AGS Geriatrics Healthcare Professionals
Leading Change. Improving Care for Older Adults.

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The American Geriatrics Society (AGS) submitted this nomination in response to the Patient-Centered Outcomes Research Institute (PCORI) call for topics for systematic reviews that support the development of evidence-based practice guidelines or practice recommendations. AGS is appreciative of the opportunity to nominate a topic for systematic review, and we look forward to collaborating on efforts to support practice guidelines and recommendations related to older adults.

Systematic Review Nomination Questions

1. **Please enter a short title for your topic for a systematic review nomination.**

Biomarker-based Diagnostic and Staging Performance for Alzheimer's Disease Across Populations

2. **Please briefly state the topic and up to four specific research questions**

Understanding the performance of biomarkers, including plasma-based biomarkers, to diagnose and stage Alzheimer's disease (AD) across different population groups.

1. What are the levels of validity, reliability, and utility in blood-based and other biomarker tests in supporting clinically valuable and accurate diagnosis and staging of AD?
2. What is the performance level of the available tests in different population groups (e.g., racial, ethnic, socioeconomic, age, morbidity, primary vs. specialty care setting, health insurance type) as valid and reliable indicators of cerebral AD pathologies?
3. Does the available evidence warrant use of biomarkers to diagnose AD, especially in asymptomatic people, across different populations and age strata, including those with various comorbid conditions? If so, what demographic, clinical, or other patient characteristics justify use of biomarker testing?
4. What is the clinical significance and impact of biomarker-based AD diagnosis and staging in various population groups, including in the context of commonly found mixed dementia pathologies?

3. **Will a review on this topic inform:**

a. Development of a new clinical guideline or evidence-based practice statement
b. Update of an existing clinical guideline or evidence-based practice statement
c. Other

4. **Please provide a brief explanation of why this topic matters to patients and clinicians and why you are suggesting this topic.**

As the aging population increases, so too will the prevalence of diseases that disproportionately affect older people—most notably Alzheimer's disease and related dementias—and the economic burden associated with these diseases. Considering the racial and ethnic disparities in the

prevalence of dementias among subpopulations and the increasing diversity among older people, it is important to determine whether age, gender, morbidity, and racial and ethnic representation in the available data are sufficient to support generalizability of new diagnostic tests (DOI:10.1016/j.jalz.2018.06.3063). The existing disparities in access to AD diagnosis and care must not be exacerbated by evidence that is based on non-representative participant populations. It would also be critically important to recognize 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 marginalized populations that have been disproportionately affected by AD and disproportionately understudied and underdiagnosed.

There are ongoing efforts, such as the Revised Criteria for Diagnosis and Staging of Alzheimer's Disease: Alzheimer's Association Workgroup, to expand the use of research criteria for AD to clinical diagnosis and care of patients, and to define AD as a condition of biomarker positivity, regardless of patients' clinical status. To do so would result in labeling asymptomatic, cognitively normal, biomarker-positive individuals as 'having Alzheimer's disease,' a condition that has been characterized based on study of *clinical cases*, not asymptomatic, biomarker-positive individuals, as a 'terminal disease.' A change of this magnitude in the public narrative about what it means to 'have AD' is likely to have significant unintended consequences for patients, families, and clinicians – there has been insufficient attention thus far to its potential impact on personal identity or social and financial consequences.

Support for the proposed change in standards for diagnosis of AD relies heavily on evidence derived from studies that are not inclusive of the full range of diversities that characterize this population generally and of people living with AD specifically (DOI:10.1016/j.jalz.2018.06.3063). Moreover, we know that biomarker positivity is associated with wide variations in cognitive trajectory. It is crucial to consider the application to the diverse population of individuals living with AD as well as how best to avoid assigning a clinical diagnosis of AD to biomarker-positive, asymptomatic individuals with normal cognition. It is still unclear how many biomarker-positive individuals will 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). Conveying a diagnosis of AD to asymptomatic, biomarker-positive individuals who may never go on to manifest cognitive decline or dementia symptoms may expose them to harms without clear benefit. If the proposed biomarker criterion for diagnosis were to be adopted, 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, as a result, carry an AD diagnosis in their health records. Furthermore, 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 mild cognitive impairment or dementia due to AD. Additionally, since current biofluid and neuroimaging biomarkers are limited chiefly to AD pathological findings of β-amyloid and tau, an individual could have a negative AD biomarker test, but could progress to dementia from Lewy body disease, limbic-predominant age-related TDP-43 encephalopathy (LATE), or other pathologies that do not yet have reliable biomarkers.

We are excited to see advances in technologies for earlier diagnosis, efforts to pinpoint the molecular mechanisms that underlie illnesses that lead to dementia, and more attention to how the exposome influences brain health in ways that often lead to health disparities in dementia. However, much more consideration is needed to the risk of exacerbating inequities in diagnosis and care that might result from recommending biomarker-based diagnosis as the single criterion for diagnosing AD. This is of particular relevance to diagnosis outside highly specialized medical settings. The majority of patients receive a first diagnosis of cognitive impairment or dementia from their primary care clinician. With widely available blood testing for AD biomarkers, it is conceivable that testing could be adopted as a routine practice without the nuanced understanding required to appropriately interpret a putatively positive test result.

AGS understands the heavy toll of Alzheimer's disease on patients, caregivers, and their families and we appreciate the benefits of identifying neurodegenerative pathologies separate from and in parallel with clinical syndromes of cognitive impairment or dementia. The rapid evolutions in our knowledge of AD will necessarily (and hopefully) lead to future shifts in clinical practice and revisions to how we diagnose, and label, conditions and pathologies associated with AD. While there is growing understanding of the biological mechanisms associated with cognitive disorders including dementias, the current evidence is not sufficient to guide the application of biomarker-based diagnosis of AD in all clinical populations.

5. **Please explain how a systematic review would be helpful in this area and how your organization would use the review.**

AGS believes a comprehensive evidence review that identifies the gaps and limitations of biomarker-based diagnosis and staging of AD and is specific to the population that is meaningfully representative of people living with AD is a critical first step in ensuring that AD diagnosis and staging is appropriately managed. We know that the relationships between biomarkers, cognitive performance, comorbid pathologies, 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). Furthermore, high-quality studies involving older patients from different ethnic groups are rare. As a result, current evidence-based literature does not serve as an adequate guide in many decision-making situations that are routinely encountered in clinical practice for AD.

We would use the review to inform our work on educational and clinical tools that support clinicians who care for older adults at risk of and currently living with AD as well as developing statements and comments that advocate for appropriate and clinically valuable guidelines and criteria related to the diagnosis, staging, and treatment of AD. AGS will continue to encourage that guidelines and criteria developed by other organizations are informed by evidence that reflects the diversity and complexity of people who are living with AD.

6. **To the extent possible, please provide information about the question(s) in PICO format: Population, Interventions, Comparators, Outcomes. Note that a response in all fields is not required.**

   a. **Population of interest: Who are the people that should be studied? (e.g., pregnant people, older adults in the community, adolescents with anxiety, the general public.)**

      The patient population should be representative of the racial, ethnic, socioeconomic, and age diversity of people living with AD, including those who are also living with co- and multimorbidity.

   b. **Interventions/options: What options should be compared? These are the decisions the research is intended to inform. Please include specific interventions, treatments or delivery models.**

      - Current diagnostic processes for AD/AD
      - Traditional biomarker testing (e.g., amyloid positron emission tomography (PET), Cerebrospinal Fluid (CSF))
      - Plasma-based biomarker testing (e.g., amyloid-tau-neurodegeneration (ATN) profile, p-tau-217)
      - Impact of tau biomarkers in addition to amyloid biomarkers on disease progression

   c. **Outcomes: How will evidence generated from this topic make a difference for patients, providers, health systems, policy makers, or other stakeholders? For example, will the evidence generated improve individual outcomes (e.g., pain control), save time, or improve access to care?**

      A systematic review may help to inform current clinical practice as well as guide clinicians in person-centered decision-making about appropriate use of biomarker information and serve as a "roadmap" for researchers who seek to address the identified knowledge gaps. It is also critically important that clinical and research guideline developers have a full understanding of the evidence that is informing the recommendations that they make. As an example, the Revised Criteria for Diagnosis and Staging of Alzheimer's Disease: Alzheimer's Association Workgroup that is currently in progress would have benefitted from such a review.

      The evidence generated may also help to reduce the risk of overdiagnosis of AD and ensure that not all people with biomarkers will be labeled as 'having AD' but instead be identified as someone who may be at higher risk of developing cognitive decline due to AD. Current evidence supports use of biomarkers in clinical practice only as part of the evaluation of individuals who may otherwise be candidates for novel anti-amyloid therapies. Yet, there are gaps in the evidence. Not all biomarker-positive individuals will experience significant cognitive decline and

we anticipate that, as an example, age-related amyloid deposition, may be benign in some individuals and not indicative of a progressive disease.

7. Please list recent guidelines on this topic of which you are aware.

Draft of the Revised Criteria for Diagnosis and Staging of Alzheimer's Disease: Alzheimer's Association Workgroup (October 2023)

Albert MS, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Focus (Am Psychiatr Publ).* 2013;11(1):96-106. doi:10.1176/appi.focus.11.1.96

8. Please list recent systematic reviews on this topic of which you are aware.

Chaudhry A, Rizig M. Comparing fluid biomarkers of Alzheimer's disease between African American or Black African and White groups: A systematic review and meta-analysis. *J Neurol Sci.* 2021;421(117270). doi:10.1016/j.jns.2020.117270

d'Abramo C, D'Adamio L, Giliberto L. Significance of blood and cerebrospinal fluid biomarkers for Alzheimer's disease: sensitivity, specificity and potential for clinical use. *J Pers Med.* 2020;10(3):116-156. doi:10.3390/jpm10030116

Gleason CE, et al. Alzheimer's disease biomarkers in Black and non-Hispanic White cohorts: a contextualized review of the evidence. *Alzheimer's Dement.* 2022;18(8):1545-1564. doi:10.1002/alz.12511

Jansen WJ, et al. Prevalence of cerebral amyloid pathology in persons without dementia: a meta-analysis. *JAMA.* 2015;313(19):1924-1938. doi:10.1001/jama.2015.4668

Olsson B, et al. CSF and blood biomarkers for the diagnosis of Alzheimer's disease: a systematic review and meta-analysis. *Lancet Neurol.* 2016;15(7):673-684. doi:10.1016/S1474-4422(16)00070-3

Pais MV, Forlenza OV, Diniz BS. Plasma biomarkers of Alzheimer's disease: a review of available assays, recent developments, and implications for clinical practice. *J Alzheimer's Dis Rep.* 2023;7(1):355-380. doi:10.3233/ADR-230029

9. Please identify the most important studies completed in this area.

Aschenbrenner AJ, et al. Comparison of plasma and CSF biomarkers in predicting cognitive decline. *Ann Clin Transl Neurol.* 2022;9(11):1739-1751. doi:10.1002/acn3.51670

Barthélemy NR, et al. Highly accurate blood test for Alzheimer's disease is similar or superior to clinical cerebrospinal fluid tests. *Nat Med*. 2024;30(4):1085-1095. doi:10.1038/s41591-024-02869-z

Brookmeyer R, Abdalla N. Estimation of lifetime risks of Alzheimer's disease dementia using biomarkers for preclinical disease. *Alzheimer's Dement.* 2018;14(8):981-988. doi:10.1016/j.jalz.2018.03.005

Erickson P, Simrén J, Brum WS. Prevalence and clinical implications of a β-amyloid–negative, tau-positive cerebrospinal fluid biomarker profile in Alzheimer disease. *JAMA Neurol.* 2023;80(9):969-979. doi:10.1001/jamaneurol.2023.2338

Hansson O, Blennow K, Zetterberg H, Dage J. Blood biomarkers for Alzheimer's disease in clinical practice and trials. *Nat Aging.* 2023;3(5):506-519. doi:10.1038/s43587-023-00403-3

Jansen WJ, Janssen O, Tijms BM. Prevalence estimates of amyloid abnormality across the Alzheimer disease clinical spectrum. *JAMA Neurol.* 2022;79(3):228-243. doi:10.1001/jamaneurol.2021.5216

Karikari TK. Blood tests for Alzheimer's disease: increasing efforts to expand and diversify research participation is critical for widespread validation and acceptance. *J Alzheimer's Dis.* 2022;90(3):967-974. doi:10.3233/JAD-215730

Matthews KA, Xu W, Gaglioti AH, Holt JB, Croft JB, Mack D, McGuire LC. Racial and ethnic estimates of Alzheimer's disease and related dementias in the United States (2015–2060) in adults aged ≥65 years. *Alzheimer's Dement.* 2018;15(1):17-24. doi:10.1016/j.jalz.2018.06.3063

Planche V, et al. Validity and performance of blood biomarkers for Alzheimer disease to predict dementia risk in a large clinic-based cohort. *Neurology.* 2023;100(5):473-484. doi:10.1212/WNL.0000000000201479

Roberts RO, et al. Prevalence and outcomes of amyloid positivity among persons without dementia in a longitudinal, population-based setting. *JAMA Neurol.* 2018;75(8):970-979. doi:10.1001/jamaneurol.2018.0629

Schindler SE, et al. Using Alzheimer's disease blood tests to accelerate clinical trial enrollment. *Alzheimer's Dement*. 2023;19(4):1175-1183. doi:10.1002/alz.12754

Schindler SE, et al. Effect of race on prediction of brain amyloidosis by plasma Aβ42/Aβ40, phosphorylated tau, and neurofilament light. 2022;99(3):e245-e257. doi:10.1212/WNL.0000000000020035

Therriault J, et al. Biomarker-based staging of Alzheimer disease: rationale and clinical applications. *Nature Review Neurology.* 2024;20(4):232-244. doi:10.1038/s41582-024-00942-2

10. **If your topic is chosen, would your organization be able to contribute dedicated staff time (estimated at a few hours a month) to this project?**

    a. Yes
    b. No
    c. Unsure

11. **If your topic is chosen, do you have subject matter experts that would be willing to advise on the basic scope of the review early in the process?**

    a. Yes
    b. No
    c. Unsure