Defining Alzheimer's Disease from a Pure Biological Point of View: The 2024 Revised Criteria by the Alzheimer's Association Workgroup

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Key highlights:

- The 2024 criteria revised the 2018 NIA-AA research framework, and a new AT_1T_2NIV biomarker schema is proposed.
  A single abnormal Core 1 biomarker (the A and T_1 biomarkers) is sufficient to diagnose Alzheimer's disease, even in cognitively unimpaired individuals.
- Blood-based markers are introduced and emphasized in this revision.
  Whether current science is strong enough to support a purely biological definition of AD *in vivo* remains controversial.

The Alzheimer's Association Workgroup formerly published revised criteria for the diagnosis and staging of Alzheimer's disease (AD) early this year [1], after addressing public concerns and comments on the draft released in 2023. Based on the 2018 National Institute of Aging and Alzheimer's Association (NIA-AA) research framework [2], the revised criteria remain biomarker-based and require the presence of core 1 biomarkers (see later) as the necessary and sufficient prerequisite to diagnose AD. Although the draft was proposed as clinical criteria, the final version clarifies its role as a "bridge between research and clinical care". The workgroup for this revision was convened by the Alzheimer's Association, in contrast, the National Institute of Aging and the Alzheimer's Association co-convened workgroups responsible for the 2011 NIA-AA criteria on the preclinical, mild cognitive impairment, and dementia phases of AD and the 2018 NIA-AA research framework.

What's new in the 2024 revised criteria

Similar to the 2018 NIA-AA research framework, AD is defined by the biological process rather than clinical syndromes. Since intermediate-level cerebral Aβ plaques and tau tangles are detected *in vivo* by positron emission tomography (PET), AD can be diagnosed before symptom onset and without neuropathologic examination. In the 2024 revised criteria, the biomarker categorization and profile used to diagnose and stage AD were modified. Several new CSF and blood-based tau measures were added to Core markers. A biological staging system was proposed, and efforts were made to integrate biological staging and clinical staging.

Biomarkers were grouped and classified by the AT(N) system (β amyloid deposition, pathologic tau, and neurodegeneration) in the 2018 research framework. While in the current revised criteria, a full biomarker profile is AT_1T_2NISV (A, Aβproteinopathy; T_1, phosphorylated and secreted AD tau; T_2, AD tau proteinopathy; N, injury, dysfunction or degradation of neuropil; I, inflammation; V, vascular

brain injury; S, α-synuclein), where A, T_1, and T_2 are Core biomarkers, N and I are biomarkers of non-specific process involved in AD pathophysiology, and S and V are biomarkers of non-AD copathology.

Recent evidence suggested different tau biomarkers have different temporal relationships with early-changing amyloid PET and later-changing tau PET, accordingly the T category was split into T_1 and T_2 subcategories. The T_1 biomarkers (secreted phosphorylated mid-region tau fragments in CSF or plasma) appear earlier at about the same time as amyloid PET. The T_2 biomarkers are other tau fragments (microtubule-binding region-tau243, other phosphorylated tau forms, non-phosphorylated mid-region tau fragments) which become abnormal later and are correlated better with tau PET. Although most CSF and none of the blood-based tau markers have received regulatory approval for clinical use, they are included under the premise of strong scientific evidence (at least 90% accuracy estimates of the PET or CSF standards) and potential future approval.

The A (fluid Aβ42 and amyloid PET), T_1, and hybrid ratios biomarkers are the Core 1 biomarkers, and a single abnormal Core 1 biomarker is sufficient for diagnosing AD. As AD is diagnosed, the biological staging can be made with an uptake pattern on tau PET. Stage A (initial) is characterized by a lack of tau PET uptake ($A+T_2-$), Stage B (early) by an uptake restricted to the medial temporal regions ($A+T_{2MTL}+$), Stage C (intermediate) by a moderate uptake in the neocortical region of interest ($A+T_{2MOD}+$), and Stage C (advanced) by a high neocortical update ($A+T_{2HIGH}+$). The six-stage clinical staging schema (Stage 1-6) in the 2018 research framework [2] was adopted largely unchanged in the revised criteria, and a new Stage 0 was added to denote asymptomatic and biomarker-negative individuals with genetically determined AD. The symptomatic and functional presentation of AD is modified by non-specific processes involving AD pathophysiology, co-pathologies, reserve, and resistance. AD biomarkers should be examined and interpreted in the context of adequate clinical assessment. An integration scheme of the numeric clinical staging and alphabetical biological staging (e.g., stage 3C) was proposed in the revised criteria to address their relatedness and independence.

Fluid neurofilament light chain (Nfl) is a marker of large-caliber axonal injury and was added to the N biomarker category in this revision. Fluid total tau was removed from N because some evidence also supported their role as a T biomarker. The new inflammatory/immune process biomarkers (I) contain two subcategories: astrocyte reactivity (fluid glial fibrillary acidic protein, GFAP) and microglial reactivity (CSF TREM2). Biomarkers of the two non-AD copathology categories are neuroimage measures for V category and alpha-synuclein seed amplification assay for S category. The AT_1T_2NISV scheme includes the most updated and validated biomarkers for diagnosis, staging, risk stratification, prognosis, and treatment effect prediction.

Controversies around the 2024 revised criteria

Many concerns arising upon the release of the 2023 draft were mentioned and addressed in the revised criteria, for example, the distinction between clinical and research application, the place of *ApoE* genetic risk factor, and criteria used to assess the performance of blood-based markers. Blood-based markers were emphasized in the revised criteria, although most have not been approved for clinical use. They are more affordable and scalable than PET and can help reduce medical inequalities when biomarkers are required to diagnose AD. However, appropriate cutoff thresholds or range of thresholds, the need for studies in populations of different ethnic and racial backgrounds, and marker specificity in the presence of comorbidities (e.g., chronic kidney disease) remain to be solved.

The NIA-AA 2018 research framework has been criticized for relying only on biomarkers for diagnosis, disregarding AD clinical phenotypes. Biomarker profiles A+T-(N)- and A+T+(N)- were assigned "Alzheimer's pathologic change" and AD, respectively. The 2024 revised criteria went further and made either A+ or T_1+ sufficient for diagnosing AD even in cognitively unimpaired individuals. The main controversy is that biomarkers alone cannot reliably predict the progression from unimpaired cognition to AD phenotypes. For example, one study found A+T+ rather than A+T- cognitively unimpaired individuals at high risk for further development of mild cognitive impairment or all-cause dementia in 3-5 years [3]. The International Working Group suggested biomarker-positive cognitively

unimpaired individuals are regarded as at risk for progression to AD, and clinical phenotypes and biomarker evidence are required for diagnosing AD. Careful clinical assessment and expertise are needed to disentangle the relationship between phenotypes and AD biomarkers, in the presence of atypicality and copathologies [4]. Since no disease-targeting intervention was indicated for cognitively unimpaired individuals, the 2024 revised criteria objected to diagnostic testing in cognitively unimpaired individuals, unless for research purposes. However, defining AD merely as the presence of Core 1 biomarkers may influence how people see the disease and the potential of seeking unnecessary workups which may bring about emotional distress in response to a biomarker positivity. Whether there will be thereby additional requirements from insurance companies and employers is not known.

Reference

[1] Jack CR, Jr., Andrews JS, Beach TG, Buracchio T, Dunn B, Graf A, et al. Revised criteria for diagnosis and staging of Alzheimer's disease: Alzheimer's Association Workgroup. Alzheimers Dement 2024. https://doi.org/10.1002/alz.13859.

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