

Position Statement Related to the Proposed NIA-AA Revised Clinical Guidelines for Alzheimer's Disease

The National Institute on Aging and the Alzheimer's Association (NIA-AA) convened workgroups that published [diagnostic guidelines in 2011](#) across the Alzheimer's disease (AD) continuum (preclinical due to AD, mild cognitive impairment due to AD, dementia due to AD) and developed a research framework in 2018 for moving forward the hypothesis of AD as a biological disease. Through these efforts several core principles emerged, including:

- Alzheimer's disease should be defined biologically, not based only on a clinical syndrome(s).
- Alzheimer's disease is a continuum that begins with the appearance of brain pathology in asymptomatic individuals and progresses through stages of increasing pathologic burden eventually leading to the appearance and progression of clinical symptoms.
- Alzheimer's disease is diagnosed *in vivo* by abnormalities on core biomarkers.

In early 2022, the Alzheimer's Association convened a steering committee to lead the revision of the NIA-AA framework. This workgroup presented its recommendations for the NIA-AA revised guidelines for clinical diagnosis of Alzheimer's disease at the 2023 AAIC Conference in Amsterdam, the Netherlands, and requested scientific input and review of the [draft manuscript](#) prior to publication. Defining neurodegenerative diseases biologically, rather than based on syndromic presentation, has become a unifying concept common to all neurodegenerative diseases, not just AD, and the proposed NIA-AA Revised Clinical Guidelines are consistent with this overarching theme.

The rationale for revising the 2018 clinical guidelines is based on three factors. First, no disease targeted therapies had received regulatory approval by 2018, but since then, several have been approved for treating early Alzheimer's disease. In response, the proposed revised guidelines have progressed from a framework for research to criteria for diagnosis and staging that are intended for clinical use, as well as research. Second, validated biomarkers in 2018 were based on either CSF assays or PET imaging. Since then, plasma-based biomarkers with excellent diagnostic performance have been developed and clinically validated. The proposed revised clinical guidelines have incorporated plasma biomarkers into updated criteria for biomarker categorization, disease diagnosis, and staging. Third, research studies have demonstrated that imaging and fluid biomarkers within a category are not equivalent for many use cases. In the 2023 proposed guidelines the working group updated biomarker classification criteria to accommodate nonequivalence between fluid and imaging biomarkers within a category.

Given this progress toward more accessible diagnostic criteria, the NTG appreciates the work of the NIA-AA working group and lauds its contribution to improving the efficiency and accuracy of diagnosis and staging of Alzheimer's disease. To this end, we offer our support to formalizing the clinical standards for determining Alzheimer's disease diagnosis using plasma biomarkers and support further investments in research in a range of biomarkers for other forms of dementia in the adult

population. We concur with the specific recognition on page 22, line 645 ff. (5.2 “Stage 0 and genetics”) of the contribution of genetics inherent in Trisomy 21, Down syndrome, to the eventual presentation of brain amyloid accumulation and expression of Alzheimer’s disease, and we laud the working group for recognizing this special situation and for providing a clinical basis for pre-symptomatic Down syndrome associated Alzheimer’s disease.

We also laud the NIA’s investment in DS-AD biomarkers research. We recommend extending this investment to determining the nature of Alzheimer’s disease biomarkers in the adult population with lifelong intellectual disabilities. Specifically, we also recommend research to determine the applicability and effectiveness of biomarker findings noted in the proposed clinical guidelines relevant to diagnosing Alzheimer’s disease in adults with intellectual disabilities other than Down syndrome. Also, such biomarker research should include other genetic syndromes associated with intellectual disability that may offer particular risk for Alzheimer’s disease or other diseases associated with dementia. We further recommend, if biomarker parameters vary with respect to Down syndrome, that the guidelines note biomarker parameters that may be idiosyncratic to Down syndrome. We also recommend that the guidelines provide clinical equivalencies to staging factors and functioning for adults with intellectual disability.

Finally, we recommend adding language to Item (9), page 27, line 800 ff., “Diversity and need for more representative cohorts,” to include adults with various lifelong neuroatypical conditions, including intellectual disabilities, in observational studies and clinical trials. Treatment studies, considering the contribution of social determinants of health, also should include diversity – reflecting cognitive impairments associated with neuroatypical conditions.

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KEY RECOMMENDATIONS

- Extend investment in research to determine the nature of Alzheimer’s disease biomarkers in the adult population with lifelong intellectual disabilities
- Determine the applicability and effectiveness of biomarker findings noted in the proposed clinical guidelines relevant to diagnosing Alzheimer’s disease in adults with intellectual disabilities other than Down syndrome
- Expand biomarker research to include other genetic syndromes associated with intellectual disability that may offer particular risk for Alzheimer’s disease or other diseases associated with dementia
- Incorporate into the guidelines biomarker parameters that may be idiosyncratic to Down syndrome
- Incorporate into the guidelines clinical equivalencies to staging factors and functioning for adults with intellectual disability
- Include adults with various lifelong neuroatypical conditions, including intellectual disabilities, in observational studies and clinical trials related to dementia