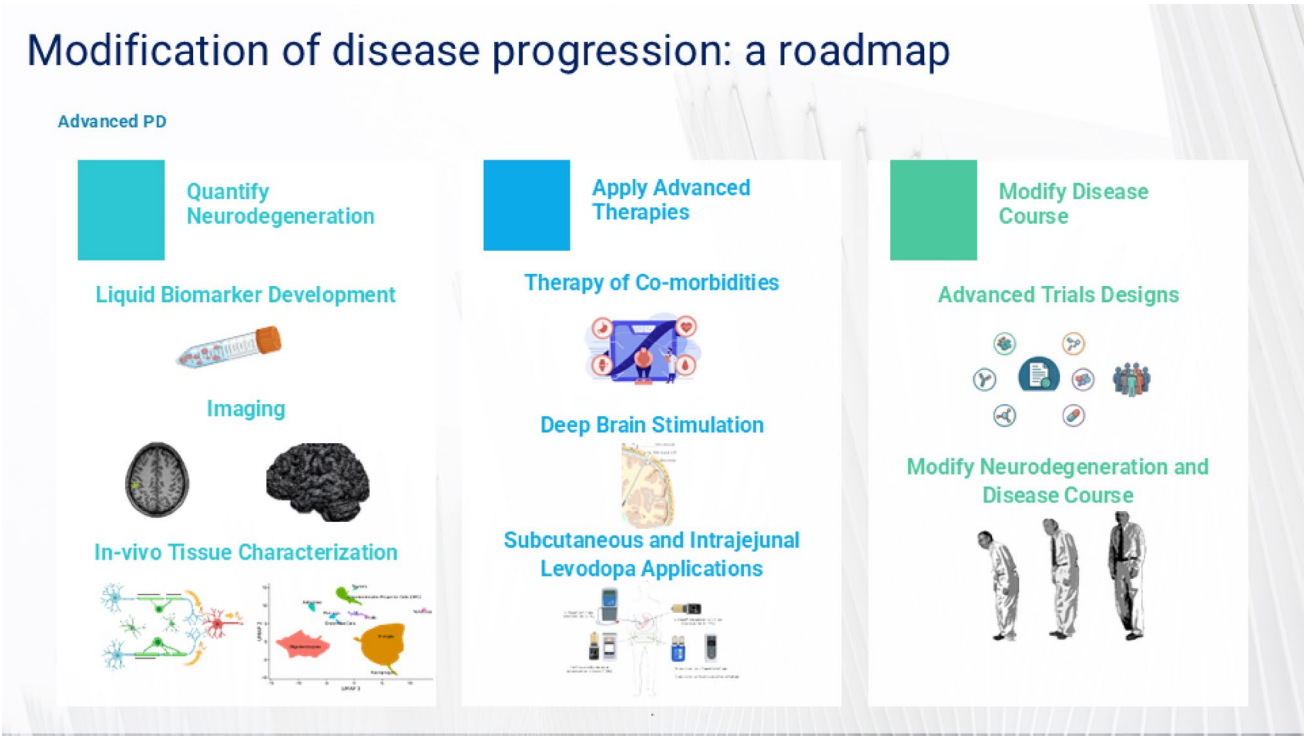

Fig. 4 A roadmap for aPD three steps approach for modifying disease progression and developing novel therapeutic strategies

frameworks in aPD by addressing the irreversible neuronal loss that symptomatic therapies cannot recover (Barker and Parmar 2025).

Tissue pathology primers that drive neurodegeneration in advanced disease stages

It is likely that the modification of the molecular and cellular phases of the disease with emerging therapies would be a changing next point after advanced therapies described above (Chopra et al. 2024). Nevertheless, given our progress in understanding relevant pathological mechanisms, such as aSyn aggregation, mitochondrial dysfunction and oxidative stress, neuroinflammation and immune-system dysfunction, proteostasis and lipidostasis dysfunction, and alterations in how the brain interacts with the periphery (e.g. gut–brain axis), we must remain confident that, at some point, manipulating these mechanisms may become not only actionable but also effective (Mouradian et al. 2025).

aSyn pathology: still a relevant target

Failure and disappointing results in clinical trials have cast doubt regarding the actual value of targeting aSyn aggregation as a therapeutic strategy (Espay et al. 2025a, b). However, whether we are "proteinopathists" or "proteinopenists", aSyn aggregation and accumulation remain central alterations in PD and related disorders, particularly in advanced stages (Espay et al. 2025a, b; Outeiro 2025; Espay and Lees 2026). Misfolded, phosphorylated, and aggregation-prone aSyn species form intracellular inclusions in neurons and glia, and experimental data suggest that pathology increases with disease progression (whether through spreading or simply due to progressive deposition). This sustained dynamic provides a rationale that interventions aimed at reducing aSyn burden, inhibiting aggregation, or enhancing degradation may still modify disease trajectories even after substantial neurodegeneration has occurred (Hung and Schwarzschild 2020).

In fact, multiple therapeutic strategies targeting aSyn are being pursued, spanning passive and active immunotherapies, small-molecule anti-aggregants, and approaches to lower aSyn expression or enhance its clearance. Antibody-based therapies seek to neutralize extracellular and trans-synaptic pathological aSyn species and thereby limit further propagation; although large phase 2 trials in early PD have yielded mixed or negative results, these programs have established target engagement and safety data that could inform future trials in more heterogeneous, treated populations. In parallel, small-molecule modulators of oligomer formation (for example, anle138b, NPT200-11/UCB0599) have demonstrated reduced aSyn aggregation, restoration of striatal dopaminergic function, and attenuation of neuroinflammation in preclinical models, raising the possibility that similar mechanisms could still confer neuroprotection in patients with established motor and non-motor complications (Fields et al. 2019).

Lowering aSyn production represents another promising avenue, particularly via antisense oligonucleotides (ASOs) or RNA interference directed against the *SNCA* gene. Preclinical studies show that partial reduction of aSyn can decrease aggregate load and improve neuronal survival without overt toxicity, suggesting that downregulation remains feasible even when pathology is widespread. For advanced PD, such approaches would likely need to be combined with robust biomarker frameworks, such as seeding amplification assays or imaging markers, to identify individuals with active aSyn-driven pathology and monitor changes in the underlying pathological burden (Menon et al. 2022).Although one may predict that such strategies may be more effective at earlier stages, it is plausible that, even at advanced stages, they may be able to modify disease progression.

Recent evidence has extended the therapeutic relevance of anti-aSyn strategies beyond PD (Pagano et al. 2024). The phase 2 AMULET trial of Lu AF82422 (amlenetug), a human monoclonal antibody targeting all major extracellular forms of α-syn, enrolled patients with MSA and demonstrated a non-statistically significant 19% slowing of clinical progression on the primary endpoint (UMSARS Total Score), with more pronounced efficacy signals in less impaired patients and consistent trends across secondary endpoints. These findings, while not definitive, support continued investigation of anti-aSyn immunotherapy across synucleinopathies and have informed the initiation of a phase 3 trial (MASCOT, NCT06706622), to which the FDA has granted Fast Track designation. Although MSA and PD differ substantially in their cellular aSyn distribution, with oligodendroglial inclusions predominating in MSA and neuronal Lewy bodies in PD, as well as in their disease trajectory, the shared aggregation-prone nature of aSyn and evidence of target engagement support the continued investigation of immunotherapeutic strategies in advanced synucleinopathies, including aPD(Buur et al. 2024).

Oxidative stress and mitochondrial dysfunction

Oxidative stress and mitochondrial impairment are integral to PD pathophysiology and appear to persist throughout the disease, fueled by, among others, dopamine metabolism, iron dyshomeostasis, and chronic neuroinflammation. Oxidative modification of dopamine generates

reactive quinones that can covalently modify aSyn, promoting toxic oligomer formation and impairing its clearance, thereby linking redox stress directly to aSyn pathology. In advanced PD, these processes may be further amplified by longstanding levodopa exposure, altered iron handling, and cumulative mitochondrial damage, which together sustain a self-reinforcing cycle of oxidative injury, protein misfolding, and neuronal dysfunction (Oliver et al. 2025).

Therapeutic efforts to counter oxidative stress have so far produced disappointing clinical results, but they provide important mechanistic insights. Classical antioxidant trials (e.g., coenzyme Q10, vitamin E) in predominantly early PD cohorts did not demonstrate robust disease modification, likely due to insufficient target engagement, lack of patient stratification, or the sheer redundancy of oxidative pathways. More targeted interventions, such as iron chelators, mitochondria-directed agents, or drugs that modulate redox-sensitive transcriptional programs, including multi-valent compounds, remain of interest and could, in principle, still be relevant in advanced disease if delivered in a way that effectively reaches vulnerable neuronal populations and is coupled to biomarkers of oxidative damage and mitochondrial function. Importantly, reducing oxidative stress in later stages might not restore lost neurons but could stabilize remaining circuits, limit non-dopaminergic degeneration, and improve resilience to further insults (Zhang et al. 2025).

Inflammatory responses and microglial activation

Chronic activation of microglia and astrocytes, together with peripheral immune changes, contributes to a pro-inflammatory milieu that appears to be sustained across the entire PD course. Misfolded aSyn itself can act as a damage-associated molecular pattern (DAMP), activating microglial receptors and promoting release of pro-inflammatory cytokines, thereby linking proteinopathy to innate immune activation. Conversely, inflammatory signaling can enhance aSyn aggregation and impair clearance, creating a bidirectional feed-forward loop that may be particularly relevant in advanced stages, where the burden of pathology and neurodegenerative debris is highest (Menon et al. 2022).

These insights have stimulated interest in immunomodulatory therapies as potential disease-modifying strategies, complementing direct aSyn-targeted approaches. Repurposed agents with anti-inflammatory or immunoregulatory properties, including non-steroidal anti-inflammatory drugs, microglial modulators, and agents targeting specific cytokine pathways, have shown variable and often modest effects. Nevertheless, their translational trajectory underscores that dampening maladaptive neuroinflammation is feasible and may influence progression. As disease advances, the window for altering innate immune responses may broaden, since microglial activation, peripheral immune dysregulation, and blood–brain barrier changes remain dynamic and potentially reversible processes. Strategically, advanced PD trials could enrich for individuals with biochemical or imaging evidence of heightened neuroinflammation and evaluate whether targeted immunomodulation slows decline in motor and cognitive domains that are poorly responsive to dopaminergic therapy (Salim et al. 2023).

Gut–brain axis and systemic contributors

The gut–brain axis has emerged as a critical interface in PD, with evidence that synucleinopathies affects the enteric nervous system and that gastrointestinal symptoms and dysbiosis may precede motor onset by many years. Dysregulation of the brain–gut–microbiota axis, increased intestinal permeability, and enteric glial dysfunction can promote systemic and local inflammation, which may in turn facilitate aSyn misfolding and propagation from the gut to the brain (Mulak and Bonaz 2015).

Although most mechanistic work on the gut–brain axis has focused on prodromal and early PD, persistent gastrointestinal dysfunction, microbiome alterations, and enteric inflammation are also observed in established disease, suggesting an extended therapeutic window. Interventions targeting the microbiome (such as defined probiotics, prebiotics, antibiotics, or fecal microbiota transplantation), intestinal barrier integrity, or enteric inflammation could, at least in theory, reduce peripheral drivers of neuroinflammation and aSyn pathology, even in advanced stages. Although rigorous evidence that such strategies modify clinical progression is currently lacking, they still offer a conceptually-attractive complement to brain-focused therapies, particularly given their relative accessibility, potential safety, and relevance to non-motor symptom clusters (constipation, weight loss, autonomic dysfunction) that dominate advanced PD morbidity (Oliver et al. 2025).

Integrating mechanisms and redefining the window for disease modification

Cumulatively, the ongoing dynamics of aSyn aggregation, oxidative stress, neuroinflammation, and gut–brain interactions argue against a strict early–late dichotomy in the window for disease modification. Instead, PD pathogenesis appears as a continuum in which multiple, partially independent pathological cascades remain active into advanced stages, albeit against a background of substantial and often irreversible neuronal loss (Tinkhauser et al. 2020). This suggests that, in advanced PD, the goal of "disease modification" may require the stabilization of surviving neurons so

they remain functional and alive rather that reverting neuronal loss (Mouradian et al. 2025).

Designing trials for disease modification in advanced PD will require careful attention to these mechanistic layers and to the unique challenges of a heavily treated, clinically heterogeneous population. Biology-driven classification and stratification, using aSyn seed amplification assays, inflammatory markers, gut-related readouts, imaging, and other emerging biomarkers, will enable us to identify subgroups in whom specific pathogenic processes are particularly active and, therefore, more amenable to targeted intervention (Chopra et al. 2024). In parallel, trial designs will need to accommodate high symptomatic treatment burden, advanced disability, and competing comorbidities while focusing on outcomes that matter most in later disease stages, such as preservation of mobility, autonomy, cognition, and caregiver burden. Within such a framework, mechanistically informed therapies targeting aSyn, oxidative stress, inflammation, and the gut–brain axis, among others may offer genuine, if incremental, opportunities to alter the course of advanced PD rather than only palliate its symptoms.

A further complexity in advanced sporadic PD is that, as disease progresses, the pathological substrate rarely conforms to a pure synucleinopathy. Post-mortem studies have consistently demonstrated that co-pathologies are highly prevalent in long-standing PD, with amyloid plaques present in over 40% of patients in their 60 s and in up to 85% of those in their 90 s, cerebral amyloid angiopathy increasing from 20% to 80% across the same age range, limbic-predominant TDP-43 encephalopathy (LATE) affecting 20–50%, and significant tau pathology present in 40–60% of older patients at autopsy (Beach et al. 2025; Jellinger 2025; Walker and Attems 2024). This polypathological reality has profound implications for disease modification: a therapeutic strategy targeting aSyn alone is unlikely to be sufficient in a patient whose cognitive decline is substantially driven by concomitant tau or amyloid burden, as supported by evidence that CSF Aβ42 and phospho-tau trajectories independently predict cognitive progression in PD cohorts (Baek et al. 2021; Batzu et al. 2022; Mantovani et al. 2024). Biology-driven stratification must therefore extend beyond aSyn status to encompass co-pathology profiling through the use of emerging CSF and plasma biomarkers for amyloid-β, phospho-tau, and neurofilament light chain, thereby enabling the identification of the dominant pathological drivers in individual patients (Cousins et al. 2023; Pan et al. 2025). In advanced PD, disease modification may ultimately require combination strategies that simultaneously address aSyn aggregation and the most clinically relevant co-pathologies, analogous to polypharmacy approaches in cardiovascular disease, which is a recognition that further strengthens the case for precision stratification and multi-target trial designs in aPD (Espay et al. 2017; Nichols et al. 2023; Zhang et al. 2025).

Modification of co-morbidities and lifestyle in aPD

In PD, particularly in advanced stages, the clinical trajectory is rarely driven by a single pathogenic pathway (Sweeney et al. 2018). As in other neurodegenerative conditions, "single-target" disease-modifying strategies have repeatedly failed to achieve meaningful clinical slowing, likely because disease progression reflects the interplay of multiple biological mechanisms and an increasing burden of co-pathologies that accumulate with advancing age (Bohnen and Albin 2011; Nichols et al. 2023). In real-world aPD, cerebral small vessel disease and cardiometabolic disorders are common and have been associated with worse gait performance, cognitive decline, mood disturbances, and overall disability (Bohnen and Albin 2011). Importantly, vascular and metabolic risk burden is well established as a determinant of life expectancy and quality of life in the general population, and its modification improves survival and functional outcomes (Naghavi et al. 2025). Therefore, it is plausible that, alongside symptomatic therapies and future mechanism-targeted interventions, systematic attention to modifiable comorbidities and lifestyle factors may represent a clinically meaningful strategy to enhance brain resilience, preserve functional reserve, and potentially attenuate downstream disability in advanced PD (Visser et al. 2024).

Modification of cardiometabolic pathology

Among the modifiable domains that deserve priority in aPD, cardiometabolic and vascular factors are particularly relevant because they are common, measurable, and potentially actionable (Sweeney et al. 2018). Cerebral small-vessel disease and white matter injury frequently coexist with PD and are associated with worse motor stage, gait dysfunction, cognitive impairment, and mood disturbances, suggesting an additive contribution to disability beyond primary dopaminergic degeneration (Bohnen and Albin 2011; Sweeney et al. 2018). Similarly, type 2 diabetes and insulin resistance have been associated not only with increased PD risk but also with faster motor and cognitive progression in observational cohorts (Chohan et al. 2021), providing a biological and clinical rationale for early metabolic optimization and explaining the interest in GLP-1 receptor agonists as potential disease-modifying candidates. Although definitive disease-modifying evidence remains mixed, systematic control of glycemia and vascular risk is justified by both

mechanistic plausibility and broader neurological outcomes. Body weight and its longitudinal variability also carry prognostic relevance in aPD (Urso et al. 2022). Although it remains difficult to disentangle whether weight change is a driver of progression or a manifestation of disease, proactive nutritional assessment and timely interventions to prevent unintentional weight loss, malnutrition, and sarcopenia are likely important to preserve functional reserve and reduce downstream disability, as in other neurodegenerative conditions.

Modifying life-style factors

Within lifestyle domains, physical activity has the strongest interventional signal. Randomized trials demonstrate that structured aerobic or high-intensity exercise is feasible, improves motor outcomes, and may be associated with favourable effects on brain connectivity and atrophy trajectories over time (Van Der Kolk et al. 2019; Johansson et al. 2022). Although long-term disease-slowing effects remain under investigation, exercise consistently enhances mobility, cardiovascular fitness, and resilience, key determinants of late-stage outcomes. Dietary patterns, particularly Mediterranean-type diets, are associated with lower PD risk and show emerging signals in relation to slower progression and improved non-motor symptoms, likely through metabolic, vascular, and anti-inflammatory pathways(Yin et al. 2021). Sleep health, including the identification and treatment of obstructive sleep apnea (OSA), is another relevant domain. OSA has been associated with an increased subsequent risk of PD and is potentially modifiable with CPAP (Neilson et al. 2026); although secondary-prevention trials in PD are limited, systematic screening and treatment remain biologically plausible and clinically justified in aPD. Although smoking has been consistently associated with a lower incidence of PD, a relationship that remains under investigation (Ritz et al. 2014), it cannot be considered protective after diagnosis and it is clearly harmful overall, so it should always be discouraged.

Although PD-specific secondary or tertiary prevention evidence for many other factors remains limited, it is still reasonable to consider exposures with consistent risk-reduction signals and strong mechanistic plausibility, such as traumatic brain injury and long-term air pollution exposure (Ben-Shlomo et al. 2024). In advanced disease, hearing and vision impairment should also be actively considered and, where possible, treated, as they can substantially worsen cognition, balance, social engagement, and caregiver burden (Urso et al. 2026). Finally, iatrogenic contributors should also be addressed. Polypharmacy and especially anticholinergic burden are independently linked to cognitive decline, delirium, falls, and worse outcomes in older adults and in PD (Crispo et al. 2016). Therefore, structured medication review and deprescribing should therefore be core elements of any multidomain disease-modification framework.

Access to care and global inequalities as determinants of disease course

Disease course modification in aPD cannot be understood solely through biological or interventional lenses. The trajectory of advanced PD is critically shaped by health system architecture, access to specialist care, and socioeconomic context. These factors function not merely as background variables but as active determinants of clinical outcomes. PD prevalence has more than doubled over the past generation and continues to rise globally, placing increasing demands on health systems and specialist care delivery (Vollset and Collaborators 2024; Su et al. 2025). Consequently, disparities in healthcare infrastructure increasingly influence disease outcomes and access to advanced treatments.

Global disparities in PD care

Marked inter-country variability exists in the management of advanced PD (Koehn et al. 2025). Access to device-aided therapies (DATs), including deep brain stimulation (DBS) and infusional therapies such as levodopa–carbidopa intestinal gel (LCIG), continuous subcutaneous apomorphine infusion, and more recently subcutaneous levodopa formulations, differs substantially across regions due to reimbursement policies, surgical capacity, regulatory frameworks, and availability of multidisciplinary expertise (Auffret et al. 2023; Jimenez-Shahed et al. 2025; Schneider et al. 2026). DAT represents the cornerstone of treatment escalation in advanced PD and is typically considered when conventional oral therapy fails to adequately control motor fluctuations and dyskinesias (Antonini et al. 2018; Phokaewvarangkul et al. 2024).

Even within high-income countries, waiting times, eligibility thresholds, and local infrastructure can significantly affect whether and when patients receive advanced interventions. As emphasised in recent clinical literature on advanced therapy utilisation, indication and implementation strategies vary widely and are strongly influenced by systemic constraints rather than purely clinical criteria (Nijhuis et al. 2021; Auffret et al. 2023; Bhidayasiri et al. 2025; Jimenez-Shahed et al. 2025). Real-world access to DAT remains inconsistent and influenced by referral patterns, clinician awareness, and health system readiness. In many healthcare systems, these therapies are centralised in tertiary centres, introducing geographic disparities in availability. Studies from Asia have further highlighted regional

disparities in access to advanced therapies, including differences in referral pathways, reimbursement policies, and availability of specialised centres capable of delivering device-aided therapies (Bhidayasiri et al. 2020; Fujioka et al. 2023). These disparities illustrate how health system organisation can significantly influence the timing and utilisation of advanced treatments in Parkinson's disease.

Globally, these disparities are amplified. PD is increasingly recognised as one of the fastest growing neurological disorders worldwide, with the largest growth occurring in low- and middle-income countries where specialist care infrastructure remains limited (Dorsey and Bloem 2018; Su et al. 2025). In many such settings, access to movement disorder specialists, advanced infusion therapies, or DBS is limited or absent, often due to cost, infrastructure gaps, and scarcity of trained personnel (Jimenez-Shahed et al. 2025). Consequently, strategies for disease course modification that rely exclusively on high-cost, invasive technologies risk being inherently non-scalable and inequitable.

Importantly, health system quality itself may modify disease trajectory. Structured multidisciplinary care, including specialist follow-up, optimised medication adjustment, physiotherapy, and telemedicine support, has been associated with improved symptom control and reduced complications in observational studies (Dorsey et al. 2016, 2020). For example, integrated care networks such as ParkinsonNet have demonstrated improved outcomes and cost-effectiveness through coordinated multidisciplinary care delivery (van de Warrenburg et al. 2021). Comprehensive care models have also been linked with reduced hospitalisation and improved quality of life compared with fragmented care. Recent work emphasising integrated care models in PD has further highlighted the importance of multidisciplinary management and coordinated healthcare delivery to optimise long-term outcomes in patients with advanced disease (Bloem et al. 2020; Rajan et al. 2020; Weise et al. 2024).

During the expert panel discussion that informed the conceptual framework of this manuscript, several participants emphasised that differences in health system organisation and access to multidisciplinary expertise may substantially influence the observed trajectory of advanced PD in clinical practice. In particular, variability in access to DATs, specialist follow-up, and structured care pathways was identified as a major contributor to heterogeneity in patient outcomes across regions.

The increasing reliance on digital biomarkers and remote monitoring introduces an additional dimension: the digital divide (Bhidayasiri et al. 2024). Older individuals with advanced PD may have limited digital literacy, and socioeconomic disparities influence access to wearable devices, smartphones, and stable internet connectivity (Campanozzi et al. 2023; Esper et al. 2024). Emerging digital tools hold promise for monitoring motor fluctuations, gait instability, and cognitive changes, but their implementation requires careful consideration of accessibility and usability (Wamala Andersson and Gonzalez 2025). Trial designs that assume universal digital inclusion risk excluding vulnerable populations and limiting external validity.

Intercountry differences in documentation and social support systems further influence outcomes. In some healthcare systems, cognitive decline is under-recognised or under-documented, affecting eligibility for formal assistance or long-term care. Variations in community rehabilitation resources, home nursing support, and respite services contribute to heterogeneity in institutionalisation rates and caregiver burden. These factors introduce systematic bias into multinational trials and complicate interpretation of "natural history" comparisons.

In this context, access to care should not be conceptualised merely as a limitation but as a modifiable, system-level lever for altering disease trajectory. A pragmatic framework for disease course modification must therefore integrate equity, scalability, and health system feasibility alongside biological plausibility.

Caregivers as determinants of disease course

In aPD, caregivers are central actors in shaping clinical trajectory. As motor disability, cognitive decline, neuropsychiatric symptoms, and autonomic dysfunction accumulate, patients increasingly depend on informal caregivers for medication management, mobility supervision, nutritional support, and recognition of complications (Martinez-Martin et al. 2023). Caregiver resilience and capacity thus directly influence the risk of falls, hospitalisations, institutionalisation, and mortality (Geerlings et al. 2023).

Caregiver burden in PD is substantial and multifactorial (Aamodt et al. 2024). Informal caregiving imposes significant emotional, physical, and social strain, and caregiver burden has been consistently associated with disease duration, functional impairment, and the presence of cognitive or neuropsychiatric symptoms in patients (Zhao et al. 2024). Importantly, caregiver strain correlates more strongly with non-motor symptom burden, including cognitive impairment, hallucinations, depression, and apathy—than with motor severity alone (Martinez-Martin et al. 2023). Studies examining PD management in Asian healthcare settings have similarly highlighted the critical role of family caregivers in supporting patients with advanced disease, particularly in regions where formal long-term care infrastructure may be limited (Phokaewvarangkul et al. 2024). Therefore, advanced stages of PD are associated with disproportionately greater caregiver burden compared with earlier disease stages (Martinez-Martin et al. 2023). As the disease

progresses, increasing dependence for activities of daily living, behavioural complications, and cognitive decline further intensify caregiving demands.

Institutionalisation in advanced PD is frequently precipitated not solely by motor disability but by caregiver exhaustion, behavioural complications, or inability to provide safe supervision (Li et al. 2024). Cognitive impairment and neuropsychiatric symptoms are among the strongest predictors of nursing home placement in PD cohorts (Aarsland et al. 2000). Consequently, caregiver capacity directly influences the timing of key disease milestones, including loss of independence and transition to institutional care.

During the expert discussion that preceded the development of this manuscript, panel members consistently emphasised that caregiver resilience and support structures represent critical determinants of real-world outcomes in advanced PD. Participants noted that in clinical practice, deterioration in caregiver capacity often precedes institutionalisation and may accelerate functional decline independently of motor symptom progression.

From a disease course perspective, caregivers function as system-level buffers against clinical decompensation. Effective supervision may prevent medication errors and reduce OFF-related instability. Early recognition of infections, dehydration, or delirium can reduce hospital admissions. Structured monitoring of nutrition and weight may mitigate sarcopenia and frailty, both associated with worse outcomes in advanced PD. Recognising caregivers as co-therapeutic partners reframes the trajectory of advanced PD as not solely governed by neurodegeneration, but by relational and environmental dynamics.

Despite this central role, caregivers are rarely incorporated as formal endpoints in clinical trials of advanced PD. Disease course modification frameworks should therefore consider caregiver-related outcomes, including caregiver quality of life, caregiver strain indices, and institutionalisation-free survival. Integrating caregiver metrics acknowledges that advanced PD progression is not solely a biological phenomenon but also a social one.

Interventions targeting caregiver support, such as structured education programmes, telemedicine follow-up, respite services, and nurse-led care coordination, may represent scalable strategies to mitigate caregiver burden and delay institutionalisation. Although PD-specific randomised data remain limited, evidence from chronic neurological conditions suggests that caregiver-focused interventions can reduce stress, improve adherence to treatment, and improve overall care quality (Jin and Cheon 2026; Tenison et al. 2026).

In advanced PD, where definitive biological disease modification remains elusive, optimising the caregiving ecosystem may represent one of the most immediately actionable approaches to altering clinical trajectory (Perepezko et al. 2023). The pursuit of disease-modifying therapies in advanced PD must therefore extend beyond molecular targets and surgical interventions to include health system design and caregiver support structures.

Conclusions and roadmap

In conclusion, disease modification in aPD may be more appropriately conceptualized not only in biological terms but also as the capacity of therapeutic interventions to modify network dysfunction and alter the long-term clinical trajectory. It is in fact difficult to parse out the many indirect effects resulting from advanced treatments such as deep brain stimulation or continuous administration of dopaminergic therapy but also improved sleep, better mood, more chances to for social engagement and continuous exercise interventions are just some of the examples of the factors that persons with aPD should practice but also be considered as confounders that future trials should take into account to measure neurodegeneration trajectories and the heterogeneity of single subjects and cohorts. The field of biomarkers of PD is steadily growing and should be validated and adapted to aPD. Further efforts are needed towards detection and quantification of the disease ‘trait’ and “states”, that should be then adapted to single disease phenotypes as defined by the genetic background, aSyn positivity or the quantification of the neurodegeneration. More work is needed to modify disease progression in the early stages, but even more so inaPD. Newer approaches should be tested in late-stage disease, alongside symptomatic and disease-modifying treatments.

Author contributions S.G., A.F., and D.U. conceptualized the study, wrote the original draft of the manuscript, and led its completion. X.Y. edited and revised the manuscript. B.P. and P.K. conducted the systematic literature search and contributed to the synthesis of evidence. T.v.L. and W.J. contributed to the critical appraisal of the included literature and provided expert commentary on specific sections of the manuscript. P.J.G.-R., R.B., and T.F.O. reviewed and critically revised the manuscript for important intellectual content. All authors read and approved the final version of the manuscript.

Funding Open Access funding enabled and organized by Projekt DEAL. Sergiu Groppa: received research funding from Patients groups, BMBF, DFG (SPP2177 Radiomics), UM Mainz, Abbott, Boston Scientific, Böhringer Foundation, Magventure, National MS Society, Precisis, Innovationsfond GBA (01NVF22107, INSPIRE–PNRM+) and Lectures fees from Abbott, Abbvie, Bial, BVDN, Merz, IPSEN, Stada, UCB. Dr. Garcia Ruiz has received personal compensation as a consultant/scientific advisory board member from Italfarmaco, Britannia, Bial, Esteve, Merz, and Stada; and speaking honoraria from Italfarmaco, Bial, Esteve and Abbvie. Roongroj Bhidayasiri has received grants from the following agencies: the Thailand Science Research and Innovation (TSRI, Programme Management Unit for Competitiveness, C01F670185), the National Economic and Social

Development Council of Thailand, Thailand Centre of Excellence for Life Sciences (TC (ERP) 31/2568), the National Research Council of Thailand (N42A680591, N35E680087), and Chulalongkorn University (CE68_028_3000_004). He is also supported by the Royal Society of Thailand, has provided consultancy services, and has received honoraria and lecture fees from industries such as Britannia, Ipsen, Teva-Lundbeck, and Mitsubishi-Tanabe. Bhidayasiri holds patents for various innovations, including a laser-guided walking stick, a portable tremor device, technology for monitoring during the night (NIGHT-Recorder), an electronic diary for Parkinson's disease symptoms, as well as the Parkinson insole and shoe, and anti-choking mugs. Furthermore, his copyrighted works comprise the mobile application for screening Parkinson's disease (Check PD), ChulaPD ADL Questionnaire, and a daily activity diary for Parkinson's disease.

Data availability No datasets were generated or analysed during the current study.

Declarations

Conflict of interest The authors declare no competing interests.

Ethical approval This study does not be required traditional ethical.

Consent to participate This study does not be required consent to participate due to its nature of being a review article. Consent to publish This study does not require consent to publish; it is a review article.

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