

# Parkinson's Disease – A Spectrum Disorder?

Orla McQuade, MSN, FNP-C, CMRD

Emory University



**AMDAPP**  
Association of Movement Disorder Advanced Practice Providers

# Orla McQuade – Relevant Financial Relationships

- No disclosures to report.

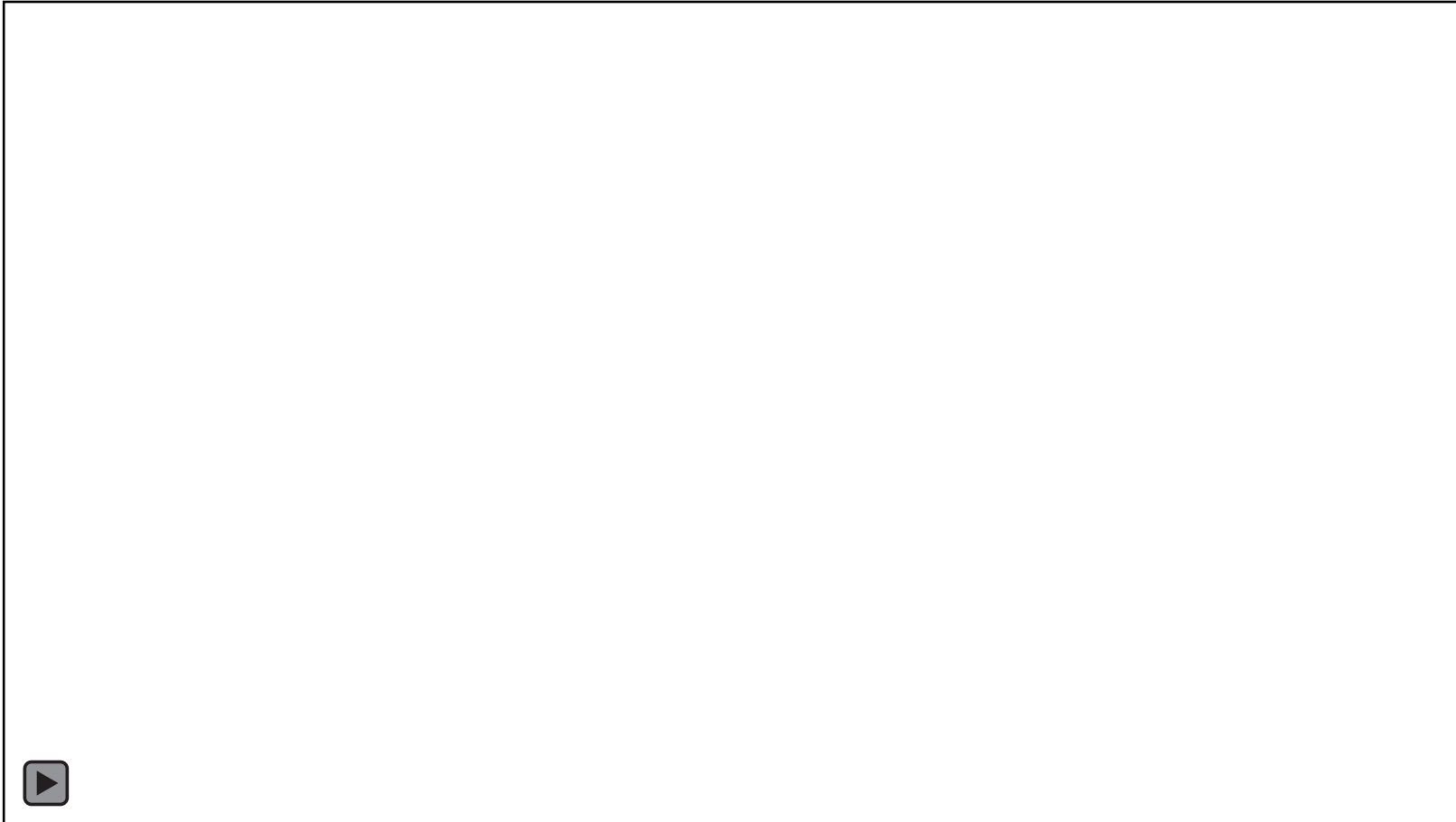
All relevant financial relationships have been mitigated

# Learning Objectives

- Describe PD as a clinical and biological spectrum
- Discuss methods of defining PD as a spectrum
- Discuss implications of PD as a spectrum disorder

# Poll

- Do you feel that Parkinson's Disease is a spectrum disorder?





# Commonalities? Differences? Dx?

# What is Parkinson's Disease

- Traditional definition
  - Bradykinesia plus either tremor or rigidity
  - Diagnosis based solely on motor symptoms
  - Dopaminergic loss in the substantia nigra is the primary pathology

# If you've seen one patient with PD, you've seen one patient with PD...

- Clinical heterogeneity:
  - Non motor symptoms (cognitive decline, autonomic symptoms, etc)
  - Age of onset
  - Tremor-predominant vs akinetic rigid vs etc
  - Response to treatment
- Single disease or multiple overlapping diseases (co-pathologies)

# Motor phenotypic subtypes

- Akinetic rigid
- Tremor predominant
- PIGD
- Hypophonia, dysphagia, dystonia...

Chou, K. L., Stacy, M., Simuni, T., Miyasaki, J., Oertel, W. H., Sethi, K., ... & Stocchi, F. (2018). The spectrum of “off” in Parkinson's disease: what have we learned over 40 years?. *Parkinsonism & Related Disorders*, 51, 9-16.

# Non-motor subtypes

- Neuropsychiatric symptoms
- Autonomic symptoms
- Sensory symptoms

Chou, K. L., Stacy, M., Simuni, T., Miyasaki, J., Oertel, W. H., Sethi, K., ... & Stocchi, F. (2018). The spectrum of “off” in Parkinson's disease: what have we learned over 40 years?. *Parkinsonism & Related Disorders*, 51, 9-16.

# The “Spectrum of OFF”

K.L. Chou et al. / Parkinsonism and Related Disorders 51 (2018) 9–16

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**Table 2**

Non-motor symptoms and their relationship to the on/off state.

NMS category	Relationship to motor OFF/ON	Response to dopaminergic treatment
<b>Neuropsychiatric</b>		
Depression	OFF > ON	Yes
Apathy	OFF > ON	Limited
Fatigue	OFF > ON	Limited
Panic attacks	OFF > ON	Yes
Anxiety	OFF > ON	Yes
Decline in cognitive performance	OFF > ON	Yes
Drowsiness	OFF > ON	Yes
Decline in attention	OFF > ON	Yes
Impulse control behavior <sup>a</sup>	ON > OFF	Yes with dose reduction
<b>Autonomic</b>		
Lightheadedness	OFF > ON	Limited
Abdominal pain and bloating	OFF	Yes
Constipation	OFF > ON	Yes
Urinary urgency	OFF > ON	Yes
Sweating	OFF > ON	Limited
Swallowing dysfunction	OFF > ON	Limited
Stridor	OFF	Yes
<b>Sensory symptoms</b>		
Diffuse pain	OFF > ON	Yes
Neuralgic pain	OFF > ON	Yes
Dysesthesia	OFF > ON	Yes
Visual disturbances	OFF > ON	Limited
Restless legs syndrome	OFF	Yes

<sup>a</sup> Can occur as medication ON peak effect. Adapted from Martinez-Fernandez et al. [9] and Storch et al. [15].

# Cognitive / Neuropsychiatric Spectrum

- Parkinson's Disease - Mild Cognitive Impairment (PD-MCI)
  - Parkinson's Disease Dementia (PDD)
  - Hallucinations and psychosis
  - Impulse control disorders
- 
- Cognitive involvement varies widely and impacts care planning

Borghammer, P., Okkels, N., & Weintraub, D. (2024). Parkinson's disease and dementia with Lewy bodies: one and the same. *Journal of Parkinson's Disease*, 14(3), 383-397.

# Autonomic Dysfunction Spectrum

- Orthostatic hypotension
- Urinary dysfunction
- Sexual dysfunction
- Gastrointestinal dysmotility
  
- Often under-recognized yet significantly disabling
- Autonomic symptom progression correlates with motor symptom progression

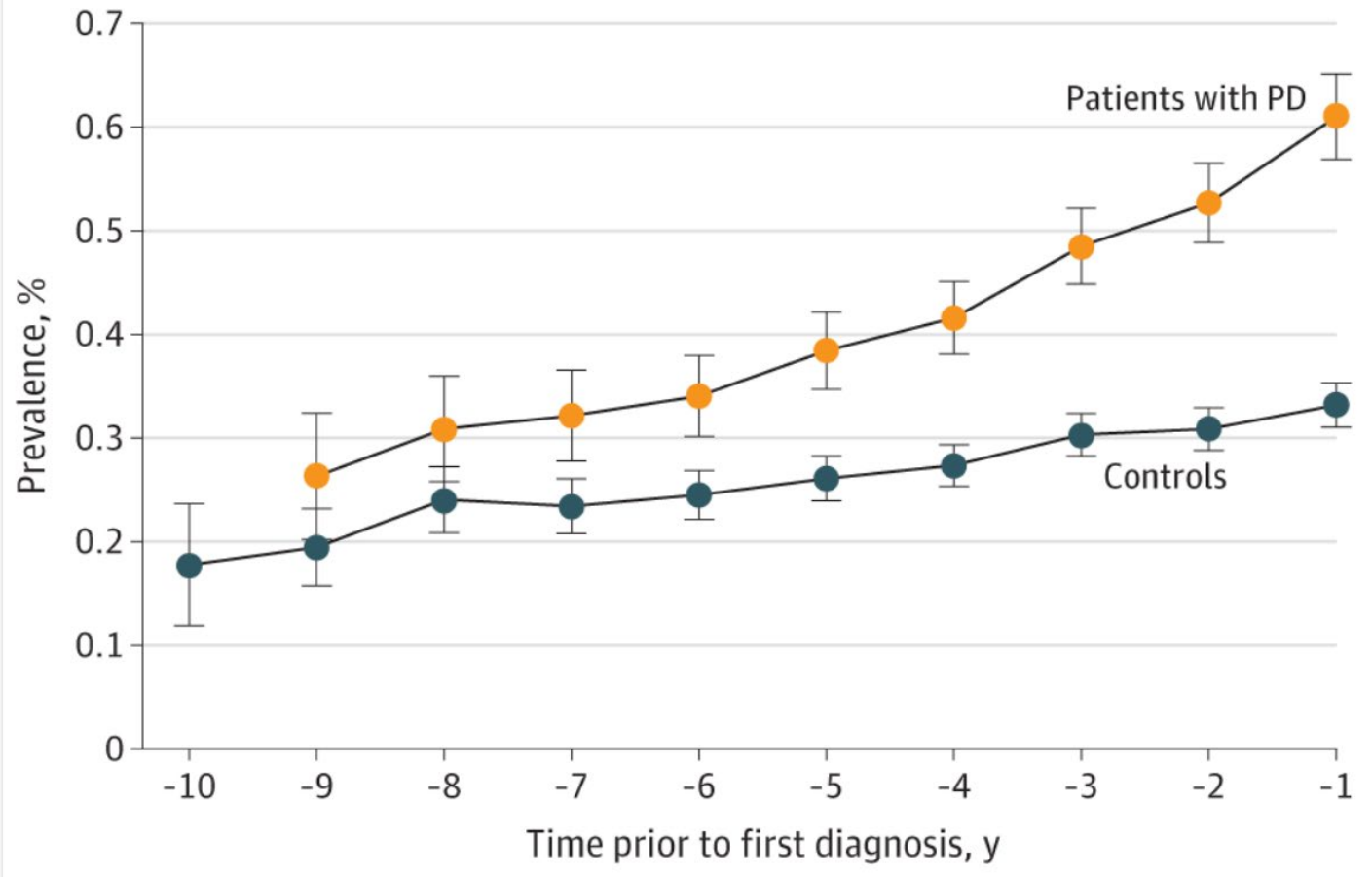
Berg, A., Bech, S., Aasly, J., Farrer, M. J., & Petersen, M. S. (2022). Autonomic dysfunction in Parkinson's disease: Results from the Faroese Parkinson's disease cohort. *Neuroscience Letters*, 785, 136789.

# Prodromal Parkinson's Disease

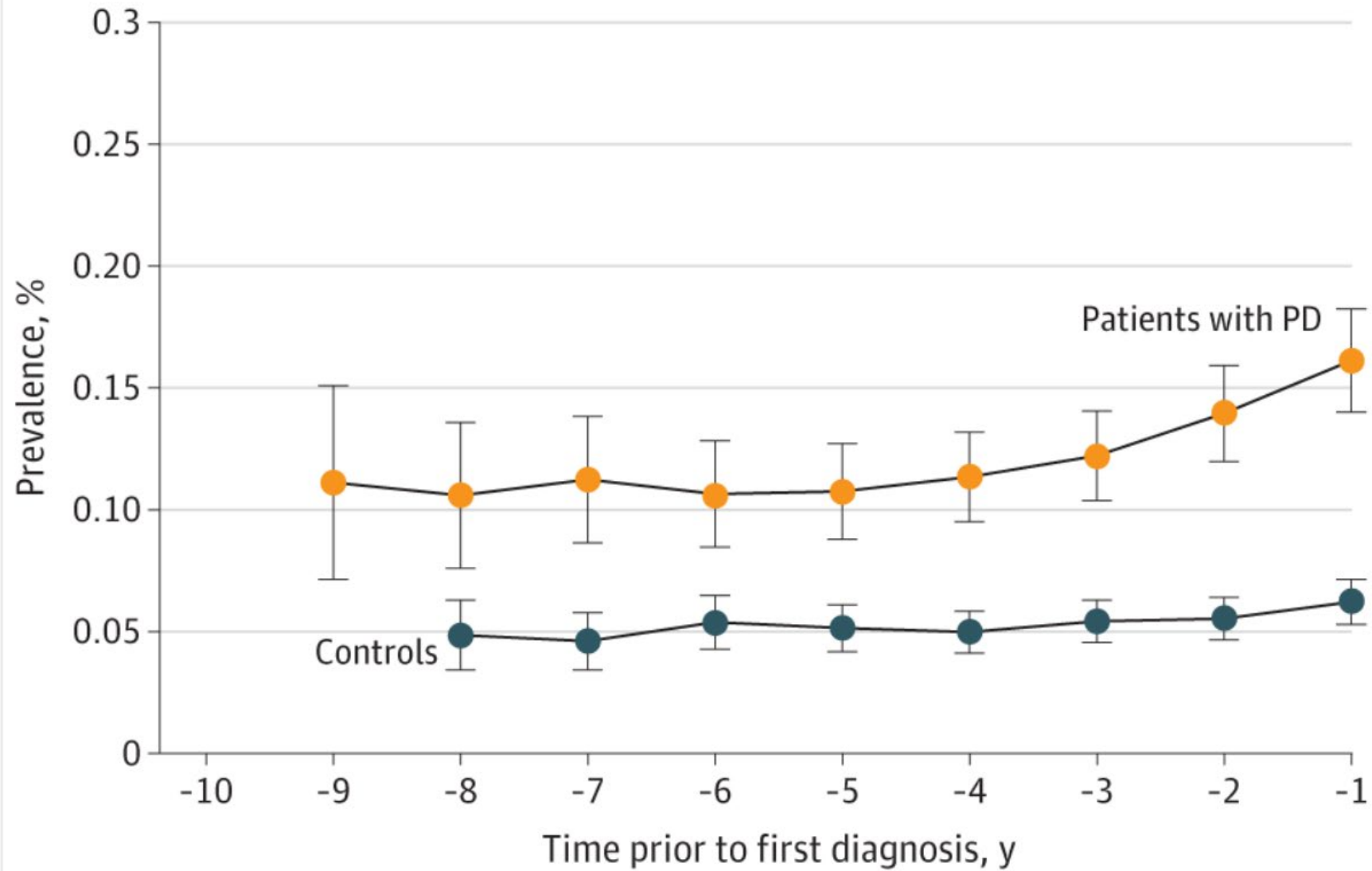
- REM Sleep Behavior Disorder (RBD)
- Hyposmia
- Constipation
- Depression/anxiety
- Implications:
  - Supports PD as a **long preclinical spectrum**
  - Opportunity for early identification and intervention

- Schrag, A., Bohlken, J., Dammertz, L., Teipel, S., Hermann, W., Akmatov, M. K., ... & Holstiege, J. (2023). Widening the spectrum of risk factors, comorbidities, and prodromal features of Parkinson disease. *JAMA neurology*, 80(2), 161-171.

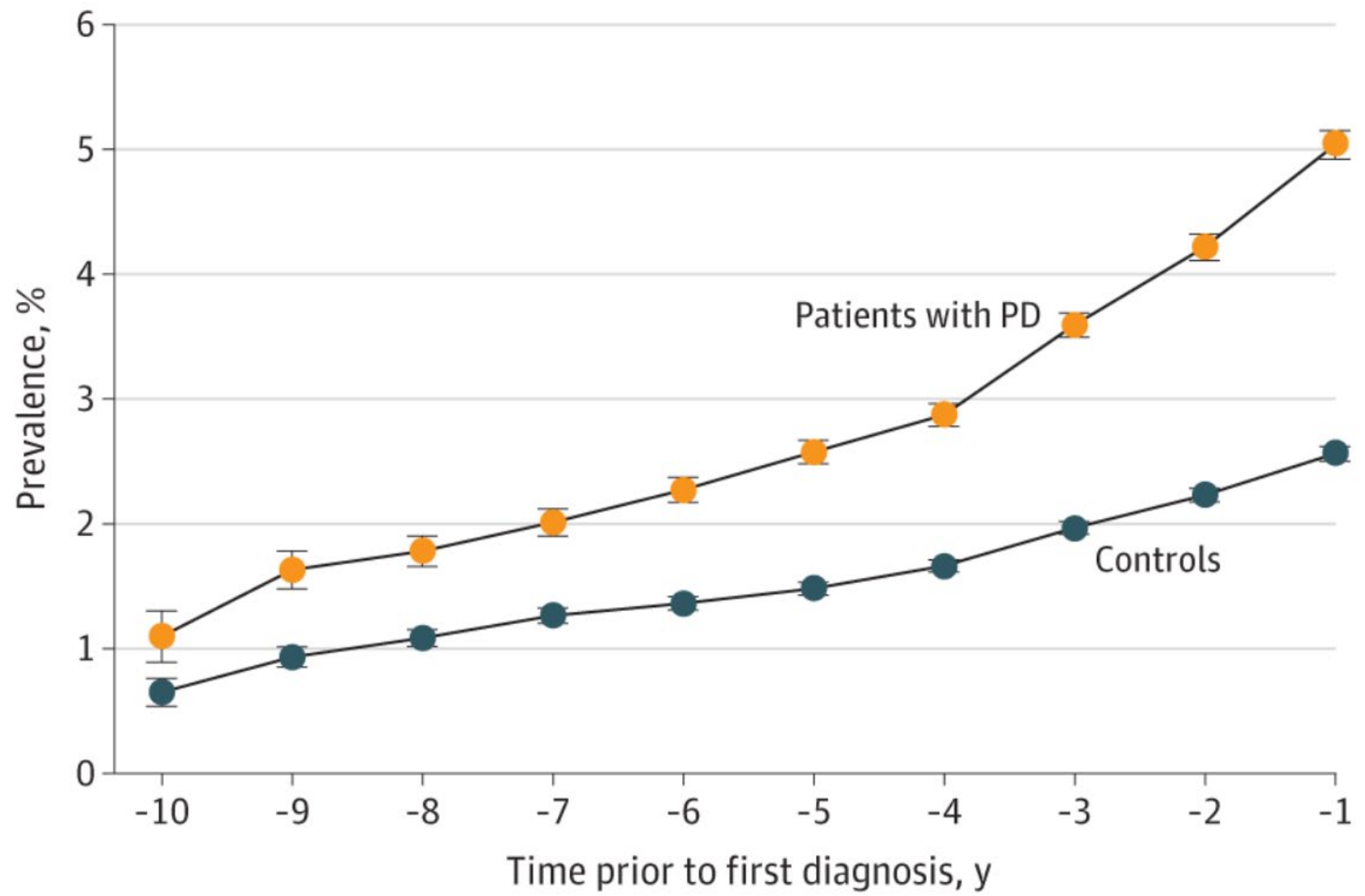
**C** Parasomnia



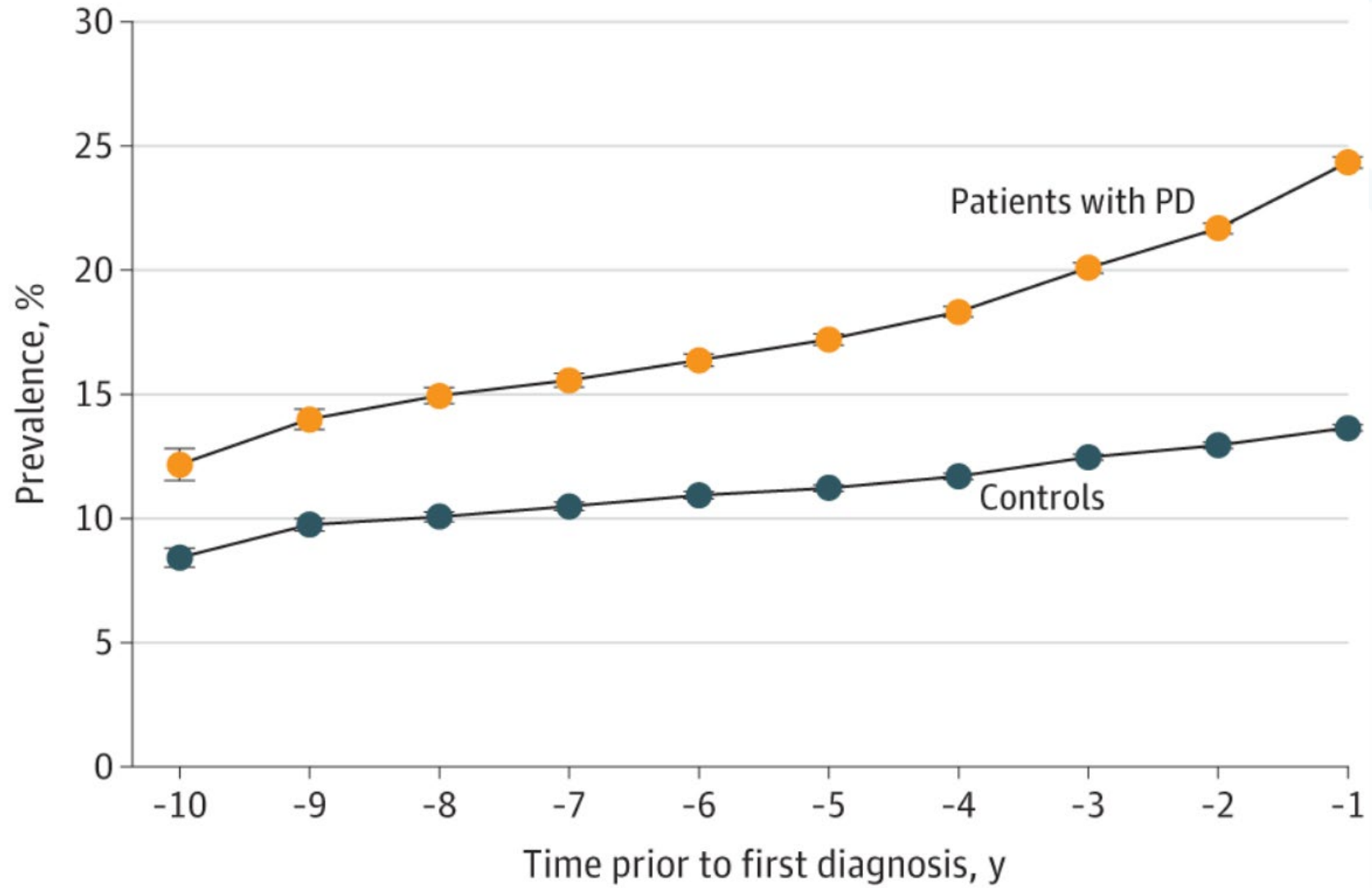
**C** Anosmia



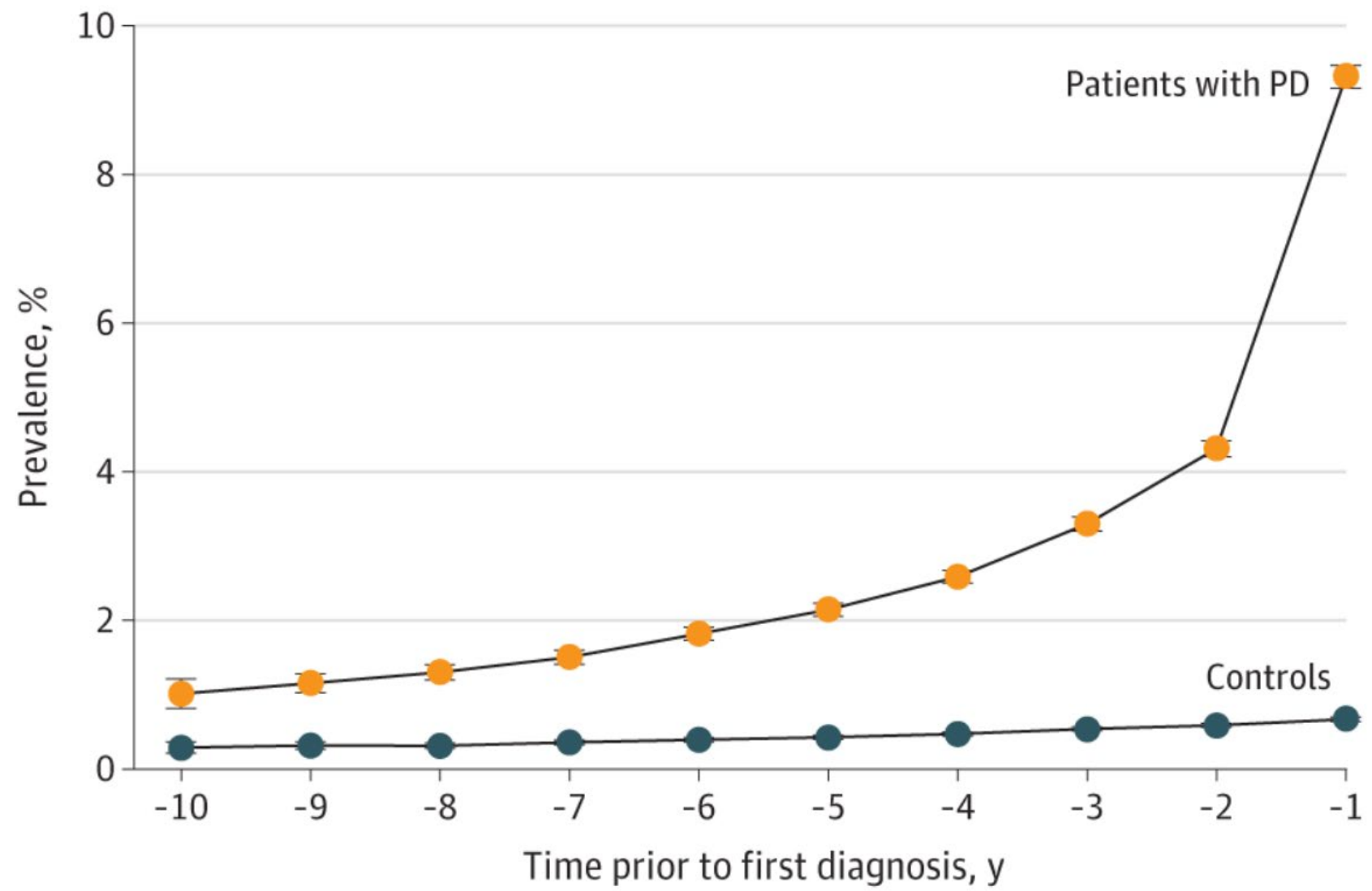
**E** Constipation



**D** Depression



**A** Tremor



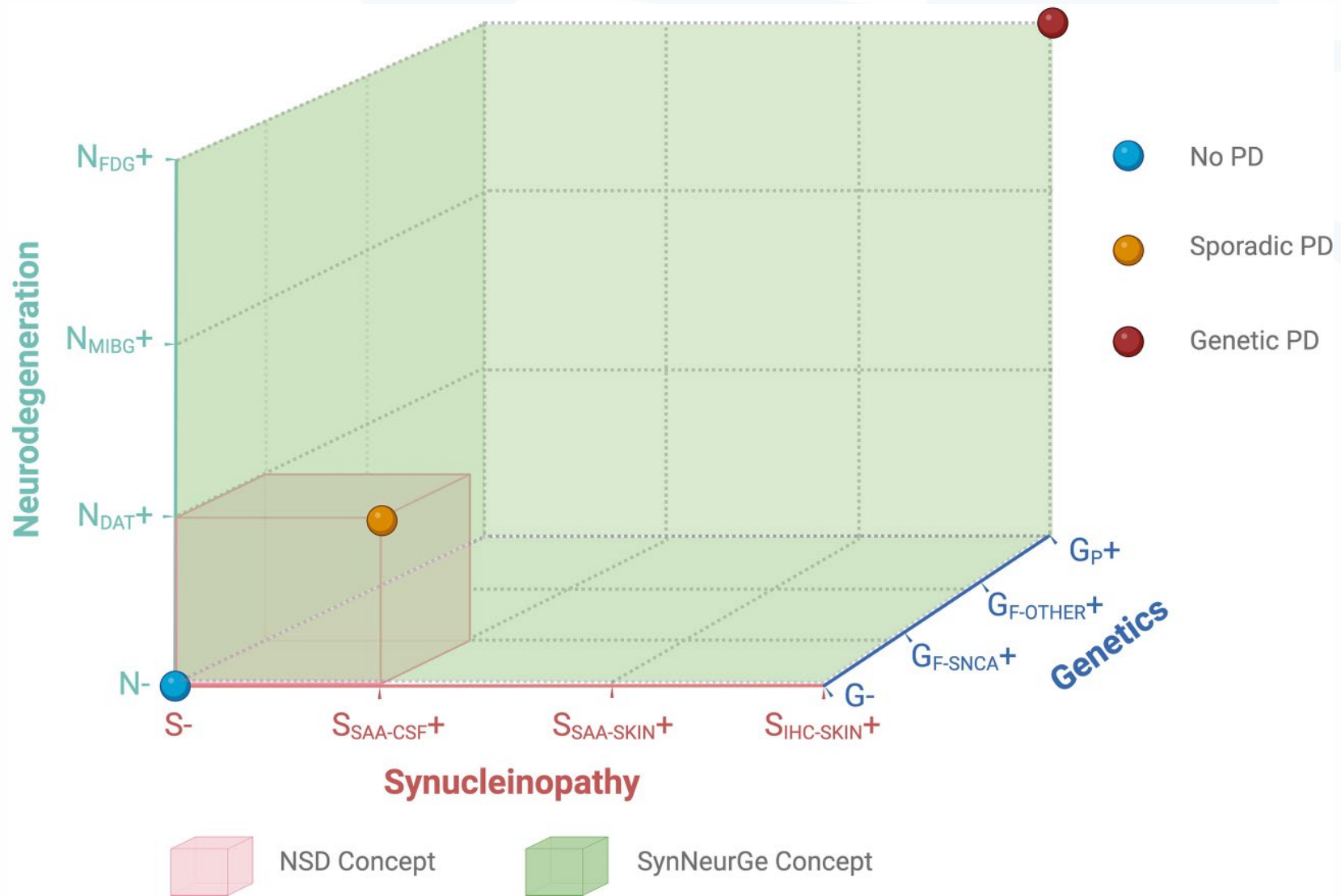
# $\alpha$ -Synucleinopathies

- PD exists within a broader synucleinopathy spectrum:
  - Parkinson's Disease
  - Dementia with Lewy Bodies (DLB)
  - Multiple System Atrophy (MSA)

# Biological definition of PD

- SynNeurGe
  - pathological  $\alpha$ -synuclein in bodily fluids
  - evidence of neurodegeneration
  - specific gene mutations
- NSD
  - $\alpha$ -synuclein aggregates in CSF
  - dopaminergic neurodegeneration using DAT
  - Introduces a more strict staging system

Höglinger, G. U., & Lang, A. E. (2025). SynNeurGe: the road ahead for a biological definition of Parkinson's disease. *Journal of Parkinson's Disease*, 15(5), 931-938.



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

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

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

# Genetics

- Genetic variants influence phenotype:
  - LRRK2: often milder, tremor-dominant
  - GBA: earlier cognitive decline, faster progression
  - PARK genes: early-onset forms
  - SNCA: early-onset forms

# What is a 'spectrum disorder'?

- And why is this important??

A spectrum model may help us explain why symptoms and patient experiences can be vastly different.

# Parkinson's Disease as a Spectrum Disorder

- Motor dominant vs non motor dominant
- Early vs late onset
- Genetic vs idiopathic
- Slowly progressive vs rapidly progressive
- Biological differences

# Implications of Diagnosis of Spectrum Disorder

- May lead to earlier diagnosis
  - Important as we work toward disease modifying treatment
- May help us develop better assessment tools (research implications)
- supports individualized care approach to treating patients

# Challenges

- May make diagnosis more complex (need for more specialists!)
- Limited access to biomarkers
- Clinical trial design more complex

# Future

- Phenotype-based clinical trials
- Disease-modifying therapies
- Earlier intervention in prodromal stages
- Integration of precision medicine

# Conclusion

- PD has marked clinical and biological heterogeneity.
- Spectrum model better reflects the patient experience.
- APPs play critical role in specialized, spectrum-based care.

# Poll

- Do you think that PD is a Spectrum disorder?

# References

- Berg, A., Bech, S., Aasly, J., Farrer, M. J., & Petersen, M. S. (2022). Autonomic dysfunction in Parkinson's disease: Results from the Faroese Parkinson's disease cohort. *Neuroscience Letters*, 785, 136789.
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# Acknowledgements



