

## **Clinical versus biomarker-based diagnosis of neurocognitive disorders**

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There is increasing dynamic to transform the diagnosis of neurodegenerative diseases from syndrome-based to biomarker-based criteria. Advantages of biomarkers as mainstays of diagnoses are their objectiveness and reproducibility, their demonstration of active disease mechanisms guiding therapeutic interventions, and their applicability in preclinical disease stages or clinically variant presentations. Disadvantages of clinical diagnoses based on syndromes are their applicability in later disease stages only, when widespread neurodegeneration has already occurred, and their relationship to anatomical regions or networks rather than to underlying molecular disease mechanisms. Although screening of asymptomatic elders will likely become standard with the expected approvals of disease-modifying therapies, at present, in most instances a clinical syndrome triggers a diagnostic workup, particularly in patients lacking a family history that might have identified a pre-clinical gene mutation-carrier.

The “intersocietal recommendations for the biomarker-based diagnosis of neurocognitive disorders”<sup>1</sup> adopts a reasonable approach to recommend a stratified biomarker-workup in patients depending on their initial clinical manifestation. While being in fundamental agreement with this approach, we believe that some specific recommendations are not supported by currently available evidence.

With regard to the Lewy body spectrum, including dementia with Lewy bodies and Parkinson’s disease, the authors recommend DAT-SPECT to demonstrate nigrostriatal dopaminergic denervation first, and, if negative, MIBG SPECT to demonstrate noradrenergic cardiac denervation. It remains unclear, why disease-related patterns on FDG-PET and alpha-synuclein seed amplification assays are not recommended, the evidence for which is summarized in the recently published SynNeurGe criteria.<sup>3</sup>

With regard to the 4R-tauopathies, including the spectrum of progressive supranuclear palsy (PSP)-associated syndromes and corticobasal syndrome (CBS), the authors propose an FDG-PET and CSF biomarkers for AD-associated A- and T-biomarkers. The diagnostic criteria of the International Parkinson and Movement Disorder Society (MDS) for 4R-tauopathies,<sup>3</sup> including PSP and CBS, do recommend atrophy or hypometabolism predominant in midbrain relative to pons, demonstrated by MRI or FDG-PET, as imaging findings supportive of the diagnosis. However, to date, there is no evidence that would prioritize irradiation-

associated, cost-intensive PET over MRI, as proposed by the “intersocietal recommendations”<sup>1</sup> Furthermore, the MDS criteria also recommend the AT-biomarkers only in clinically diagnosed CBS, not in other PSP-associated syndromes, since only the former is associated with AD-pathology in a relevant percentage of cases.

We would therefore caution against the adoption of selected “intersocietal recommendations”<sup>1</sup> in the light of other recommendations<sup>2-4</sup> with regard to cost, irradiation-exposure, invasiveness, and off-label use, as compared to the expected diagnostic benefit and therapeutic consequences.

### **Contributors**

GUH, ALB, and AEL contributed to the study design, literature search, and writing of this article.

### **Declaration of interests**

Günter U. Höglinger participated in industry-sponsored research projects from Abbvie, Bial, Biogen, Biohaven, Novartis, Sanofi, Takeda, UCB; served as a consultant for Abbvie, Alzprotect, Aprineua, Asceneuron, Bial, Biogen, Biohaven, Kyowa Kirin, Lundbeck, Novartis, Retrotope, Roche, Sanofi, UCB; received honoraria for scientific presentations from Abbvie, Bayer Vital, Bial, Biogen, Bristol Myers Squibb, Kyowa Kirin, Roche, Teva, UCB, Zambon; received publication royalties from Academic Press, Kohlhammer, and Thieme; holds a patent on the Treatment of Synucleinopathies. United States Patent No.: US 10,918,628 B2 / European Patent Patent No.: EP 17 787 904.6-1109 / 3 525 788.

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Anthony E. Lang has served as an advisor for AbbVie, AFFiRis, Alector, Amylyx, Aprinoia, Biogen, BioAdvance, BlueRock, Biovie, BMS, CoA Therapeutics, Denali, Janssen, Jazz, Lilly, Novartis, Paladin, Pharma 2B, PsychoGenetics, Retrophin, Roche, Sun Pharma, and UCB; received honoraria from Sun Pharma, AbbVie and Sunovion; is serving as an expert witness in litigation related to paraquat and Parkinson's disease, received publishing royalties from Elsevier, Saunders, Wiley-Blackwell, Johns Hopkins Press, and Cambridge University Press.

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## References

1. Frisoni GB et al., European intersocietal recommendations for the biomarker-based diagnosis of neurocognitive disorders *Lancet Neurol* 2024;23(3):302-312.
2. Jack CR et al., NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease. *Alzheimers Dement.* 2018;14(4):535-562.
3. Höglinger GU et al., A biological classification of Parkinson's disease: the SynNeurGe research diagnostic criteria. *Lancet Neurol.* 2024 Feb;23(2):191-204.
4. Höglinger GU et al., Clinical diagnosis of progressive supranuclear palsy: The movement disorder society criteria. *Mov Disord.* 2017 Jun;32(6):853-864.