Letters to the Editor: Editors' Choice

Author Response: The Great Debate in Diagnosing Alzheimer Disease: More Than Just a β Test

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In their response to our recent editorial[1] addressing their paper,[2] Bieger et al. proposed that the Alzheimer Association (AA) 2024 framework may improve prognostic accuracy compared with the National Institute on Aging-AA 2018 criteria. This assertion may hold true when considering the average prognosis of the 2024 broad β-amyloid–anchored Alzheimer disease (AD) category.[3] By contrast, in their paper, Bieger et al.[2] considered the now-defunct Alzheimer's pathologic change category separately.

We concur with Bieger et al. that biomarker thresholds and combinations are crucial for prognosis. Individuals with positive amyloid or soluble phosphoTau biomarkers exhibit highly diverse prognoses based on the presence of symptoms, Tau PET neocortical signal, or high amyloid load in conjunction with APOE4.[4]

We also appreciate the emphasis Bieger et al.[2] placed on using future symptom risk as a key anchor in validating AD criteria, supporting an emerging consensus. It is crucial to prevent AD, a debilitating disease and major public health issue, from being redefined into a spectrum of heterogeneous outcomes, including predominantly benign clinical conditions.[3,5] Further agreement is essential for biologic conditions with low symptom risk, as exemplified by the former "Alzheimer's pathologic change" category. A separate nosologic category may be warranted, similar to approaches in other medical fields.[5] Encouraging updates to this criteria validation study and fostering debates will be crucial in reaching a consensus.

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2. Bieger A, Brum WS, Borelli WV, et al. Influence of different diagnostic criteria on Alzheimer disease clinical research. *Neurology*. 2024;103(5):e209753. doi:10.1212/WNL.0000000000209753
3. Moscoso A, Villain N. 2024 AA criteria for Alzheimer's disease diagnosis: mainly anchored at Aβ not tau. *Alzheimers Dement*. 2024;20(12):9079-9081. doi:10.1002/alz.14340
4. Ossenkoppele R, Pichet Binette A, Groot C, et al. Amyloid and tau PET-positive cognitively unimpaired individuals are at high risk for future cognitive decline. *Nat Med*. 2022;28(11):2381-2387. doi:10.1038/s41591-022-02049-x
5. Villain N, Planche V. Disentangling clinical and biological trajectories of neurodegenerative diseases. *Nat Rev Neurol*. 2024;20(12):693-694. doi:10.1038/s41582-024-01004-3

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