AGS Geriatrics Healthcare Professionals
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THE AMERICAN GERIATRICS SOCIETY
40 FULTON STREET, SUITE 809
NEW YORK, NEW YORK 10038
212.308.1414 TEL
www.americangeriatrics.org

American Geriatrics Society Response – Draft NIA-AA Revised Clinical Criteria for Alzheimer's Disease
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The American Geriatrics Society (AGS) submitted these comments on the draft National Institute on Aging-Alzheimer's Association (NIA-AA) Revised Clinical Criteria for Alzheimer's Disease (AD), an update of the 2018 NIA-AA Revised Clinical Guidelines for Alzheimer's. The AGS appreciates the opportunity to provide feedback on the proposed changes to the guidelines, including our concerns about the proposal to expand the guidelines to include usage in clinical care, the role and authority of NIA in the updates and the alignment with NIA's mission to provide research resources, and biomarker-based diagnosis as a single criterion for AD diagnosis given the potential exacerbation of inequities and care that might result from this approach.

Comments

AGS believes that the rapid evolutions in our knowledge of Alzheimer's Disease and Related Dementias (ADRD) will necessarily (and hopefully) lead to future shifts in clinical practice and revisions to how we diagnose, and label conditions and pathologies associated with ADRD. We recognize that defining AD as a biological construct has advantages for research. We therefore agreed with the following definition that was articulated in the 2018 guidelines given its stated purpose: "This unifying update is labeled a 'research framework' because its intended use is for observational and interventional research, not routine clinical care."

The draft 2023 update of the guidelines proposes to expand their use into clinical care: "A major new direction therefore is to expand the 2018 framework from a research-only focus to one that provides recommendations that are applicable for both research and clinical care. The title of this modular update, NIA-AA Revised Clinical Criteria for Alzheimer's Disease, reflects this progression in focus." The AGS believes that the proposed expansion of the 2023 guidelines to include use in clinical practice is premature. Practitioners, patients, and society have not been sufficiently prepared for this shift, and the current evidence base is underdeveloped to support it.

The reality is that there is no current evidence that discovery of biomarker positivity in a cognitively normal individual should lead to initiation of a specific clinical intervention. While discovery of an asymptomatic cancer during a routine screening colonoscopy justifies a diagnosis of colon cancer and initiation of specific treatment, as of now, there is no evidence that removing amyloid helps a cognitively normal person who is biomarker positive. We are concerned that the proposed expansion of the NIA-AA guidelines to include usage in clinical care will place many older and multimorbid people at risk of overdiagnosis, which in turn could lead to initiation of treatments with limited benefit and high potential for harm in this population. Unintended harms that this expansion could cause also include potential requirements from insurance companies, employers, and others that individuals be tested as a condition of insurance or employment. We believe that the risk of these potential harms is greater due to the proposal that the guidelines continue to carry the imprimatur of two well-respected organizations – NIA and AA.

We outline our specific concerns in more detail below.

General Concerns

We have three general concerns related to this, the third modular update of the NIA-AA Guidelines:

- The first concern is the composition of the workgroup that is proposing the guidelines be expanded to include use in clinical practice. According to the AA website, seven of the workgroup members are from the industry, and a number of other members have disclosed significant conflicts of interest. The makeup of the workgroup may be appropriate for a framework aimed solely at research criteria but is wholly inappropriate for a clinical guideline that includes recommendations for clinical practice. *The Council of Medical Specialty Societies (CMSS) Principles for Clinical Practice Guidelines* recommend that clinical guideline panels be comprised of members who are free of conflicts of interest and that there be a process for identifying and resolving any potential conflicts. The CMSS principles build upon the 2011 recommendations from the Institute of Medicine of the National Academies of Science, *Clinical Practice Guidelines We Can Trust*. In this proposed update, the guidelines document itself is lacking a disclosure of the workgroup members' conflicts, nor is there any description of how the conflicts inherent in industry representation on the workgroup were resolved and how the conflicts of other workgroup members were mitigated. At minimum, the guidelines document should be revised to include the following directly in the 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. Unfortunately, this will not address the major flaw which is the presence of industry representatives on the workgroup in the first place.

- The second concern is the guideline's disregard of important distinctions across fields of 'clinical practice.' Clinical practice in cognitive neurology is not like clinical practice in geriatrics, family medicine, or internal medicine. Statements about 'adoption of biomarker diagnosis in clinical practice' should specify which disciplines would be adopting this, 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. Further, the guidelines should account for the very substantial differences between medical disciplines in purpose, context, societal function, and population impact. It 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. Simply put, it is not enough, as the revised guidelines do, to state that this 2018 research framework is now ready for use in clinical care.

- The third concern is that the draft text of this proposed expansion does not reflect the same level of collaboration between AA and the NIA that was evident in the 2011 guidelines and the 2018 modular updates which had the intended purpose of providing a research framework, a usage that is consistent with the mission of the NIA. For both earlier editions, the expert workgroups were co-convened by AA and the NIA, whereas for this update, AA has indicated that it is the sole convener of the guidelines workgroup and has stated that comments received during this comment period will only be reviewed by the workgroup. Given the organizational structure and the statement about who is responsible for review of the comments, our perception is that AA is in full control of the content of the proposed updated guidelines. We recognize that there is *ex officio* representation from the National Institute on Aging (NIA) at the National Institutes of Health on the Steering Committee and on the workgroup. What is missing

from the document is a description of how the NIA was and is engaged in the work of updating these guidelines and whether the NIA has any decision-making authority over the recommendations that are being made. In the absence of an explicit definition of NIA's role, it appears that AA is proposing continued branding to both AA and NIA. This branding signals to clinicians, policymakers, and the public that the NIA is a full partner in this modular update inclusive of authority over the final content of the guidelines. For transparency, we recommend that the workgroup add an explicit statement about how the NIA has been engaged in this proposed update that is specific as to NIA's role in the development, review, and approval of any recommendations that are made in these guidelines. Further, as noted earlier in these comments, the proposed expanded usage of the guidelines is inconsistent with the NIA's mission and AGS recommends that the NIA consider whether the NIA-AA Revised Clinical Criteria for Alzheimer's Disease (AD) should continue to carry the NIA name.

Concerns around adoption of biomarker-based diagnosis in clinical practice

AGS appreciates the benefits of diagnosing neurodegenerative pathologies separate from and in parallel with clinical syndromes of cognitive impairment or dementia. We agree that there is an emerging understanding of the biological basis that is associated with characteristic brain pathology. However, we believe it is premature to make currently available single biomarkers of amyloid or tau a basis for clinical diagnosis, or to label all people with amyloid biomarkers or AD-associated tau markers as having Alzheimer's disease.

- The proposed guidelines state that the impetus for the proposed change was that several therapies targeting the biology of AD have received regulatory approval since the 2018 guidelines was published, and these approved treatments target only AD. This requires a method of diagnosing AD with high specificity in cognitively impaired individuals; however, there are no targeted therapies to date that have been shown to improve patient level outcomes in individuals who are biomarker positive but cognitively normal.
- The guidelines outline use cases for biomarkers and in Table 1 (Biomarker Categorization) and Table 2 (Use Cases), the guidelines note that the biomarkers listed are currently suitable for clinical use, while biomarkers available for research use can be seen in Table 3 (Additional biomarkers currently suitable for AD research and possible for future clinical use). As stated in the guidelines, "Biomarkers were placed into Tables 1, 2 vs. Table 3 based on the committee's assessment of the strength of available evidence of high diagnostic accuracy (sensitivity, specificity) compared to a valid gold standard, high reproducibility, and diagnostic utility based on clinical studies in real world settings." We believe it is important to understand and have in writing the criteria for assessing the strength of the evidence and process used by the workgroup to do this assessment and make these recommendations.
- The proposed guidelines rely heavily on evidence derived from population-based data that may not be representative of the racial and ethnic diversity and age distribution of people living with ADRD (DOI:10.1016/j.jalz.2018.06.3063). More biomarker studies representing diverse study populations need to be conducted in order to test the validity of the cut-off values of amyloid and tau (A/T) biomarkers across different populations and age strata. Much remains to be learned about how plasma-based biomarkers perform as true indicators of specific brain pathologies in broad clinical populations, including those with various comorbid conditions (DOI:10.1038/s41591-022-01822-2), before implementation into routine clinical care.
- Much more thought needs to be given to the potential exacerbation of inequities in diagnosis and care that might result from recommending biomarker-based diagnosis as a single criterion

for diagnosing AD. It is well known that several minoritized populations are both disproportionately affected by ADRD and disproportionately underdiagnosed.

- Dementia specialists, pharmaceutical companies, and AD advocates have been highly successful in catastrophizing AD for the general public. We are deeply concerned the guidelines fail to address what a biomarker-based AD diagnosis can convey for personal identity. Due to heterogeneity in cognitive prognosis associated with biomarker positivity, the workgroup may want to consider how best to avoid assigning a clinical diagnosis of AD to biomarker-positive, asymptomatic individuals with normal cognition. Not only do 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) but most people who die with dementia die *with*, not *of*, dementia. It may be useful, however, to create a medically codable designator for 'elevated risk state' to facilitate clinical tracking over time and we would encourage the AA to consider how to move this concept forward into practice.

The AGS understands the heavy toll of Alzheimer's disease on patients, caregivers, and their families and we are gratified to see promising new therapeutic options on the horizon with the potential to reduce the significant impact associated with ADRD. Additionally, we applaud ongoing work to develop therapies that may be deployed early in neurodegenerative processes, which we hope will one day prevent or delay cognitive changes associated with dementia. We are excited to see advances in technologies for earlier diagnosis, efforts to pinpoint the molecular mechanisms that underlie dementing illnesses, and more attention to how the exposome influences brain health in ways that often lead to health disparities in dementia. In the future, if significant evidence supports implementing biomarker-based diagnosis into clinical practice, our community will need to engage in intensive public and professional education efforts that prepare society that some people may be diagnosed with Alzheimer's disease yet never live to develop objective evidence of cognitive impairment or progress to meet clinical criteria for dementia. Significant evidence now supports recommendations that cancer screening and treatment should not be applied uniformly in all populations; in contrast, we do not have the evidence to guide how biomarker-based diagnosis of Alzheimer's disease should be handled in all clinical populations. Until then, purely biomarker-based diagnoses could result in significant psychological and practical harm.