The Journal of Prevention of Alzheimer's Disease 13 (2026) 100584

Contents lists available at ScienceDirect

The Journal of Prevention of Alzheimer's Disease

journal homepage: www.elsevier.com/locate/tjpad

Editorial

Beyond amyloid positivity: Biological heterogeneity in the real-world use of lecanemab

ARTICLE INFO

Keywords:
Amyloid
Anti-amyloid
ARIA
Real-world evidence
Alzheimer's disease

With the approval of lecanemab and donanemab, disease-modifying therapy for Alzheimer's disease (AD) has moved from concept to clinic. Yet, as these agents transition from tightly controlled phase 3 trials [1,2] to heterogeneous real-world populations, a familiar tension has emerged: trial-defined eligibility hinges on amyloid positivity, while clinical experience reveals that amyloid positivity alone is not synonymous with a uniform disease state. In this context, the study by Kurihara and colleagues [3], offers a timely, rigorous, and clinically grounded exploration of biological heterogeneity among patients treated with lecanemab in routine practice.

Using the recently revised Alzheimer's Association criteria [4] and its expanded ATNIVS biomarker framework, encompassing amyloid (A), tau (T1 and T2), neurodegeneration (N), inflammation (I), vascular pathology (V), and α-synuclein (S), the authors describe a remarkably diverse biological landscape within a cohort that would conventionally be labeled "early AD." Their findings carry important implications for diagnosis, prognosis, risk stratification, and shared decision-making in the era of anti-amyloid therapy.

In clinical practice, confirmation of cerebral amyloid pathology has appropriately become the essential biological prerequisite for anti-amyloid therapy, reflecting its central role in AD pathogenesis. However, as demonstrated by Kurihara et al., amyloid positivity does not define a biologically homogeneous population. Notably, 21% of treated individuals exhibited only regional amyloid PET positivity rather than the diffuse cortical involvement typically associated with symptomatic AD. This subgroup was older, more often in milder clinical stages, and had substantially lower centiloid burden.

These observations underscore an important refinement of the diagnostic framework: while amyloid remains a necessary driver of disease biology and a rational therapeutic target, it may not always be the sole determinant of clinical expression. The presence of cognitive impairment in individuals with limited or focal amyloid deposition suggests that comorbid pathologies frequently shape the clinical trajectory, even in patients who meet biomarker criteria for AD. Consistent with this, the association between regional amyloid positivity and higher Fazekas scores implicates cerebrovascular disease as a meaningful contributor to symptom burden in this subgroup.

From a practical perspective, these data highlight the importance of contextualizing amyloid PET results, particularly when centiloid values are near diagnostic thresholds or when uptake is regionally restricted. While regulatory and payor frameworks currently prioritize binary amyloid positivity, clinicians are increasingly confronted with intermediate or ambiguous biological states. The present study provides concrete evidence that such states are not rare in real-world practice.

The authors' careful examination of CSF Aβ42/40 ratios adds further texture to this discussion. Although all treated patients met the requirement for amyloid positivity, a small subset exhibited values within the "likely-positive" range. Notably, this group showed greater variability in downstream biomarkers, including plasma NfL and tau PET stage.

While underpowered for definitive conclusions, these observations underscore an important principle: biomarker thresholds are probabilistic rather than absolute. Patients near cut points may represent transitional biological states or mixed etiologies, and their response to anti-amyloid therapy, both in terms of efficacy and safety, remains unknown.

Tau pathology remains the strongest biological correlate of clinical impairment in AD [5], yet tau PET has been notably absent from clinical decision-making due to limited availability and coverage. Kurihara et al. leverage a valuable subset of tau PET data using the second-generation tracer 18F-MK6240 to illustrate just how variable tau burden can be among patients receiving lecanemab.

The observed range, from tau PET Braak stage 0 to VI, reinforces that patients at similar clinical stages can occupy vastly different positions along the tau trajectory. Particularly noteworthy is the presence of patients with minimal tau burden but clear clinical impairment, as well as those with advanced tau pathology who remain at the MCI stage. These discordances echo growing evidence for resilience, cognitive reserve, and the modifying effects of co-pathologies.

https://doi.org/10.1016/j.tjpad.2026.100584
Received 20 April 2026; Accepted 21 April 2026
Available online 7 May 2026
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As anti-amyloid therapies are increasingly viewed as upstream interventions, understanding concurrent tau burden may become central to realistic expectation setting. Patients with high tau burden may experience less clinical benefit despite robust amyloid removal, while those with minimal tau pathology may represent optimal candidates for long-term disease modification. Although tau PET is not currently required for clinical use, studies like this one make a compelling case for its future integration, whether through PET imaging or validated blood-based proxies.

Beyond amyloid and tau, the study's analysis of neurodegeneration, inflammation, and vascular pathology illustrates the multidimensional nature of real-world AD. Plasma NfL and GFAP spanned wide ranges, with heterogeneous relationships to amyloid burden, tau stage, and MRI findings. White matter hyperintensities, scored systematically using the Fazekas scale, further revealed variable cerebrovascular contributions, even among patients deemed suitable for lecanemab under national guidelines.

These findings matter because N, I, and V biomarkers are likely to influence both clinical trajectories and treatment risk. Neurodegeneration and vascular disease may accelerate decline independent of amyloid, while inflammation and small vessel disease may increase susceptibility to amyloid-related imaging abnormalities (ARIA). Yet these dimensions are seldom incorporated into treatment algorithms in a structured way.

Kurihara et al. do not argue that such biomarkers should exclude patients from therapy. Rather, their data supports a more sophisticated approach: using ATNIV profiles to inform prognosis, risk communication, and safety monitoring intensity.

Perhaps one of the most clinically provocative aspects of the study is the inclusion of α-synuclein seed amplification assays. The finding that approximately one quarter of tested patients were α-syn SAA positive, despite minimal clinical features of Lewy body disease, underscores just how frequently synuclein co-pathology may accompany biologically defined AD. Emerging longitudinal data suggest that α-synuclein pathology may accelerate cognitive decline and modify symptom profiles. Whether it also influences response to anti-amyloid therapy or risk of adverse events remains unknown. By demonstrating the feasibility of incorporating α-syn SAA into real-world biomarker panels, this study opens the door to a more integrated view of neurodegenerative disease biology, one that moves use towards real-world personalized medicine.

ATNIV profiles can help clinicians explain why two patients who "both have early AD" may have different expected trajectories, different tolerances for risk, and different therapeutic priorities. They also remind us that anti-amyloid therapy does not occur in a biological vacuum. Its effects unfold against the backdrop of tau pathology, neurodegeneration, vascular injury, and co-proteinopathies. The present report focuses on baseline characteristics, but its true significance may lie in what comes next. Longitudinal studies linking ATNIV heterogeneity to clinical outcomes, ARIA risk, functional decline, and treatment persistence are urgently needed. The work by Kurihara et al. provides a strong conceptual and methodological foundation.

More broadly, this study exemplifies the evolution of AD therapeutics from binary eligibility criteria toward biologically informed precision medicine. As additional disease-modifying therapies emerge , targeting amyloid, tau, inflammation, or synuclein, understanding who has which biology, and when, will become central to optimizing patient care.

CRediT authorship contribution statement

Michael S. Rafii: Writing – original draft.

Disclosures

Contracts: Eisai and Eli Lilly; Consultant to AC Immune and Ionis; Data Safety Monitoring Board/Scientific Advisory Board for Aerska, Alzheon, Alnylam, Biohaven, Embic, Otsuka, Positrigo, Recall Therapeutics, Sumitomo Pharmaceuticals.

There was no use of generative AI and AI-assisted technologies in scientific writing or in figures, images and artwork.

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