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American Geriatrics Society Response – Revised Criteria for Diagnosis and Staging of Alzheimer's Disease: Alzheimer's Association Workgroup
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The American Geriatrics Society (AGS) submitted these comments on the 3rd draft of the Alzheimer's Association document, Revised Criteria for Diagnosis and Staging of Alzheimer's Disease: Alzheimer's Association Workgroup, an update of the 2018 NIA-AA Revised Clinical Guidelines for Alzheimer's.

AGS Response

The AGS appreciates that the Alzheimer's Association (AA) Workgroup continues to engage with and incorporate recommendations from the scientific and clinical communities, including our prior comments, as it works on the Revised Criteria for Diagnosis and Staging of Alzheimer's Disease: Alzheimer's Association Workgroup. Given that practitioners, patients, and society have not been sufficiently prepared for a shift in Alzheimer's disease (AD) diagnosis, and there is no current evidence to support use of the revised criteria in routine clinical care, AGS remains concerned that this proposed expansion will place many older and multimorbid people at risk of overdiagnosis, which in turn could lead to initiation of treatments with as yet unproven clinical benefit, particularly in an asymptomatic population, and high potential for harm.

In light of the heavy toll of AD on patients, caregivers, and their families, we recommend that the AA Workgroup carefully reconsider whether the available evidence warrants moving from a research framework to the proposed use of the revised criteria to inform clinical care, including the proposed shift to use biomarkers to diagnose AD. Below, we offer our observations and recommendations that reflect the most relevant and appropriate considerations for older patients living with AD.

General Comments

Asymptomatic Individuals

The AGS position is that the framework proposes a clinical diagnosis of AD in biomarker-positive asymptomatic individuals with insufficient attention to the potential impact on their personal identity or social and fiscal consequences. Given the heterogeneity in cognitive trajectory associated with biomarker positivity, we recommend considering how best to avoid assigning clinical diagnosis of AD to biomarker-positive, asymptomatic individuals with normal cognition at this time. Many key stakeholders (i.e., insurers, lay public, non-specialist medical community) will not be aware of this change in classification and therefore may misinterpret the meaning of newly applied diagnoses of AD in asymptomatic individuals. The AA Workgroup should also address the potential impact of a change in diagnostic standards on the coding of dementia diagnoses in medical records, and on the willingness of non-specialist clinicians to enter any cognitive diagnosis in a patient's chart. A helpful concept might be to create a medically codable designator for 'elevated risk state' to facilitate clinical tracking over time. Having stated this, the reality is that many biomarker-positive individuals never develop cognitive impairment, (DOI:10.1016/j.jalz.2018.03.005; DOI:10.1001/jamaneurol.2018.0629; DOI:10.1001/jamaneurol.2021.5216; DOI:10.1001/jamaneurol.2023.2338) and most people diagnosed with dementia will die *with*, not *of*, dementia. Therefore, conveying a diagnosis of AD to asymptomatic,

biomarker-positive individuals who will never go on to manifest dementia symptoms only exposes them to harms with no potential for benefit.

AGS encourages the AA Workgroup to include a discussion about the risks of labeling someone as having AD if cognitively normal as well as the risk of diagnosing 40-50 million individuals with AD who test positive for amyloid which is the potential result of the workgroup adhering to the current version of the criteria (DOI:10.1016/j.jalz.2017.10.009). At this juncture, a cognitively normal 50-year-old would have a 1 in 10 chance of testing positive for amyloid (DOI:10.1001/jama.2015.4668) and then carry an AD diagnosis in their health records. Accordingly, we contend that biomarker evidence of AD in asymptomatic individuals does not define an obligatory AD clinical stage, but rather may identify individuals as being at elevated risk to develop AD.

As currently drafted, the proposed criteria are inconsistent as to where the AA stands on the matter of whether asymptomatic individuals should be tested. Early in the document (lines 143-144), the AA Workgroup notes that "Core 1 biomarkers are useful in identifying the presence of AD in both symptomatic and asymptomatic people." Later on (Lines 337-338), the AA Workgroup emphasizes that "in the absence of approved interventions in asymptomatic individuals, we do not advocate routine diagnostic testing in this population currently… at present we do not see how results of AD diagnostic testing in asymptomatic individuals would produce medically actionable information." This inconsistent position is present throughout the document, and we encourage the AA Workgroup to be consistent in its position to not advocate routine testing in asymptomatic individuals. It is critical that the AA itself ensure this clarity given the advent of direct-to-consumer testing kits in the marketplace and the significant conflicts of interest on the AA Workgroup.

Expansion of Framework to Inform Clinical Care

We reiterate our position, submitted in response to the previous version of the draft criteria, that it is premature to expand the criteria to inform a standard of clinical diagnosis and care (lines 38-39). In this revision, the AA Workgroup continues to propose an expansion of 2018 framework into clinical care while noting that the criteria is not intended as a clinical practice guideline (lines 38-39). Yet, the AA Workgroup retained language that emphasizes the update having "a major new direction" which "is to expand the 2018 framework from a research-only focus to one that provides diagnostic and staging criteria to inform both research and clinical care" (lines 63-65). The benefits and harms of broadly adopting biomarker criteria for clinical staging and care are far from supported by scientific evidence or consensus. At most, biomarkers might be included in a panel of patient assessments that would then be subjected to rigorous study and critical analysis. Further, stating that something is not a clinical guideline does not obviate the need to document how evidence was rated and the process for resolving conflicts of interest.

While AGS understands that defining AD as a biological construct has advantages for research, the current evidence base is underdeveloped to support clinical utility. We recognize that expert opinion may vary as to the prognostic meaning *for individuals* of having high amyloid levels in their brain or AD biomarkers in blood. We also appreciate the importance of identifying biological disease when pathology-specific treatments are available to reduce human suffering. However, we assert that there have not been sufficiently large and representative cohorts of asymptomatic people across a wide age range who have undergone positron emission tomography (PET) or lumbar puncture (LP) and then been followed to death to know the true population prevalence and natural course of asymptomatic AD biomarker positivity. AGS believes answering this question is one among several critically important steps that must occur before the framework can be validly applied to clinical care.

We encourage AA to step back from recommending such a transition at this time due to potential for harm. There may be large numbers of people who harbor Core 1 biomarkers but will never experience associated symptoms. Encouraging providers to detect these biomarkers and assign a diagnosis when patients are asymptomatic distracts from the broader aim of ensuring high quality health care for individuals who already have cognitive impairment or dementia. Moreover, while emerging treatments aim to address the underlying pathobiology of AD, it remains unclear whether they reduce progression of AD outside of highly selected clinical trial settings with restricted and unrepresentative participant samples, and if the potential benefits outweigh potential harms.

Diagnosis of AD by Biomarkers

AGS is concerned about the rationale of making Core 1 biomarkers the basis for clinical diagnosis or labeling all people with amyloid biomarkers as "having AD." Such action ignores decades of social science research on the often-adverse effects of labeling, including promotion of stigma, and begs the question as to what purposes biomarker-based diagnosis might serve in patient care. Current evidence supports use in clinical practice only as part of the evaluation of individuals who may otherwise be candidates for novel anti-amyloid therapies. Yet even here, there are gaps in the evidence. As noted above, not all biomarker-positive individuals will experience significant cognitive decline. We anticipate that age-related amyloid deposition may be benign in some individuals and not indicative of a progressive disease. We know that the relationships between biomarkers, cognitive performance, and prognosis are heterogeneous and that important gaps remain in understanding individual and intersectional effects across different population groups (age, race/ethnicity, socioeconomic, morbidity, and others).

Although we agree that there is an emerging understanding of the biological basis associated with characteristic brain pathology, diagnosing AD currently relies on pre-mortem biomarkers (similar to prostate specific antigen (PSA)), not true pathology. In addition, since age-related amyloid deposition may be benign in some individuals and not reflective of true early AD, it is unclear how those biomarkers perform in the oldest-old group of older adults. It is important to consider that the field did not have the ability to make biology-based diagnoses pre-mortem for many years because brain biopsies could not be performed and as a result, providers have been using behavioral symptoms to diagnose people with AD. The public, patients, clinicians, and others currently understand cognitive disorders as clinical problems based on observable features and changes in function of individuals. Without proper preparation and education, including a common understanding of the clinical significance of biomarkers across all population groups, confusion is likely and potentially harmful outcomes. We believe the revised criteria should take into account the real need to better understand the meaning of AD biomarkers in large populations. More biomarker studies representing diverse study populations would allow testing the validity of the cut-off values of Core 1 biomarkers across different populations and age strata, including those with various comorbid conditions. While some of this work is underway with research funding, it is not yet sufficient to support firm conclusions. We also recognize that results of ongoing secondary prevention trials may one day justify interventions for asymptomatic individuals, but for now, this evidence is lacking. Further, there is no adequate observational study evidence base for people who are older, have chronic conditions, or from historically underrepresented groups to know how well these biomarkers reflect true AD pathology to justify routine testing for everyone.

Restriction of AD Biomarker Testing to Specific and Defined Conditions and Purposes

AGS recommends that the AA Workgroup revise its recommendation about performing biomarker testing under the supervision of a physician (lines 321-322) to include restricting biomarker testing to

specific, clearly detailed circumstances including the patient's cognitive status, clinical picture, whether their conditions and preferences suggest candidacy for amyloid-reducing treatment, and/or family history of possible AD with desire for biomarker testing to help think ahead about what might be coming in light of that history. We also suggest including a recommendation that specific counseling be available to those who are being tested in all situations where biomarker testing is used outside of a research setting.

Diversity and Equity Considerations

AGS disagrees with the removal of the need for observational studies with more diverse and representative cohorts in the Future directions section. The revised criteria are heavily reliant on evidence from population-based data that may not be representative of the people living with AD. Much remains to be learned about how biomarkers perform as true indicators of specific brain pathologies across different clinical populations, including those with various comorbid conditions (DOI:10.1038/s41591-022-01822-2), before implementation into routine clinical care. Considering the racial and ethnic disparities in the prevalence of AD and other dementias among the subpopulations and increasing diversity among older people, it is important to determine whether age, gender, and racial and ethnic representation in the data is sufficient to support generalizability (DOI:10.1016/j.jalz.2018.06.3063). The existing disparities in access to AD diagnosis and care must not be exacerbated by evidence based on non-representative participant populations. It would also be critically important to understand the impact of biomarker-based diagnosis on different populations as well as any potential or unintended harms, including inequities in diagnosis and care, particularly for the historically minoritized populations that have been disproportionately affected by AD and disproportionately understudied and underdiagnosed. We recommend explicitly calling out the critical need for diversity and inclusion of underrepresented groups in AD trials and research in this section.

Differences Across Clinical Practices

AGS notes that this revision of the criteria did not incorporate our recommendations on specifying the disciplines that would be adopting the criteria, the circumstances under which seeking a biomarker diagnosis would be appropriate, and how the practicing clinician is to guide person-centered decision-making about appropriate use of biomarker information in life planning. Clinical practice in cognitive neurology is not like clinical practice in geriatrics, family medicine, or internal medicine. As an example, neurologists have a longstanding tradition of classifying and subclassifying neurological disorders and syndromes as a major professional activity. Such classification is important for clarity and parsimony when communicating among professionals, but it is not directly concerned with patients or patient care, including how to communicate with non-health professionals about a condition or risk factor of interest. AGS recommends that the criteria account for the very substantial differences between medical disciplines in purpose, context, societal function, and population impact.

Workgroup Composition and Roles

We recognize the addition of the statement on the National Institute on Aging (NIA) working with the criteria workgroup as advisers on the AA website. While we also recognize that NIA was removed from the formal title of the revised criteria, NIA's role in the development, review, and approval of the document is not clear. This is further exacerbated by beginning with a history of the criteria instead of a statement about who is responsible for the current update (the AA Workgroup), why the AA thought an update was needed, and a statement of purpose. To ensure transparency, a clear description of how NIA participated in the process of developing the prior versions of the criteria (2011 and 2018) and how NIA and the National Institutes of Health (NIH) were engaged in the current update should follow the introduction to this document.

With the potential influence of financial ties between key stakeholders who make decisions on definitions and diagnostic thresholds, transparency is critically important for such updates particularly when the risks are unknown. A cross-sectional study found that many guideline panels had a high proportion of ties with the industry, including panel chairs, and a majority of the panels' studies proposed changes to disease definitions that would increase the number of individuals diagnosed with that disease while none included an assessment of the potential risks due to the broader definition (DOI:10.1371/journal.pmed.1001500).

As we recommended in our prior comments, workgroup members' disclosures should be included in the document as well as a description of how the conflicts inherent in industry representation on the workgroup were resolved and how the conflicts of other workgroup members were mitigated. Given some of the members have significant conflicts of interest, the following should be directly included in the draft criteria document: (1) a list of workgroup members inclusive of their disclosures; (2) a description of how conflicts were addressed with respect to industry representatives; and (3) how any conflicts of other workgroup members were mitigated.

Specific Comments

- *Lines 25-26: "Since then, plasma-based biomarkers have been developed and clinically studied; some (but not all) demonstrate excellent diagnostic performance."*

  The statement should include a description of the populations in which plasma-based biomarkers demonstrated excellent diagnostic performance.

- *Lines 180-183: "An analogy can be drawn with adult-onset diabetes, where most individuals are diagnosed by screening HbA1C or fasting glucose testing while asymptomatic. Symptoms from adult-onset diabetes may not appear for years after initial diagnosis, but the disease exists at this initial stage and is routinely diagnosed while patients are asymptomatic. This biological definition of AD is consistent with the distinction between a disease vs illness. A disease is a pathobiological condition that will ultimately manifest with symptoms if an affected individual survives long enough. In contrast the term illness denotes signs and symptoms that result from the disease."*

  This analogy is not aligned with the statements on routine testing in asymptomatic patients with biomarker positivity. Diabetes is a lab diagnosis by definition and diabetes mellitus (DM) related organ diseases are not necessarily symptomatic (maybe direct issues related to ketoacidosis, hyperosmolarity). Type 1 DM is not usually diagnosed by screening and hyperosmolarity is not inevitable or usual.

- *Line 234: "Intermediate/high ADNPC is considered sufficient to produce dementia."*

  AGS recommends providing evidence to support this statement.

- *Lines 257-259: "c) clinical validation, including validation data in the intended use population, showing clinical accuracy, positive and negative predictive value at the medical decision limit (i.e. predetermined cut-point(s)) in each intended use population, and safety (which includes the effect of incorrect test diagnosis)."*

We suggest clarifying the clinical use relevance here as well as considering medical decision-making as an important component to clinical validation.

- *Lines 309-310: "And the committee strongly recommends that clinicians should not be restricted by payers in pursuing further testing when this is indicated by clinical judgement."*

  Though AGS agrees with this statement, we believe it is not related to clinical care and does not align with the purpose of the draft criteria and should be eliminated from the document.

- *Lines 334-336: "The major intended use for the biological diagnosis of AD in clinical trials is as an inclusion criterion. While a purely symptomatic therapy may not require documentation of AD biology, therapy directed toward a biological target requires confirmation of that biology."*

  We recommend clarifying whether confirmation of that biology only applies to trials.

- *Lines 344-346: "Rather we emphasize that treatment in symptomatic individuals with biologically proven AD should be based on clinical assessment of risk/benefit at the individual patient level (Text box 4)."*

  AGS is pleased with the addition of this statement to emphasize treatment that is based on clinical assessment of risk/benefit at the individual patient level. We encourage referencing it earlier in the document and taking into consideration testing in more advanced dementia for which there is no biologically based treatment.

AGS applauds ongoing work to prevent or delay cognitive changes associated with dementia, including advances for earlier diagnosis and efforts to pinpoint the molecular mechanisms underlying dementing illnesses. Unfortunately, we do not currently have the evidence to guide how biomarker-based diagnosis of Alzheimer's disease should be handled in all clinical populations. AGS prioritizes what matters most to patients, their families, and other care partners as well as consideration of the whole person. Until compelling evidence emerges, implementing purely biomarker-based diagnoses could result in significant psychological and practical harm.