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COMMENTARY

Time to align sensitive cognitive assessment with protein biomarkers in Alzheimer's disease

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In the last decade, Alzheimer's disease research has seen large shifts, particularly regarding diagnostic criteria and the use of protein biomarkers. The Alzheimer's Association (AA) workgroup has recently revised their previous 2018 research criteria (Jack Jr et al., 2018) for diagnosis and staging of Alzheimer's disease to now inform both research and clinical care (Jack Jr et al., 2024a), maintaining a biological definition that primarily relies upon protein biomarkers, such as amyloid and tau levels, to identify the disease even in the absence of cognitive symptoms (e.g. memory and language impairment). In counter-response, the International Working Group (IWG) advocates for an integrative clinical-biological approach, emphasizing that the diagnosis of Alzheimer's disease should not rely solely on protein biomarkers but must also incorporate phenotypic expression such as objective cognitive impairment (Dubois et al., 2021, 2024).

The debate over a biological versus clinical-biological definition of Alzheimer's disease has been ongoing for years but was reignited earlier this year after the release of the revised AA criteria (Jack Jr et al., 2024a). Petersen et al. (Petersen et al., 2024). presented a well-balanced comparison of the overlapping standpoints and differences between the AA and IWG frameworks. Proponents of the biological-only approach have argued that focusing on protein biomarkers, such as amyloid and tau, allows for earlier detection of the disease, providing a window for intervention during the preclinical stage before a significant cognitive decline occurs (Jack Jr et al., 2024b). Jack Jr et al (Jack Jr et al., 2024a) highlight that protein biomarkers offer a more standardized and objectively replicable framework, reducing the variability seen in clinical assessments alone. Critics of the biological framework point out significant limitations and risks. Many researchers caution that a protein biomarker-only approach may lead to overdiagnosis, unnecessary anxiety and stigma for individuals who may never clinically express the underlying disease pathology (Petersen et al., 2024). This perspective reflects concerns about the potential psychological, social and ethical ramifications of labelling asymptomatic individuals as having Alzheimer's disease based purely on protein-biomarker positivity, given the variability in symptom progression and the influence of factors such as cognitive reserve (Glymour et al., 2018; Kiselica et al., 2024).

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While a positive protein biomarker test may justify a diagnosis of a disease, the debate raises the question of whether this diagnosis should be 'Alzheimer's disease', the same label traditionally associated with progressive cognitive decline and underlying neuropathology. Using the same term for asymptomatic individuals with abnormal protein biomarkers and symptomatic patients creates both conceptual and practical dilemmas. The AA framework argues that it seeks to ensure scientific accuracy by distinguishing Alzheimer's pathology from Alzheimer's clinical symptoms. However, this goal could still be achieved when using a different label that indicates protein biomarker-positivity as a distinct disease that is a risk factor for dementia (Villain & Planche, 2024). Effective communication requires precise terminology, in which there is little room for lexical ambiguity when discussing a disease that affects millions of people worldwide, including patients, caregivers, clinicians, researchers and industry professionals. Instead, establishing distinct terminology for protein biomarker-positive, asymptomatic individuals would emphasize the presence of Alzheimer's disease-related pathology without implying the presence of clinical disease—as also proposed by the IWG (Dubois et al., 2024). Changing the traditional concept of Alzheimer's disease, rather than adopting a distinct term for asymptomatic individuals with abnormal protein biomarkers, also sidelines the critical role of cognitive and behavioural assessments. While protein biomarkers serve as valuable indicators of underlying pathology, cognitive and behavioural measures anchor the diagnosis in real-world impacts, ensuring that interventions target what matters most to patients and their families (Tochel et al., 2019).

The debate hinges on whether the absence of cognitive symptoms should preclude a diagnosis of Alzheimer's disease. The revised AA framework is founded on the core principles that Alzheimer's disease is a biological process first detected by abnormal protein biomarkers when an individual is *asymptomatic*; symptoms emerge and progress only after a sufficient pathological burden has been reached, with the entire disease course spanning potentially up to 30 years (Jack Jr et al., 2024b). In the ongoing debate, however, we seem to easily forego what the concept of '(a)symptomatic' denotes in the context of Alzheimer's disease diagnosis. While the field of protein biomarkers has seen remarkable advances, first with neuroimaging and more recently with blood-based techniques, mainstream cognitive instruments continue to rely on standard tests developed decades ago. Such standard cognitive tests include the Mini Mental State Examination (MMSE) from 1975 (Folstein et al., 1975), Montreal Cognitive Assessment (MoCA) from 1995 (Hobson, 2015; Nasreddine et al., 2005), several subtests of the Wechsler Memory Scale—Revised (WMS-R) from 1987 (Wechsler, 1987) and Wechsler Adult Intelligence Scale (WAIS) originally from 1955 (Wechsler, 1955), Rey Auditory Verbal Learning Test (RAVLT) from 1958 (Rey, 1958) (or variations on its concept), and the Boston Naming Test (BNT) from 1983 (Kaplan et al., 1983). The biological-only framework suggests that cognitive symptoms appear much later than the onset of neuropathologic features (Jack Jr et al., 2024b), but what if these symptoms are already present in the early stages of neuropathologic change? Multiple meta-analytic studies have shown subtle amyloid- and tau-related cognitive impairment in cognitively healthy individuals (Baker et al., 2017; Pelgrim et al., 2021). However, these symptoms are often so subtle that standard neuropsychological measures lack the sensitivity to reliably detect this impairment at an individual level or even within smaller samples. Thus, while we know that cognitive symptoms often manifest many years prior to a clinical diagnosis in protein-biomarker-positive individuals, they continue to go unnoticed for years with standard neuropsychological tools, marking these individuals as 'asymptomatic' during this time.

In theory, the preclinical stage is defined by the presence of Alzheimer's disease protein biomarkers in the absence of any clinical symptoms (Dubois et al., 2016; Sperling et al., 2011), while any presence of subtle cognitive impairment would indicate a transition to the prodromal stage, including a status of mild cognitive impairment (Albert et al., 2013; Dubois & Albert, 2004; Petersen et al., 2001). In practice, knowing that cognitive impairment is possible in the preclinical stage makes its definition somewhat flexible; if more sensitive measurement instruments emerge, what is currently designated as 'preclinical' due to the absence of measurable symptoms might be reclassified as 'prodromal' when employing more sensitive tools. What is identified as 'preclinical' today may actually include undetected subtle cognitive impairments, blurring the line between the preclinical and prodromal stages before the presence of clinical dementia. This blurring of lines underscores the need for improved cognitive measures that can detect early changes and refine our staging of the disease.

Although several efforts are underway to develop more sensitive cognitive measures, these innovations have yet to be widely implemented, as evidenced by the majority of coarse cognitive outcome measures used in clinical trials to date (Takeshima et al., 2020). Evaluating treatments based solely on biological endpoints, without demonstrated phenotypic expression, risks prioritizing protein biomarker changes over meaningful improvements in patients' cognitive and functional well-being. Thus, protein biomarkers should not be viewed in isolation, but as previously discussed, standard cognitive tests are also not sufficiently equipped to assess individual risk for dementia in the earliest stages of the disease. Bridging this gap is crucial for bringing the AA and IWG frameworks closer together. Both sides agree that Alzheimer's disease should be treated early and both sides agree that Alzheimer's disease protein biomarkers are important in establishing the diagnosis; their primary disagreement lies in the role of cognitive impairment in diagnosis. Improved sensitivity of cognitive measures could help reconcile these perspectives by recognizing both protein biomarker and cognitive abnormalities in the earliest stages, leading to better participant selection for clinical trials in research and avoiding fear, stigma and overtreatment in clinical practice. The digital era offers a wealth of opportunities to enhance cognitive assessments and improve early detection of cognitive impairment in at-risk individuals with relatively low patient burden. These advancements include remote assessments that increase accessibility, frequent longitudinal monitoring to track subtle cognitive changes over time, passive monitoring through wearable devices or smartphone usage patterns and advanced speech analysis techniques that detect linguistic markers of cognitive decline. Additionally, digital tools can leverage machine learning techniques to personalize assessments, identify intra-individual changes and integrate multimodal data (e.g., behavioural patterns, voice recordings and reaction times) for more comprehensive and sensitive evaluations. By combining these advancements with protein biomarker data, the field can move closer to a balanced, integrated approach that respects both biological and clinical dimensions of Alzheimer's disease in its earliest stages.

In sum, despite the framework revisions and responses by both the AA and IWG advocates over the past several years, the core arguments remain unchanged and the field does not appear to be converging on a unified solution. The debate has cast protein biomarkers as the main character, with extensive development of their sensitivity, specificity and diagnostic role in recent years, while cognition remains a sidelined supporting character, whose role has seen little advancement across decades and now risks being written out entirely. It is time to bring cognition into the spotlight as a main character alongside protein biomarkers. Cognitive assessment deserves the same focused investment and innovative development that protein biomarkers have undergone in recent years to improve the quality and sensitivity of how cognitive symptoms are assessed. Improving the sensitivity of cognitive tools could help bridge the divide between biological and clinical-biological perspectives on Alzheimer's disease by aligning the detection of clinical symptoms more closely with the presence of pathophysiological changes in individuals truly at risk for dementia. This alignment would allow cognitive tools and protein biomarkers to advance together, working in synergy to foster a more unified and effective framework for diagnosing and understanding Alzheimer's disease in research and clinical settings.

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Jet M. J. Vonk: Conceptualization; writing – original draft; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

Jet M. J. Vonk reports no conflicts of interest.

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