

Comments received for the second draft (October 2023) through the Alzheimer’s Association website or through written communication to one of the workgroup members. Although submitter name(s) and their affiliation have been removed, other identifying information may remain within the body of the submitted text.

Below are the comments received for the second draft (July 2023) of the Alzheimer’s Association Diagnostic Criteria through the association website and through communication to one of the committee members. Although organization names have not been removed, other identifying information has been removed.

Updated drafts are now available at [alz.org/diagnostic criteria](https://alz.org/diagnostic-criteria) for open comments.

Comments received after October 1, 2023-November 16, 2023 include:

Opinion
<p>My comments address the designation of a preclinical (asymptomatic) stage of Alzheimer’s disease diagnosis. Dementia is unquestionably devastating to the individuals who live with it, their families and communities, and dementia demands much from social safety nets, health care systems, and social services. Thus, it is of critical interest to be able to identify people without cognitive symptoms who will go on to develop dementia if it is possible to safely intervene to alter their trajectory so that their cognitive symptoms are minimal if present at all. The use of plasma biomarkers for this purpose has appeal, as it fits with the model of continuum of Alzheimer’s disease from pathology-only phenomenon to dementia. It must be true that people who develop the clinical syndrome of dementia have passed through a sequence of pathologic and mild symptom phases, even if those passages were not measured when they occurred. Moreover, extensive evidence indicates that, at the population aggregate, biomarker concentrations in CSF or plasma correspond to higher dementia risk. However, as a raft of evidence suggests, the presence of Alzheimer’s pathology whether in the brain or in CSF or blood is not a guarantee that a specific person will subsequently develop cognitive symptoms, including those of the most feared degree, dementia. The quality of individual-level prediction is critical for diagnostic and treatment decisions about individuals. The distinction here is similar to the contrast between observing an adverse association between smoking and cardiovascular disease in a population, and using smoking status to diagnose an individual with early-stage cardiovascular disease. For example, a large clinicopathologic study found that of people who did not have dementia upon death, more than 40% had Alzheimer’s brain pathology upon autopsy (Kapasi et al., 2017). Likewise, other evidence suggests that the sequence and timing of pathologic and clinical events in Alzheimer’s disease progression, at least as marked by CSF biomarkers, is far from uniform (Lespinasse et al., 2023). There is still limited evidence as to what cut-points of biomarkers would be used to make diagnoses and clinical decisions. Although some research groups have attained what seems to be reasonable predictive accuracy as indicated by the area under the curve index, three features of this evidence stand out: (1) blood biomarkers offer little value in predicting dementia risk beyond cognitive testing and other traditional measures (Planche et al., 2023); (2) the specificity of some proposed cut-points, while high remain low enough to generate a non-trivial number of false-positives and therefore mistaken diagnoses (e.g., Janelidze et al., 2023); and (3) sparse evidence on the accuracy of the plasma biomarkers in subgroups of the population, defined, for example, by chronic disease status and racialization. The possibility of identifying people as having stage 1a or stage of Alzheimer’s disease who never go on to develop symptoms deserves our attention, especially in light of well-intended attempts to designate pre-clinical stages of other conditions or use of screening test to identify persons who likely have an early stage of a condition. Whereas as some of these efforts, such as the pap smear for screening for cervical cancer, have yielded clear benefits and little harm to individuals,</p>

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other efforts have resulted in wasted resources and even potential harm to individuals, such as with osteopenia (as an early stage of osteoporosis), or biomarker-based tests of prostate cancer for older men. At issue is that imperfect specificity means that many of the positive biomarker tests will result in mislabeling people, subject them to further testing, and/or subject them to inappropriate and potentially risky treatment. Assuming that 1 in 4 adults will develop dementia during their lives, a cut-point sensitivity of 0.9, and a specificity of 0.85, 1 in 3 of all positive tests will be in people who never go on to develop dementia. This is a staggering burden to those testing positive, their families, and health care systems. It also represents a diversion of resources from those who truly will go on to develop dementia. Finally, there is a notable lack of evidence about the performance of plasma biomarkers among persons living with chronic disease (notably renal illness, which could affect plasma concentrations), and among person in racialized communities. This is especially concerning given that persons with these characteristics bear disproportionately high risks of dementia. A definition and diagnosis of pre-clinical Alzheimer's disease will serve us well when approaches are available that do not burden people who are truly not at risk for dementia, and that result in better dementia outcomes among people who truly are. With the measures on hand, we are not there yet. Janelidze S, Bali D, Ashton NJ, BarthÃ©lemy NR, Vanbrabant J, Stoops E, Vanmechelen E, He Y, Dolado AO, Triana-Baltzer G, Pontecorvo MJ, Zetterberg H, Kolb H, Vandijck M, Blennow K, Bateman RJ, Hansson O. Head-to-head comparison of 10 plasma phospho-tau assays in prodromal Alzheimer's disease. *Brain*. 2023 Apr 19;146(4):1592-1601. doi: 10.1093/brain/awac333. PMID: 36087307; PMCID: PMC10115176. Kapasi A, DeCarli C, Schneider JA. Impact of multiple pathologies on the threshold for clinically overt dementia. *Acta Neuropathol*. 2017 Aug;134(2):171-186. doi: 10.1007/s00401-017-1717-7. Epub 2017 May 9. PMID: 28488154; PMCID: PMC5663642. Lespinasse J, Dufouil C, Proust-Lima C. Disease progression model anchored around clinical diagnosis in longitudinal cohorts: example of Alzheimer's disease and related dementia. *BMC Med Res Methodol*. 2023 Sep 5;23(1):199. doi: 10.1186/s12874-023-02009-0. PMID: 37670234; PMCID: PMC10478286. Planche V, Bouteloup V, Pellegrin I, Mangin JF, Dubois B, Ousset PJ, Pasquier F, Blanc F, Paquet C, Hanon O, Bennys K, Ceccaldi M, Annweiler C, Krolak-Salmon P, Godefroy O, Wallon D, Sauvee M, Boutoleau-BretonniÃ¨re C, Bourdel-Marchasson I, Jalenques I, Chene G, Dufouil C; MEMENTO Study Group. Validity and Performance of Blood Biomarkers for Alzheimer Disease to Predict Dementia Risk in a Large Clinic-Based Cohort. *Neurology*. 2023 Jan 31;100(5):e473-e484. doi: 10.1212/WNL.0000000000201479. Epub 2022 Oct 19. PMID: 36261295; PMCID: PMC9931079.

Both the process and the product in writing these criteria are flawed. There is no justification to have a balanced membership including individuals with a major financial interest in the outcome of the recommendations. This is like saying we have a balanced jury- half the members will make millions of dollars if the determination is guilty but the other half are unbiased. The idea that a panel with appropriate expertise could not be convened without industry representation is absurd. Let industry representatives' comment on the criteria like everyone else. I suggest individuals who stand to draw any financial benefit from the outcome of the criteria withdraw from the authorship group. There is nothing at all wrong with working for industry or taking industry money. It is, however, a serious problem of integrity to take industry money and pretend you are immune to any influence of such financial conflicts. The egregious financial conflicts are all the more troubling given the expertise that is missing or severely underrepresented from this committee, e.g., public health leaders and biostatisticians. Does the Alzheimer's Association truly not recognize the value of expertise from other major clinical and diagnostic challenges, such as prostate cancer, breast cancer, HIV, or even ulcers? The premise that diseases should be based on biological, rather than symptomatic definitions, is stated

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in these criteria as if it's a clever contemporary idea that will vastly improve care. This idea is neither contemporary nor, in this setting, clever. When there is uncertainty about the core biological/pathological process for a disease, it is certainly not preferable to define the disease based on that process. Even when there is clarity about the biological process, we distinguish between that core pathophysiology and the physiologic manifestations, e.g., we distinguish between HIV infection and AIDS. This distinction is obviously incredibly important for patients, families, clinicians, and policy makers. There is substantial potential harm to defining a disease as a biomarker when there is any uncertainty in the physiology of the disease or measurement of the biomarker. The earliest detectable changes linked to AD emerge 20+ years prior to diagnosis, suggesting the development of dementia -- from very first changes to clinical diagnosis -- takes at least 20 years, and possibly longer. In vivo amyloid assessments were only developed (almost) 20 years ago. We have no direct data on amyloid PET and the development of AD following the earliest detectable signs of AD through to clinical manifestations. What we have are cross-sectional studies or studies with follow-up windows far shorter than the natural history of disease. Given that the link between any known biomarkers and cognitive manifestations of AD is uncertain -- we do not know if dementia will ever occur in the individual's lifetime and if so, when -- the justification for tying the biomarkers to Alzheimer's disease is unclear. Call the biomarkers what they are: measures of amyloidosis or tauopathy. The proposed use of biomarkers is even more troubling given where we are in the development of the biomarkers. Standards are not clear. The gold standard is often defined in a circular fashion or validation is based on an extremely low bar, eg., distinguishing currently impaired to unimpaired individuals (or distinguishing people who will become impaired within a year to those who remain healthy). The test-retest reliability of blood-based biomarkers is not established. Comorbid conditions may impact biomarker performance in critical ways. Available evidence is in profoundly non-representative samples and (further) samples selected with extreme bias. These biases may mean our understanding even for people in the studies is wrong, and certainly we have very limited information on biomarker performance in people who are not White, are not urban residents, are of lower socioeconomic status, etc. As noted by colleagues, serious consideration must be given to the consequences of substantial changes in the use of labels and underlying biological framework that the public and patients associate with the 1:1 presence of a disease with clinical consequences. These criteria are worse than half-baked. Start over with an independent committee. Prioritize above all what will improve the health and well-being of people who are now or will be affected by Alzheimer's disease.

Revised Criteria for Diagnosis and Staging of Alzheimer's Disease: Alzheimer's Association Workgroup: Comments by SNMMI Brain Imaging Council (BIC), Endorsed by the SNMMI Mary Ellen Koran, MD, PhD, Neil Horner, MD, Satoshi Minoshima, MD, PhD, Ciprian Catana, MD, PhD on behalf of the SNMMI Brain Imaging Council Helen R. Nadel, MD President, Society of Nuclear Medicine and Molecular Imaging We would like to commend the authors for their comprehensive review of the subject. We applaud the incorporation of a biological definition of diseases. As nuclear medicine physicians and diagnostic radiologists, we routinely assess PET for the spatial pattern and severity of disease, in addition to proteinopathic information, across a spectrum of conditions. Therefore, we would recommend the inclusion of a more nuanced interpretation of tau PET, moving beyond a dichotomous (+/-) classification. As research progresses and establishes associations between the location of tau deposition and symptom presentation, we anticipate that a more specific localization of tau in the neocortex will prove crucial for distinguishing the five characteristic AD phenotypes outlined in the guidelines and other tauopathies. However, further research will be necessary to implement such distinctions. We also value the emphasis placed by the group on the non-interchangeability of

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imaging and fluid biomarkers for many intended purposes. Notably, fluid biomarkers currently lack the capacity to offer biological staging based on the topographic localization of tau. Additionally, the guidelines appropriately highlight the need for further evaluation of clinical scenarios confounding plasma biomarkers before their widespread approval and utilization. It is pertinent to underscore the significant role of FDG PET in the evaluation of dementia patients. FDG PET serves as a well-established entry point in the molecular imaging evaluation, particularly in cases of atypical dementia presentation where the diagnosis of AD is not straightforward. Over decades, FDG PET has played a pivotal role in differentiating AD from frontotemporal lobar degeneration and Dementia with Lewy bodies. Moreover, until a TDP-43 biomarker becomes available, there is evidence suggesting the crucial role of FDG PET in diagnosing limbic-predominant age-related TDP-43 encephalopathy (LATE), a prevalent and clinically significant condition. On a practical note, the accessibility and affordability of FDG with the challenges associated with obtaining amyloid and tau agents in certain regions of the country. Given the extensive use of FDG PET in the United States as well as in the rest of the world, its established role in evaluating dementia patients merits greater attention in the criteria. We express our appreciation for the guidelines' recognition of the importance of quantitative analysis in amyloid and tau PET imaging. We advocate for the consideration of quantitative analysis as a requisite in interpreting FDG PET examinations, as it enhances both sensitivity and specificity, facilitating more accurate longitudinal follow-up of disease progression. Furthermore, we believe it is imperative for quantification algorithms to undergo evaluation with scans representative of diverse population demographics, various scanners, and radiotracers used in clinical settings. Additionally, uniform recommendations for imaging acquisition protocols and specified anatomic regions defining the medial temporal or neocortical meta-ROIs for tau quantitation will be crucial. References (alphabetical) Brown RK, Bohnen NI, Wong KK, Minoshima S, Frey KA. Brain PET in suspected dementia: patterns of altered FDG metabolism. *Radiographics*. 2014 May-Jun;34(3):684-701. doi: 10.1148/rg.343135065. PMID: 24819789 Buciuc M, Botha H, Murray ME, Schwarz CG, Senjem ML, Jones DT, Knopman DS, Boeve BF, Petersen RC, Jack CR Jr, Petrucelli L, Parisi JE, Dickson DW, Lowe V, Whitwell JL, Josephs KA. Utility of FDG-PET in diagnosis of Alzheimer-related TDP-43 proteinopathy. *Neurology*. 2020 Jul 7;95(1):e23-e34. Epub 2020 Jun 9. PMID: 32518145 ChÃ©telat G, Arbizu J, Barthel H, Garibotto V, Law I, Morbelli S, van de Giessen E, Agosta F, Barkhof F, Brooks DJ, Carrillo MC, Dubois B, Fjell AM, Frisoni GB, Hansson O, Herholz K, Hutton BF, Jack CR Jr, Lammertsma AA, Landau SM, Minoshima S, Nobili F, Nordberg A, Ossenkoppele R, Oyen WJG, Perani D, Rabinovici GD, Scheltens P, Villemagne VL, Zetterberg H, Drzezga A. Amyloid-PET and 18F-FDG-PET in the diagnostic investigation of Alzheimer's disease and other dementias. *Lancet Neurol*. 2020 Nov;19(11):951-962. doi: 10.1016/S1474-4422(20)30314-8. PMID: 33098804 Frisoni GB, Bocchetta M, ChÃ©telat G, Rabinovici GD, de Leon MJ, Kaye J, Reiman EM, Scheltens P, Barkhof F, Black SE, Brooks DJ, Carrillo MC, Fox NC, Herholz K, Nordberg A, Jack CR Jr, Jagust WJ, Johnson KA, Rowe CC, Sperling RA, Thies W, Wahlund LO, Weiner MW, Pasqualetti P, Decarli C. Imaging markers for Alzheimer disease: which vs how. *Neurology*. 2013 Jul 30;81(5):487-500. doi: 10.1212/WNL.0b013e31829d86e8. PMID: 23897875 Grothe MJ, Moscoso A, Silva-RodrÃ©guez J, Lange C, Nho K, Saykin AJ, Nelson PT, SchÃ©ll M, Buchert R, Teipel S; Alzheimer's Disease Neuroimaging Initiative. Differential diagnosis of amnesic dementia patients based on an FDG-PET signature of autopsy-confirmed LATE-NC. *Alzheimers Dement*. 2023 Apr;19(4):1234-1244. doi: 10.1002/alz.12763. Epub 2022 Aug 15. PMID: 35971593 Minoshima S, Cross D, Thientunyakit T, Foster NL, Drzezga A. 18F-FDG PET Imaging in Neurodegenerative Dementing Disorders: Insights into Subtype Classification, Emerging Disease Categories, and Mixed Dementia with Copathologies. *J Nucl Med*. 2022 Jun;63(Suppl 1):2S-12S. doi: 10.2967/jnumed.121.263194. PMID: 35649653

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Neurodegenerative Diseases (220.6.13).¹ Wwww.cms.gov, www.cms.gov/medicare-coverage-database/view/ncd.aspx?ncdid=288&ncdver=2&=. Accessed 9 Nov. 2023. Nelson PT, Dickson DW, Trojanowski JQ, Jack CR, Boyle PA, Arfanakis K, Rademakers R, Alafuzoff I, Attems J, Brayne C, Coyle-Gilchrist ITS, Chui HC, Fardo DW, Flanagan ME, Halliday G, Hokkanen SRK, Hunter S, Jicha GA, Katsumata Y, Kawas CH, Keene CD, Kovacs GG, Kukull WA, Levey AI, Makkinejad N, Montine TJ, Murayama S, Murray ME, Nag S, Rissman RA, Seeley WW, Sperling RA, White CL 3rd, Yu L, Schneider JA. Limbic-predominant age-related TDP-43 encephalopathy (LATE): consensus working group report. *Brain*. 2019 Jun 1;142(6):1503-1527. doi: 10.1093/brain/awz099. PMID: 31039256 Roytman M, Chiang GC, Gordon ML, Franceschi AM. Multimodality Imaging in Primary Progressive Aphasia. *AJNR Am J Neuroradiol*. 2022 Sep;43(9):1230-1243. doi: 10.3174/ajnr.A7613. Epub 2022 Aug 25. PMID: 36007947 Sawyer DM, Kuo PH. Top-Down Systematic Approach to Interpretation of FDG-PET for Dementia. *Clin Nucl Med*. 2018 Jun;43(6):e212-e214. doi: 10.1097/RLU.0000000000002115. PMID: 29659399 Shivamurthy VK, Tahari AK, Marcus C, Subramaniam RM. Brain FDG PET and the diagnosis of dementia. *AJR Am J Roentgenol*. 2015 Jan;204(1):W76-85. doi: 10.2214/AJR.13.12363. PMID: 25539279

The revised clinical criteria for Alzheimer’s disease (AD) represent an updated version of previous criteria, which partially incorporate feedback and inputs received during a first drafting phase. In the revised version, certain concepts have been reinforced, while other aspects have been either rejected or accepted but with significant modifications. We list here some relevant issues that would need consideration: 1. It is commendable and intriguing that the new criteria aim at keeping up as much as possible with the times and at serving as a bridge between research and clinical care. This is most important in a transitional phase like this with disease-specific therapies that begin to emerge, and novel biomarkers that are increasingly finding their own role in clinical settings. However, it is crucial to acknowledge that, from a global perspective, the real world may not yet be fully prepared to implement these criteria, at least in clinical settings. 2. Notably, the upcoming new disease-modifying therapies are going to be available in a few countries only, and so far there are no plasma biomarker assays that have received regulatory approval for clinical use. Moreover, despite being ²expected to change soon³, there is still an inadequate amount of peer-reviewed data to support an equivalent use between cerebrospinal fluid (CSF) and blood-based biomarkers. Furthermore, Tau PET imaging, which is going to assume a more and more remarkable role in AD diagnosis and staging (as acknowledged in this second version of the criteria), is accessible in a limited number of specialized centers only. Importantly, the proposed staging system is strongly grounded on tau PET-imaging findings, while the status of the fluid biomarkers is defined as ⁴conceptual⁵. Given the limited availability of Tau PET-imaging facilities, this represents a serious limitation for a general application of the new criteria. 3. The distinction of Tau biomarkers into two categories, T1 and T2, appears reasonable, considering that the most commonly used phosphorylated N-terminal fragment analytes (i.e., ptau 181, 217, and 231) correlate better with the amyloid burden than assessments based on Tau-imaging. Nonetheless, Core 2 biomarkers are currently not applicable for clinical use. Considering the strict association between Core 2 biomarkers and the level cognitive impairment, their availability is crucial for the therapeutic decision algorithm , especially at early clinical stages in the absence of clear-cut cognitive symptoms. 4. Although Table 1 and 2 explanatory legends clarify that pT205, MTBR-243 and non-phosphorylated tau fragments do not have undergone the same level of validation testing that other biomarkers did, they are listed as biomarkers intended for clinical use. In the first draft of the new criteria, there was a clear distinction between those biomarkers that are ready for clinical use (Table 1 and Table 2) and those biomarkers that are suitable for research and for potential clinical use in the future (Table 3, which does no longer exists in the new version of the manuscript). The rationale

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for removing this separation is unclear. 5. Still, the distinction between T1 and T2 categories risks to generate some confusion. The A-T1 and A-T2 profiles need to be better defined. In particular, it is unclear whether it is recommended or not to proceed with the assessment of status A using any possible method (i.e., CSF, PET, blood) before concluding for a negative status A. This issue seems of particular relevance considering the potentially decisive role of the A-T1 profile in determining patients' eligibility for disease-modifying treatments. 6. The new version of the criteria makes their practical application difficult on a large scale. Assessment of core biomarkers is currently inaccessible to most clinical settings worldwide, and restricts the possibility to take part in research projects a large proportion of Centres. In other words, the new criteria proposed here, are conceptually very advanced, but their generalized application seems problematic at the moment outside the USA. 7. It remains to be fully clarified the reason why some well consolidated biomarkers of neurodegeneration and neuroinflammation were not considered for their use at present or at least in the future. For instance, neurogranin has shown a strong correlation with measures of cognitive impairment; YKL-40 is potentially more specific than GFAP as biomarker of astrocytic activation; sTREM2 is the only reliable biomarker we currently have for microglial activation; etc. While the criteria are very innovative and comprehensive in considering most potential biomarkers of tauopathy they appear more restrictive with other valuable biomarkers. 8. The biological definition of Alzheimer's disease (AD), in line with the differentiation between disease and illness, holds scientific validity. However, it is crucial to recognize the profound fear associated with the concept of Alzheimer's disease within the general population, particularly among cognitively unimpaired individuals with AD who may mistakenly associate their diagnosis with dementia, dependency, and mortality. It should be stressed more the concept of disease as essential, major risk factor for developing illness, whose clinical progression remains hardly predictable on a single subject basis. In other words, defining the disease solely based on its pathological substrates, rather than considering the clinical phenotype, could potentially lead to diagnostic confusion. Relying exclusively on a biomarker-based diagnosis would demand robust evidence of a strong link between biomarker positivity and a significantly high likelihood of subsequent clinical progression. Yet, data on the follow-up of cognitively unimpaired individuals who are biomarker-positive indicate that the majority of them do not exhibit cognitive decline over time. Finally, assuming that A+ populations will develop dementia if they live long enough is a very strong concept. Timing for passing from the Core 1 to Core 2 tau condition is indeed unknown. This means that, in principle, no therapy might be administered to patients with disease but without illness. 9. The attempt to move from clinical heterogeneity to a neurobiological staging of AD is definitely the most urgent need to be addressed in the framework of DMTs becoming available. Nonetheless, precision medicine is becoming a more and more relevant issue in medicine. The effort of identifying quantitative measures reflecting individual indexes of risk/resilience to AD pathology is also important. At a single subject level, FDG-PET imaging (in combination with measures of pathological burden) might contribute in providing such an information. 10. Again, defining diseases biologically, rather than based on their syndromic presentation, has become a standard in many areas of medicine (e.g., oncology), and is becoming a unifying concept common to all neurodegenerative diseases, not just AD. This stands in strong contrast with the proposal of development of a personalised Alzheimer's disease risk profile in asymptomatic at-risk people (Dubois et al., 2021). A very interesting theoretical paper about the disease/illness distinction (Tresker, 2020) introduces an useful qualification: "The key to differentiating when conditions such as AD should be viewed as risk instead of disease may be the confidence with which diagnostic methods can unequivocally identify if and when the asymptomatic cases will turn into symptomatic cases and the prodromal cases will turn

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into manifest cases (e.g., dementia). High confidence might call for viewing as disease whereas low confidence might all for viewing as risk. However, this is easier said than done and the typology cannot directly help in this regard. Can we confidently state that we have robust data for quantitative prediction for all the conditions diagnosed on the basis of Core 1, and staged clinically as 1,2 and even 3? This is a crucial condition to use the term disease rather than risk. Emphasizing the distinction between Alzheimer's disease and Alzheimer's dementia / Alzheimer's cognitive impairment could be a useful approach. Even though the term "prodromal AD" or "patients at risk" has been excluded, the Authors should operationalize some research criteria to detect cognitive disorders at this stage. Actually, no suggestion or proposal to research minimal signs by using innovative neuropsychological tests have been proposed in the present document. This distinction can help to reduce the stigma associated with the diagnosis and provide a more accurate representation of the continuum from preclinical to clinical stages of the disease. We reiterate here again some other concerns that were already raised in our previous comment: 1) The criteria state that AD can be diagnosed based on the presence of any abnormal core AD biomarker. However, the scenario of individuals who are A- and T+ (e.g., with elevated levels of CSF p-tau due to high increase in CSF t-tau) is not adequately addressed. This common occurrence deserves consideration in the criteria to avoid potential misdiagnoses. The manuscript should provide guidance on how to interpret such cases and whether an A+ biomarker is always needed for an accurate diagnosis. 2) Concerning the conceptual Biological Staging with Fluid Biomarkers it is surprising that the A+T1- profile, commonly observed in both cognitively unimpaired and cognitively impaired subjects in clinical practice, is not discussed in this context. Addressing the significance of this profile in the context of biological staging for fluid biomarkers would provide a more comprehensive understanding of the criteria's applicability. 3) While the potential role of connectivity EEG as a biomarker is briefly introduced, we think that its use as a biomarker of brain connectivity should be further explored in order to provide hints to intercept those patients who will progress from the disease to the illness 4) The list of confounding conditions on biomarker results should mention autoimmune encephalitis (Bastiaansen, 2021) In conclusion, we once again judge these revised criteria an important step towards a biologically defined AD diagnosis and staging. However, the global applicability of these criteria faces challenges related to standardization, harmonization, accessibility, and cost-effectiveness of most of the biomarkers considered. The whole criteria, in this new version, may be too intricate for clinical use outside few specialized centers. While the use of these novel criteria and the consideration of a wide range of A, T, N, I, S and V biomarkers may be appropriate and commendable in research contexts, we still consider that some refinements and simplifications may be necessary to enable seamless implementation in clinical contexts globally.

Joint comments on behalf of the LuMind IDSC Foundation (www.lumindidsc.org) and the National Task Group on Intellectual Disabilities and Dementia Practices (www.the-ntg.org) regarding the Revised Criteria for Diagnosis and Staging of Alzheimer's Disease: Alzheimer's Association Workgroup. LuMind IDSC and the National Task Group on Intellectual Disabilities and Dementia Practices vigorously support the NIA-AA revised clinical criteria for Alzheimer's disease. Key recommendations pertinent to Down syndrome-associated Alzheimer's disease (DS-AD) and our comments for these recommendations are: 1. Down syndrome should be considered Stage 0 Alzheimer's disease. We concur this separate stage 0 should recognize Down syndrome and other genetically determined Alzheimer's disease. This recommendation is appropriate and justified by the pathophysiology of DS-AD, which is comparable to other forms of AD such as LOAD, and the fact that DS-AD is a genetic form of AD that is highly penetrant (up to 95%, McCarron et al. 2017) and with average age of symptom onset in the mid-50s (Iulita et al. 2022) in the DS population. 2. AD diagnosis using plasma biomarkers

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should be an objective as part of the biological diagnostic criteria. As the draft revision states: The most significant advance in AD diagnostics in recent years has been the development of plasma biomarkers with excellent diagnostic performance. This now makes biological diagnosis of AD (which previously required PET or CSF assays) generally accessible and is projected to revolutionize research and clinical care. We endorse the recommendation to move toward biological criteria for diagnostic staging of AD through plasma biomarkers, but in the case of DS-AD, the plasma biomarkers being developed rapidly for the general population have not been validated for the DS population, which requires separate plasma biomarker cut-points to be established or LOAD cut-points to be confirmed to be the same in DS-AD. For example, cut-points that correlate A+ by Aβ PET with plasma Aβ₄₂/40 or p-tau₂₁₇ have not been determined yet. Therefore, the plasma biomarkers are not generally accessible yet for early AD diagnosis in the DS population. We recommend noting any variations in cut-points specific to Down syndrome as they are determined. 3. Categorization of fluid analyte and imaging biomarkers may slightly differ in DS-AD. NFL is categorized in Table 1 as a "Biomarker of non-specific processes involved in AD pathophysiology". In DS-AD where the AD population is younger and there are less co-occurring neurodegenerative diseases, NFL is more likely to be caused by AD than it is in LOAD. We recommend to add a comment to that effect after the Table 1. 4. Progression in the biological stages might be accelerated in DS-AD. Based on recent data from Wisch et al. under submission, tau pathology acceleration in DS-AD is significantly faster in DS-AD than in ADAD. We recommend adding below Table 6 a comment to that effect or by extending the sentence with the words in italic "will often be due to co-morbid pathology or from having Down syndrome." 5. Diversity should include considerations for the DS population and for other populations with neuroatypical conditions. We recommend adding to Item (10), page 26, line 792 ff., "Diversity and need for more representative cohorts," language to include adults with Down syndrome and with various lifelong neuro-atypical conditions, including intellectual disabilities, in more observational studies, clinical trials and post-marketing studies. The Down syndrome population served as a key resource for the research and discovery of the pathobiological basis for AD, yet this population is being left behind for diagnostic and therapeutic access to disease modifying therapies. We strongly recommend the inclusion of people with Down syndrome in on-going and future observational studies that determine the biological criteria for the presence of Alzheimer's disease or other forms of dementia. We thank you for including the Down syndrome population in these Revised Criteria for Diagnosis and Staging of Alzheimer's Disease as it will help address important inequities that this population is still facing.

The current draft guidelines for Alzheimer's Disease (AD) research, focusing heavily on advanced diagnostics like biomarkers and PET imaging, present significant challenges for low- and middle-income countries (LMICs). These challenges create a risk of exclusion from global AD research initiatives. Integrating a step-wise approach, akin to the World Health Organization's (WHO) STEPwise approach to noncommunicable disease (NCD) surveillance, could offer a more inclusive and adaptable framework for AD research across diverse economic contexts. Challenges for LMICs with Current AD Research Guidelines: * Resource Constraints: High-tech diagnostics like PET scanners and advanced laboratory infrastructure for biomarker analysis are often scarce or entirely unavailable in LMICs. For example, using IAEA data, only 7 African countries can access a PET scanner, with a ratio of less than 1 PET scanner(s) per million people (Algeria, Egypt, Kenya, Libya, Morocco, South Africa, Tunisia). This lack of resources can exclude these countries from participating in or contributing to AD research that adheres to these guidelines.? * Cost Implications: The financial burden of acquiring, maintaining, and operating advanced diagnostic technology is prohibitive for many LMICs. This includes the costs of

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training personnel and establishing quality control mechanisms. ? * Accessibility and Equity Issues: The focus on high-tech diagnostics may exacerbate global health inequities. Populations in LMICs, already underserved in healthcare, would be further marginalized in AD research and potentially in deriving benefits from research advancements. ? Advantages of Incorporating a Step-Wise Approach: * Flexible Adaptation: A step-wise approach allows for customization based on available resources. Initial steps can focus on low-resource methods (e.g., questionnaires and basic physical exams) to assess risk factors and early signs of AD, while later steps could incorporate more advanced diagnostics as resources allow. * * Emphasis on Comparative Information: By focusing on core, expanded, and optional modules of data collection, a step-wise approach facilitates cross-country research. It ensures that even with varying levels of technological advancement, countries can contribute valuable data that are comparable at a global level. It would also facilitate comparisons over time, allowing for data to be cross-walked by location and time. ? * Capacity Building: This approach can help build local capacity in AD research and care. LMICs can progressively develop their diagnostic capabilities, starting with basic assessments and moving towards more advanced technologies as resources become available. ? * Inclusivity in Global Research: Integrating a step-wise approach would ensure that LMICs are not excluded from global AD research networks. This inclusivity is crucial for understanding the global epidemiology of AD and for developing interventions that are applicable across diverse settings. ? * Potential for Broader Health System Strengthening: Implementing a step-wise approach in AD research could have spillover benefits for other areas of healthcare in LMICs, as it requires and promotes the development of basic healthcare infrastructure, surveillance systems, and workforce training. ? The current AD research guidelines emphasize state-of-the-art diagnostics, their implementation may be impractical or exclusionary for many LMICs and lower resourced settings in HIC. Integrating a flexible, step-wise approach would ensure broader participation, enhance the comparability of data across countries, and ultimately contribute to a more equitable and comprehensive understanding of AD globally.

When the 1984 NINDS/ADRDA criteria were updated to address the then newly available in vivo biomarkers in new 2011 research/clinical criteria for Alzheimer's disease (Jack et al., 2011), the addition of a research diagnosis of preclinical AD (Sperling et al., 2011) was a critical turn for the field. In 2018, the field moved further along this new road to a research staging system that ignored clinical symptoms altogether (Jack et al., 2018). While some hailed this as a new medical era for AD others raised concerns, notably setting aside exactly what matters to families and patients and premature closure for etiologic and mechanistic research (e.g., Glymour et al., Eur J Epidemiol, 2018). These concerns are brought to higher relief in the present document, which elevates this staging system to diagnostic criteria in the setting of more widely available plasma biomarkers, new marginally effective and potentially risky therapies, and increasing evidence that dementias of mixed pathology are the most common among older adults. Redefining the pathology as the disease has some advantages but is problematic for a number of reasons. The term Alzheimer's disease is widely used by physicians and the general public to indicate what may have surpassed cancer as our most dreaded disease. Using the same term to refer to the underlying pathology irrespective of symptoms will introduce potential misunderstandings among physicians, their patients, and the broader public. To avoid confusion, fear, and anxiety that could be an unintended consequence of the proposed criteria, many of us would prefer a term like brain amyloidosis or the neuropathologists' Alzheimer disease neuropathologic changes (ADNC; Hyman et al, Alzheimer's & Dementia, 2011) to stress the difference, i.e., using a term that specifically refers to the detected neuropathological phenomena rather than the clinical correlates of those changes. More broadly, since this confusion is likely here to stay and can have

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significant emotional consequences, I suggest that clinicians and researchers alike now avoid using the term Alzheimer disease alone, and instead either refer to Alzheimer disease neuropathologic changes (for the pathology) or to Alzheimer dementia ([or MCI due to AD] for the clinical syndrome). Another major problem is the current lack of clarity about when and even whether someone with positive biomarkers might develop the clinical syndrome, which makes the distinction between the pathology and clinical disease more critical. We have long seen pathology without a history of symptoms in post-mortem studies, and in vivo measurement confirms that pathology can be present for a long time without clinical disease. Because we've only had biomarkers available during life for a limited time, and we can't know how long pathology has been present at baseline, along with limited observation times due to mortality and loss to follow up, it is difficult to characterize the true duration of pathology before symptoms arise, and whether everyone eventually would become impaired if they lived long enough. We do know, however, that predictive value is limited as to whether an individual will develop dementia, and very poor for when (for this, imaging is a bit better). Indeed, the disease trajectory is heterogenous, and the manifestation of clinical syndromes at a given level of pathology is ultimately a function of multiple other factors such as genetics, life experiences, and comorbid conditions. Larger studies with diverse representation will be required to fully estimate person-specific risk. Notably, current samples are heavily biased toward the white and highly educated, those with family history, and those with symptoms (recognized or not); all of these may bias estimates toward greater risk sooner. When we move from CSF biomarkers to plasma, where analyte concentrations are much lower, the problems can be more complex. Plasma biomarkers have improved greatly, but still have issues with technical reliability, day-to-day variability, changes with renal and other physiologic measures, and other unknown factors. Lack of reference standards for plasma biomarkers combined with fuzzy "indeterminate zones" further complicates matters. More critically, perhaps, like the more established CSF and imaging biomarkers, their ability to predict future cognitive status—the issue of relevance to patients and their families—is limited, and data are particularly lacking on persons from racially and ethnically minoritized communities. Moreover, the major advantage of plasma biomarkers is their potential widespread availability, a double-edged sword given the complex issues in interpretation. With respect to treatment implications, the new criteria do not advocate early intervention, in keeping with current indications for anti-amyloid therapies, but they do pave the way. The hoped-for scenario is therapy early, before symptoms, with a blood test and FDA-approved treatment with appealing potential to center initial dementia screening and care in primary care, which is probably a logistical and economic necessity. However, at present, too little is known about amyloid's role in the pathological cascade and how it plays out over time to allow risk-benefit discussions about the use of anti-amyloid therapeutics in those without symptoms. This pre-clinical designation of Alzheimer's disease is being presented as carcinoma in situ, but we don't know whether the biomarkers' performance will compare to screening colonoscopies (which extensive evidence suggests saves lives) or to the prostate-specific antigen test ([PSA] which extensive evidence suggests does more harm than good). The confusion of a test that claims to detect Alzheimer's disease (rather than serving as a marker of future risk) and a therapy with complex adverse effects could lead to false hopes, and costly, potentially dangerous off-label use. Such use is unlikely at present given cost and insurance reimbursement limits but seems invited by the diagnostic framework itself. I believe that a more circumspect title and more cautious framework is in order.

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The American Geriatrics Society (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

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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

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(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

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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

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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: ¶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.

I would like to express my sincere appreciation of how the scientific community is integrated in the process of this project. All major concerns I had with the first version have been addressed. I thank the authors for the openness and the significant adjustments that have been made from version 2 to version 2. There are conceptual issues, which are not shared by all (e.g. AD diagnosis based on amyloid only, AD diagnosis in asymptomatic individuals) and there are concerns about the clinical applicability given the high complexity and dynamics of the concept. Beyond this, however, I do not have any specific comments anymore. Great work and great community engagement!

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Feedback provided here - however, I will also email Maria Carrillo to provide the feedback in a more reader friendly mode. 2023 AA Criteria Draft 2 Feedback Submitted by: Akin Akinwonmi, Global Medical Affairs¹; Joana Amorim Freire, Global Scientific Communications¹; Laura Lenzo, Global Scientific Communications¹; Margherita Carboni, Indication Lead Neurology¹; Martin Guess, Global Medical Affairs¹; Sayuri Hortsch, Principal Biostatistician²; Alexander Jethwa, Research and Development²; Laura Parnas, US Medical and Scientific Affairs³; Maria-Magdalena Patru, US Medical and Scientific Affairs³; Anuja Neve, Product Development Neuroscience⁴; Susanne Ostrowitzki, Product Development Neuroscience⁴ 1Roche Diagnostics International, Rotkreuz, Switzerland 2Roche Diagnostics GmbH, Penzberg, Germany 3Roche Diagnostics Corporation, Indianapolis, USA 4F. Hoffmann-La Roche Ltd, Basel, Switzerland Link to Guideline draft: <https://aaic.alz.org/nia-aa.asp> Summary: We welcome the AA Revised Criteria for Diagnosis and Staging of Alzheimer's Disease, in which the workgroup has carefully considered feedback from a broad array of stakeholder groups. The revised draft has taken important feedback into consideration and has been developed in a very open and collaborative way. In the updated draft, the workgroup has clearly considered the feedback and incorporated a number of important changes, including clarifications on the way biomarkers are categorized (eg. as individual or hybrid ratios), as well as acknowledging the importance that clinical validation and regulatory approvals play in bringing biomarker assays into routine clinical practice. While these changes are well received, we welcome the opportunity to contribute and would like to bring the below considerations to the workgroup prior to publication. We hope that our feedback is of value and will help ensure that this document is comprehensive and will support the transition from research to future clinical guidelines in Alzheimer's Disease (AD). Our feedback focused on: A framework for clinical use should be clearly presented, and the document should be consistent about the regulatory status of the assays being discussed, for example blood-based biomarkers (BBBM) which are validated and approved for a specific intended use. It is important to convey that for currently approved hybrid ratios, the regulatory approval is against a reference standard (e.g. Amyloid PET). The authors should consider including total-Tau and sTREM in table 1. For biomarker assays with an indeterminate zone, the workgroup should clarify that it is not a requirement and provide guidance on what further testing may be needed in patients falling in an indeterminate zone of plasma or CSF biomarker tests. This will reduce the potential for unnecessary testing and diagnostic delay. The workgroup proposes that these guidelines form a basis for the separation of biological and syndromic diagnosis of Alzheimer's disease and neurocognitive disorders. It should be acknowledged that there is no consensus on this. Lastly, due to the complexity and rapid changes in the field of Alzheimer's disease, we ask that a brief synopsis is made available alongside the full publication. Framework for clinical use: The fact that no blood-based biomarker has yet received formal approval by regulatory entities should be consistent throughout the text. Along the main text (Line 26, 68-69), it is mentioned that some (but not all) [blood-based biomarkers] demonstrate excellent diagnostic performance. Consider acknowledging in the text that while there are studies demonstrating excellent diagnostic performance for blood-based biomarkers, additional prospective studies which better reflect their real-world performance are needed for clinical implementation, such as their use in clinical practice in different settings (primary vs secondary), and on diverse populations (e.g. race, comorbidities), along with their regulatory approval/clearance which underscores their safety and effectiveness. Line 69-71 [blood-based biomarkers diagnostic performance] now makes the biological diagnosis of AD (which previously required PET or CSF assays) generally accessible and is projected to revolutionize clinical care and research. The focus, here, is on the use of blood-based biomarkers to replace CSF/PET confirmatory testing. However, blood-based biomarkers are expected to streamline the AD diagnostic

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pathway and show clinical value through several intended uses. They may be used in clinical practice as a triage test to rule out patients without amyloid pathology, rule in, or replace CSF/PET confirmatory testing in some patients, monitor disease progression or monitor treatment, among others.¹ Each intended use needs to be validated in the appropriate intended use population and the specific BBBM needs to be approved by the regulatory entities. Therefore, although they hold the promise to make AD diagnosis more accessible and are projected to revolutionize clinical care and research, we strongly suggest to make it clear throughout the text that none of these assays (except plasma Sysmex Ab42/40, which has received regulatory approval in Japan²) have yet received formal approval as an in vitro diagnostic (IVD). Moreover, it should be noted that currently, CSF and amyloid PET are the only two recommended methods to qualify patients for the amyloid targeting therapies³. Line 242 states In contrast plasma p-tau is used as a standalone assay. We suggest replacing it with "In contrast, plasma p-tau demonstrated very good clinical performance in clinical trials and studies as a standalone biomarker. Table 2 shows intended uses for imaging, CSF and plasma biomarker assays. The first intended use is defined as Diagnosis" where, instead of focusing on proteinopathies, a classification more useful for research purposes than for clinical practice, this table should group assays by their ability to identify amyloid or tau pathology based on how they correlate with either amyloid, or with tau PET scans. This will also clarify the use of the hybrid ratios" for amyloid pathology detection based on their clinical performance and concordance with amyloid PET scan (see paragraph C). This classification will therefore include all ratios concordant with amyloid PET, as well as pTau217 (and pTau181 as per paragraph D). The tau pathology category would include biomarkers which correlate well with tau PET, which might also include pTau217 and pTau181, as per recent literature^{4,5}. Please see a suggestion for Table 2 below: Identification of pathology (Triage testing - rule in/out, Confirmatory testing) *Plasma **CSF Imaging Amyloid pTau181, pTau217, pTau217/np-tau 217 Abeta42/40, pTau181/Abeta42, tTau/Abeta42 Amyloid PET Tau pTau181, pTau217, pTau217/np-tau 217 Tau PET *No FDA approved/cleared assays at this time **FDA approved/cleared assays concordant with amyloid PET scan available. The same approach for the A/T1/Hybrid ratios could be applied for the Staging, prognosis and as an indicator of biological treatment effect intended use in Table 2. The classification used for the hybrid ratios is impractical and confusing. If the focus currently is on detecting amyloid pathology using fluid biomarkers, by the way of amyloid PET concordance, then, it would be more useful to split it into assays which detect amyloid positivity and include all ratios listed here, as well as pTau217, and pTau181 as per table 2 suggestion and comment below. Plasma pTau181 is not included in Table 2, as per the argument that it has "not yet demonstrated diagnostic accuracy equivalent to approved CSF assays" (Line 146-148). Based on recent literature, we suggest to include pTau181 as a plasma assay that can be used both for identifying amyloid pathology, as well as tau pathology^{5,7,8,9}. Studies have shown that plasma pTau181 differentiated AD dementia from non-AD neurodegenerative diseases with data from one study showing an accuracy similar to that of CSF p-tau181 and Tau PET (AUC = 0.94-0.98)¹⁰; another study showed that plasma pTau181 is an excellent predictor of both amyloid PET and tau PET, validating these findings in two large cohorts¹¹. It is important to emphasize that accuracies demonstrated in the current literature may not reflect the diagnostic accuracy in routine clinical use, as currently, the high clinical performance of many of these assays is only demonstrated in retrospective batch measurements in research cohorts for specific disease stage populations, which may not be representative of the real-world scenario (e.g. in terms of minorities/comorbidities and preanalytical handling, both of which can have an impact on biomarker levels and thus potentially also clinical performance). Biomarker categorization: Following on our feedback on the first version of this document, we reiterate our

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advise toward the inclusion of total Tau (tTau) as a non-specific marker of neurodegeneration in Table 1, as it is elevated in a range of conditions associated with neuroaxonal injury and the results of plasma tTau studies suggest that its role is akin to CSF tTau[™]s as a non-specific biomarker of neurodegeneration¹². Additionally in Table 1, we suggest to include soluble TREM2 together with GFAP in the I (inflammation) category, since it is becoming increasingly studied in the field, and it is described in the text as "another I biomarker that received recent attention in research [...] which reflects microglial reactivity" (Line 646-648). Clinical performance of the FDA approved/cleared biomarkers: Line 208-211 : "Accordingly, regulatory approval of CSF assays (Supplemental Table 1) was anchored to positive/negative visual reads of amyloid PET: sensitivity/specificity (or positive % agreement/negative % agreement) of approved CSF assays ranged from 97%/84% to 91%/89% to 88%/92% against this reference standard. 50-52". We would like to ask for these values to be corrected as per their respective Decision Summaries and references updated as needed: For the first assay, the 97%/84% for sensitivity/specificity data do not represent the clinical performance at the same cutoff; as the assay has two cutoffs and an indeterminate zone, sensitivity and specificity for each of the two cutoffs should be included for clarity¹³. The performance for the other two assays should be listed as: 88%/93%¹⁴ and 85%/94%¹⁵ Certified reference materials: In Text Box 3, the first limitation of biomarkers lists "Lack of certified reference methods and materials (except for CSF A β 42/40, where these are available)". This is inaccurate as the Certified Reference Materials is only available for A β 42, not for A β 40¹⁶. Buolo et al describes the first amyloid A β 1-42 certified reference material for re-calibrating commercial immunoassays¹⁷. Indeterminate zone: Regarding the section "3.5) Conservative treatment of values near a cutpoint; the indeterminate zone, and based on our previous feedback on the first version of this document, Most available clinical assays are able to provide a single validated cutpoint that optimizes sensitivity and specificity for the clinical intended use, without the need for two cutoffs and an indeterminate zone in between". We would like to highlight that the presence of an intermediate zone versus a unique cut point is based not only on analytical capabilities of the assay, but also on its clinical performance (i.e. separation of normal vs abnormal) and biomarker characteristics (disease specificity, biological variability, renal excretion, etc). Moreover, the presence of an indeterminate zone implies the pursuit of confirmatory testing, and we suggest for that to be explained in the main text. In case an indeterminate zone exists for an assay there should be clear recommendations on how the clinicians should handle the patients with results in this zone. Alzheimer's Disease diagnosis definition: Regarding the AD diagnosis definition presented in this document, Line 10 states that These include, AD should be defined biologically, not based on a clinical syndrome(s). The fact that there is currently no consensus on this ought to be acknowledged¹⁸. We would like to reiterate again from the last feedback provided that AD diagnosis should be made in the clinical context, no diagnosis should be made only with biomarkers, and that imperative should be made clearer throughout the text. In concordance, the current FDA/IVDR approved/cleared assays include in their insert packages, in the Intended Use section: The Lumipulse G A β -Amyloid Ratio (1-42/1-40) results must be interpreted in conjunction with other patient clinical information. This test is not intended as a screening or stand-alone diagnostic test. A positive result does not establish a diagnosis of AD or other cognitive disorder. The pTau181/Abeta42 ratio result is used as an adjunct to other clinical diagnostic evaluations. This is contradictory with the framework presented where the authors propose biological parameters sufficient to diagnose the disease, "In this update we propose that abnormality on specific Core 1 biomarkers is sufficient to diagnose AD." (L 160-161). We strongly suggest for this to be clarified. How the document is to be used remains unclear: Please clarify that these criteria are a bridge between research and clinical practice. The

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document states "First, no treatments that target core disease pathology had received regulatory approval in 2018 but since then several have. In response, the present document has progressed from a framework for research, to criteria for diagnosis and staging that are intended to inform both research and clinical care" but then it also states Finally, we point out that these are not intended to be specific clinical practice guidelines, but rather criteria to inform diagnosis and staging of AD that reflect current science. Finally, given the broader scope of the present document, it feels necessary to add a synopsis or summary of the criteria, as part of the document, to make its interpretation clearer. Final considerations: In summary, we continue to welcome the timely and appropriate proposed revisions of the AA research framework and transition to a research and clinical framework. These updates will be an important step forward for the AD field, in an important and transformative moment for the patients. We encourage the Working Group to, once more, consider our comments and feedback carefully to ensure that clear recommendations are made, and to make sure they bring a positive impact on the diagnosis and management of AD patients in the future. References: Blennow, K, Galasko, D, Perneczky, R, et al. The potential clinical value of plasma biomarkers in Alzheimer's disease. *Alzheimer's Dement.* 2023; 1-12. <https://doi.org/10.1002/alz.13455>
<https://www.sysmex.co.jp/en/news/2022/221222.html> Accessed on 13.11.2023 Cummings, J., Apostolova, L., Rabinovici, G.D. et al. Lecanemab: Appropriate Use Recommendations. *J Prev Alzheimers Dis* 10, 362–377 (2023). <https://doi.org/10.14283/jpad.2023.30> Mundada NS, Rojas JC, Vandevrede L, Thijssen EH, Iaccarino L, Okoye OC, Shankar R, Soleimani-Meigooni DN, Lago AL, Miller BL, Teunissen CE, Heuer H, Rosen HJ, Dage JL, Jagust WJ, Rabinovici GD, Boxer AL, La Joie R. Head-to-head comparison between plasma p-tau217 and flortaucipir-PET in amyloid-positive patients with cognitive impairment. *Alzheimers Res Ther.* 2023 Sep 22;15(1):157. doi: 10.1186/s13195-023-01302-w Emma M. Coomans, Inge M.W. Verberk, Rik Ossenkoppele, Sander C.J. Verfaillie, Denise Visser, Mariam Gouda, Hayel Tuncel, Emma E. Wolters, Tessa Timmers, Albert D. Windhorst, Sandeep S.V. Golla, Philip Scheltens, Wiesje M. van, der Flier, Bart N.M. van Berckel, Charlotte E. Teunissen. *Journal of Nuclear Medicine* 2023, 64 (3) 437-443; DOI: 10.2967/jnumed.122.264279 Mundada NS, Rojas JC, Vandevrede L, Thijssen EH, Iaccarino L, Okoye OC, Shankar R, Soleimani-Meigooni DN, Lago AL, Miller BL, Teunissen CE, Heuer H, Rosen HJ, Dage JL, Jagust WJ, Rabinovici GD, Boxer AL, La Joie R. Head-to-head comparison between plasma p-tau217 and flortaucipir-PET in amyloid-positive patients with cognitive impairment. *Alzheimers Res Ther.* 2023 Sep 22;15(1):157. doi: 10.1186/s13195-023-01302-w Shorena Janelidze, Divya Bali, Nicholas J Ashton, Nicolas R Barthélemy, Jeroen Vanbrabant, Erik Stoops, Eugeen Vanmechelen, Yingxin He, Anna Orduña Dolado, Gallen Triana-Baltzer, Michael J Pontecorvo, Henrik Zetterberg, Hartmuth Kolb, Manu Vandijck, Kaj Blennow, Randall J Bateman, Oskar Hansson, Head-to-head comparison of 10 plasma phospho-tau assays in prodromal Alzheimer's disease, *Brain*, Volume 146, Issue 4, April 2023, Pages 1592–1601, <https://doi.org/10.1093/brain/awac333> Bayoumy, S., Verberk, I.M.W., den Dulk, B. et al. Clinical and analytical comparison of six Simoa assays for plasma P-tau isoforms P-tau181, P-tau217, and P-tau231. *Alz Res Therapy* 13, 198 (2021). <https://doi.org/10.1186/s13195-021-00939-9> Yu, L., Boyle, P.A., Janelidze, S. et al. Plasma p-tau181 and p-tau217 in discriminating PART, AD and other key neuropathologies in older adults. *Acta Neuropathol* 146, 1–11 (2023). <https://doi.org/10.1007/s00401-023-02570-4> Janelidze S, Mattsson N, Palmqvist S, Smith R, Beach TG, Serrano GE, Chai X, Proctor NK, Eichenlaub U, Zetterberg H, Blennow K, Reiman EM, Stomrud E, Dage JL, Hansson O. Plasma P-tau181 in Alzheimer's disease: relationship to other biomarkers, differential diagnosis, neuropathology and longitudinal progression to Alzheimer's dementia. *Nat Med.* 2020 Mar;26(3):379-386. doi: 10.1038/s41591-020-0755-1. 7 Karikari TK, Pascoal TA, Ashton NJ, Janelidze S,

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Benedet AL, Rodriguez JL, Chamoun M, Savard M, Kang MS, Therriault J, SchÅ¶ll M, Massarweh G, Soucy JP, HÅ¶glund K, Brinkmalm G, Mattsson N, Palmqvist S, Gauthier S, Stomrud E, Zetterberg H, Hansson O, Rosa-Neto P, Blennow K. Blood phosphorylated tau 181 as a biomarker for Alzheimer's disease: a diagnostic performance and prediction modelling study using data from four prospective cohorts. *Lancet NeuroL*. 2020 May;19(5):422-433. doi: 10.1016/S1474-4422(20)30071-5 Holper S, Watson R, Yassi N. Tau as a Biomarker of Neurodegeneration. *Int J Mol Sci*. 2022 Jun 30;23(13):7307. doi: 10.3390/ijms23137307 https://www.accessdata.fda.gov/cdrh_docs/reviews/DEN200072.pdf. Accessed on 13.11.2023 https://www.accessdata.fda.gov/cdrh_docs/reviews/K221842.pdf. Accessed on 13.11.2023 https://www.accessdata.fda.gov/cdrh_docs/reviews/K231348.pdf. Accessed on 13.11.2023 <https://crm.jrc.ec.europa.eu/?ref=1>. Accessed on 13.11.2023 Boulo, S, Kuhlmann, J, Andreasson, U, et al. First amyloid ÅŸ1-42 certified reference material for re-calibrating commercial immunoassays. *Alzheimer's Dement*. 2020; 16: 1493â€“1503. <https://doi.org/10.1002/alz.12145> Petersen RC, Weintraub S, Sabbagh M, et al. A New Framework for Dementia Nomenclature. *JAMA NeuroL*. Published online October 16, 2023. doi:10.1001/jamaneuroL.2023.3664

I read with interest the newly proposed criteria. My suggestion refers to the neuroimaging marker used for vascular contributions, namely WMH. My opinion is that we should shift to include diffusion imaging markers to indicate small vessel disease contributions to cognitive impairment and dementia. These include Free water or peak-width skeletonized mean diffusivity (PSMD). We have shown that these markers have excellent instrumental properties, are automated (unlike infarcts), and are related to cognitive impairment - more so than WMH. Furthermore, they are more sensitive to SVD in younger populations (Hispanics experience cognitive impairment at younger ages). I think the field needs to evolve and use more sensitive SVD biomarkers.

Although we are in full support of the separation of tau into T1 and T2 groups, we believe that some confusion remains in exactly what T1 is to represent and what group(s) are being referred to when ÅŸ™ is used by itself in the document. We recommend directly stating in Tables 1 and 2 (e.g., in a footnote) that tests employing T1 biomarkers are appropriate for assessing amyloid pathology as part of Alzheimer's diagnosis. Similar statements are made in the text of the documents and this addition would clarify the main conclusions communicated by the Tables that currently have some confusion by way of the different parentheticals after A and T1. To elaborate further, multiple sections within the document (e.g., lines 129-138, 383-384, 410-414 and 437-441) note that identification of ÅŸ-amyloidosis is needed for diagnosis and that that can be established with the Core 1 biomarkers (noted in Table 1 as A and T1). In Tables 1 and 2, AT2NIVS, are listed with their corresponding condition yet T1 is simply described as the analytes. As brought up by audience members at the recent CTAD meeting, this can cause confusion over whether certain taus can be used to identify the presence of amyloid pathology. Clarifying this is paramount to proper utilization and it is recommended that core biomarkers be noted as markers of amyloidosis as the text states (or an equivalent such as Alzheimer pathology) rather nothing phosphorylated and secreted AD tau. Additionally, we recommend that when ÅŸ™ is referred in the text it is explicitly designated as T1, T2 or T1 and T2 to clarify the intent. Stating ÅŸ™ alone could lead to confusion when interpreting the text. For example, the text only references A or T in several places (e.g., lines 743-745, 410-417) and it is unclear if/when T1 is being referenced.

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The present comment is sent on behalf of the European Association of Nuclear Medicine (EANM). The comment was written by the members of the Neuroimaging Committee of EANM and approved by the EANM Board. We would like to thank all the Alzheimer's Disease experts who contributed to the two drafts of the revised A/T/N criteria for the possibility to provide comments also on this second draft of the new criteria. We support the general idea underlying the present work and the need to pave the path for early identification of cognitive impairment and etiological diagnosis based on AD-associated pathology. We fully agree this is crucial to maximize benefits for treatment including lifestyle interventions and to accelerate access to upcoming disease-modifying drugs. In this regard we believe that the committee has done a great work in integrating a rapidly evolving field; however, several aspects related to the position and suggested use of TAU PET imaging do not correctly reflect the available evidence on the pathophysiology, emerging clinical meaning and, most of all, validated technical features of TAU PET tracers (either considering [18F]Flortaucipir alone or considering also other TAU PET tracers, especially based on the level of validation they already reached). The general concept of, in case of the different available first- and second-generation tau PET tracers, writing only about tau PET, and on the other side, in case of fluid tau markers, discussing a wide range of different markers and ratios, is unbalanced. Different generations of tau tracer have different properties and different diagnostic/staging potentials, and that should be acknowledged, as it is done for the different fluid tau markers. With respect to this second draft of the revised criteria we would like to express our concerns regarding the revision for the intended use of Core biomarkers as described in the text and schematically summarized in table 2. Briefly, the Working groups proposes a categorization of both fluid analyte and imaging tools in Core 1 and Core 2 biomarkers building this classification on the capability of the different core biomarkers to capture all the features of AD pathophysiology (and on the timeframe in which these tools become abnormal in the course of the disease). In this regard, we recognize the utility of defining Core 1 biomarkers as biomarkers able to become abnormal around the same time as amyloid PET thus defining the initial stage of AD detectable in vivo. We agree that Core 2 biomarkers are expected to become abnormal later in the evolution of AD and to be more closely linked with the onset of symptoms than Core 1 biomarkers. Then, when this staging-oriented concept moves to the intended use of biomarkers in diagnosis, in this second draft, Core 1 biomarkers are considered sufficient to diagnose AD while all Core 2 biomarkers are considered not typically used as standalone diagnostic tests for AD. Notably, Core 1 biomarkers include amyloidosis biomarkers, fluid assays described as T1 category and some hybrid ratios for both CSF and blood biomarkers while TAU PET (including the FDA approved TAU PET tracer [18F]Flortaucipir) is part of Core 2 biomarkers together with plasma and CSF biomarkers that are commented by the Working group itself as presently representing a conceptual scheme requiring extensive validation testing for clinical implementation, likely to change given the rapidly changing nature of the fluid biomarker field. The draft also reports that the inclusion of some of these fluid biomarkers was based on the sufficient accuracy definition consistent with recent recommendations on minimum acceptable performance criteria for blood-based biomarkers (although the reference is still missing in text of the draft). When moving to the diagnostic use of Core 2 biomarkers, the working group timely states that A-T2+ biomarker profile is rare and not consistent with a diagnosis of AD. In keeping with this concept Table2 includes A, T1 and some hybrid ratios as biomarkers intended for diagnostic use (so able to confirm A+) while TAU PET is included among biomarkers used for staging, prognosis or as an indicator of biological treatment effect. We believe that the position of TAU PET is misleading for several reasons but for the sake of clarity we will discuss only a very practical scenario. More importantly, we would like to suggest an operational way (in keeping with the A/T/N framework) to better reflect TAU PET diagnostic

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role in the A/T/N criteria: When discussing intended diagnostic use", we are looking for an accurate confirmation of the etiological diagnosis of AD but we are not necessarily aiming to candidate patients to anti-amyloid treatment. In this regard, when discussing the diagnostic role of [18F]Flortaucipir (FTP-PET), it is important to remind that, based on post-mortem results, a positive TAU PET demonstrated to reflect tau neurofibrillary pathology (NFT score of B3 corresponding with Braak stages V and VI) as well as high NIA-AA level of Alzheimer disease neuropathologic change (ADNC). Specifically, a positive TAU PET based on autopsy-validated criteria demonstrated to correspond also to the presence of high amyloid burden (meeting the NIA-AA criteria for high levels of ADNC at autopsy). The extensive validation process of TAU PET (again based on neuropathology) also allows to state that, on turn, isolated increased medial temporal FTP-PET uptake may occur in the absence of amyloid- β positivity. Accordingly, individuals with TMTL may not be in the pathologic trajectory toward AD unless proof of brain amyloidosis is also provided. Based on the same autoptic data and on further studies using amyloid PET as gold standard, strong evidence is thus available that patients with moderate neocortical uptake at TAU PET (described in Table3a of this second draft as stage C pathological stage) and patients with high neocortical uptake at TAU PET (stage D) have amyloid pathology. Even today prescribing information for Flortaucipir clearly define that a positive TAU PET corresponds to neocortical activity in posterolateral temporal, occipital, or parietal/precuneus region(s), with or without frontal activity (while increased neocortical activity isolated to the mesial temporal, anterolateral temporal, and/or frontal regions is the description of a negative scan). As a matter of fact, if, for any reason, a positive [18F]Flortaucipir PET (based on these validated criteria) is obtained and the patient is not candidate to an anti-amyloid treatment, the patient can be accurately (etiologically) diagnosed as AD and there are no reasons to complete the diagnostic workflow with an amyloidosis biomarker. This patient will NOT be a A-T+ while, it is relatively easy to classify this kind of patients (following the A/T/N framework) as AxT+ (more specifically they can be AxTMOD+ or AxTHIGH+). Among Core 2 biomarkers TAU PET has the power, accuracy, and validated reading criteria to support the definition of AD diagnosis labelled as AxT+. This kind of label is very similar to what is presently done in the field of oncology. Patients with cancer are surgically treated, so T staging is defined and sometimes (for many different reasons) the presence of long-distance metastasis (M) can also be defined but there might be no clinical reasons to (invasively) obtain information about the lymph nodal staging. So, the patient will be labelled as T1NxM1 (for example). From the practical point of view, we propose to move TAU PET, in Table2, among the biomarkers intended for diagnosis explaining this concept in the text and adding a foot note to Table2 remarking that AxT+ with a TAU staging corresponding intermediate or high staging can support as diagnosis of AD similarly to A-T- (while it is clearly not the case for A-T+ patients, or patients with TAU accumulation confined in the MTL, which is, in any case, considered negative in the prescribing information of Flortaucipir).

FURTHER REMARKS: 1. Table 2: On page 4, it is noted Criteria the committee used for inclusion in Table 2 were: the imaging, CSF, or plasma biomarker has either received regulatory approval or has played a prominent role in recent clinical research and, in the opinion of the committee, enough evidence exists to support its clinical value and the assumption that it may receive regulatory approval in the future. At least one second-generation tau PET tracer (namely PI-2620) is currently in Phase 3 testing/has great chances for regulatory approval in the near future, and has potential to serve as a Diagnosis/T1 biomarker. This needs to be considered. 2. The statement Phosphorated N terminal fragment analytes (ptau 181, 217 and 231) become abnormal around the same time as amyloid PET and well before tau PET17,18,22,23 (page 5) is superficial/incorrect: Apart from the fact that this question can only be answered by longitudinal (and not - like done so far in most projects - by cross-sectional) studies, for at

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least one second-generation tau tracer this differs: MK6240 (Reference 23 above; wrongly used to support the above statement). Again, second-generation tau PET tracers are diagnostic biomarkers of AD. 3. Page 8. Sentence Thus, our definition of plasma assays that may suffice as standalone diagnostic tests for AD are those with accuracy of approximately 90% to detect abnormal amyloid PET by visual read in the intended use population, or more simply, plasma assays that have diagnostic performance equivalent to approved CSF assays. Comment: Visual reading of amyloid PET might represent a suboptimal measure to validate external biomarker. More in general, since 2022 quantitative information generated by CE-marked image quantitation software for the quantification of amyloid-beta PET scans is used as an adjunct to visual interpretation. 4. Page 9. Sentence Cutpoints denoting normal vs abnormal values may be selected by various means and will vary with the fluid assay, and for PET will depend on the specific ligand and details of the analytic pipeline for quantitative analyses. Comment: this statement does not fit amyloid PET pipeline as centiloids have been validated for comparison across tracers (and centers). 5. Page 10. Sentence We recognize that regulatory approval for assays are usually based on a single validated cutpoint; however, the package insert for one approved CSF assay does include a range described as likely consistent with a positive amyloid PET scan result which conveys the notion of an indeterminate zone. Comment: The metric used to define a positive amyloid PET is relevant when validating external assays. A positive amyloid PET based on visual or semiquantitative measure such as centiloids might correspond to different cut-off value for the fluid biomarker validated with amyloid PET. 6. Page 10 When PET is assessed quantitatively, however, images should still be inspected visually by a qualified expert to assure adequate image quality. Comment: despite the increasing importance of semiquantification of amyloid and TAU PET we believe that this statement is very important, and we are happy to reinforce it! 7. Page 185. Sentence Collection of PET data immediately following injection contains information about cerebral perfusion that may also be useful as a measure of vascular physiology or neurodegeneration. Comment: the sentence is too vague. Actually, not all PET tracers can provide information on cerebral blood flow. Amyloid and TAU PET tracers can, so this needs to be specified. Moreover early perfusion imaging with Amyloid or TAU PET it is mainly of interest to reflect neurodegeneration as a surrogate for FDG (vascular physiology seems a bit misleading). We suggest reformulating. A possible reformulation might be The early uptake phase for amyloid and TAU PET tracers provides information about perfusion rate and can thus serve as surrogate marker of neurodegeneration. Finally, two references are provided but both are related to amyloid PET. We suggest replacing one of them with one reference on early perfusion TAU PET imaging. References 1. Fleisher AS, Pontecorvo MJ, Devous MD Sr, Lu M, Arora AK, Trucchio SP, Aldea P, Flitter M, Locascio T, Devine M, Siderowf A, Beach TG, Montine TJ, Serrano GE, Curtis C, Perrin A, Salloway S, Daniel M, Wellman C, Joshi AD, Irwin DJ, Lowe VJ, Seeley WW, Ikonomic MD, Masdeu JC, Kennedy I, Harris T, Navitsky M, Southekal S, Mintun MA; A16 Study Investigators. Positron Emission Tomography Imaging With [18F]flortaucipir and Postmortem Assessment of Alzheimer Disease Neuropathologic Changes. *JAMA Neurol.* 2020 Jul 1;77(7):829-839. doi: 10.1001/jamaneurol.2020.0528. Erratum in: *JAMA Neurol.* 2023 Aug 1;80(8):873. PMID: 32338734; PMCID: PMC7186920. 2. Costoya-Sánchez A, Moscoso A, Silva-Rodríguez J, Pontecorvo MJ, Devous MD Sr, Aguiar P, Schöll M, Grothe MJ; Alzheimer's Disease Neuroimaging Initiative and the Harvard Aging Brain Study. Increased Medial Temporal Tau Positron Emission Tomography Uptake in the Absence of Amyloid- β Positivity. *JAMA Neurol.* 2023 Oct 1;80(10):1051-1061. doi: 10.1001/jamaneurol.2023.2560. PMID: 37578787; PMCID: PMC10425864. 3. Prescribing information <https://pi.lilly.com/us/tauvid-uspi.pdf> 4. Völter F, Beyer L, Eckenweber F, Scheifele M, Bui N, Patt M, Barthel H, Katzdobler S, Palleis C, Franzmeier N, Levin J, Perneczky R, Rauchmann BS,

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Sabri O, Hong J, Cumming P, Rominger A, Shi K, Bartenstein P, Brendel M. Assessment of perfusion deficit with early phases of [18F]PI-2620 tau-PET versus [18F]flutemetamol-amyloid-PET recordings. *Eur J Nucl Med Mol Imaging*. 2023 Apr;50(5):1384-1394. doi: 10.1007/s00259-022-06087-y. Epub 2022 Dec 27. PMID: 36572740; PMCID: PMC10027797.

The intent to define Alzheimer's Disease according to the presence of neuropathological biomarkers alone (amyloid, tau) runs against the widely held notion of the disease being defined by cognitive impairment. We know neuropathology is present in the brains of many older adults who do not show significant signs of cognitive impairment at death. It is my opinion that the public will not want a diagnosis based on neuropathological markers alone without cognitive impairment since fundamentally the public is concerned about cognitive impairment. There is also a danger of a stereotype threat effect and this has not been studied enough. Finally, much of the biomarker scientific literature is based on non-representative, non-diverse samples. We do not know enough about how biomarkers look in these samples to go ahead with this reconceptualization of AD. Minoritized communities are always left behind in new health initiatives, and these will be the ones that will struggle most with the implications of these new criteria for health and treatment.

1. Inclusion: these revised criteria could be viewed as an exercise done exclusively by the Global North. Many members have received pharma funding which increases bias. At the AAIC meeting, people from LMIC were decrying the lack of applicability to most of the global population. The fact that the NIA-NIH has withdrawn their endorsement is a reflection of the potential for this to be viewed as an "echo-chamber". 2. Risk: The presence of amyloid in your brain in people who are asymptomatic is associated with an OR~5 of developing AD in the next 10-15 years according to Rabinovici, Sperling and others. It does not mean you will develop AD. Many, many people would be harmed by this knowledge or go on to be treated with DMTs that do harms including death. This is unacceptable. We cannot diagnose someone with a disease on the basis of an odds ratio. 3. Health Equity: Most BBB studies have been done in Whites/European Caucasians without other medical comorbidities. Just as there are multiple reasons for raised PSA that are not prostate cancer, we know that that abnormal amyloid/tau levels can be due to renal impairment, concurrent infection, etc. We know that their performance is different in Asians, American Blacks, and we know almost nothing about their use in First Nations peoples. The

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promotion of abnormal BBB=AD at any stage compounds these inequities. In addition, if diagnosed with AD, they would not be eligible for any currently available DMTs. Thus we would be diagnosing AD in someone (who may not have it) and then be telling them that there are no treatments. This is unethical. 4. A fully inclusive panel or set of work groups should be convened to reconsider the use of BBB in AD diagnosis and prediction and the criteria be rewritten.

These proposed revised diagnostic and staging criteria represent another unfortunate step in the loss of credibility of the Alzheimer's Association and the associated experts whose views are distorting the field with false hope and unrealistic expectations. They say the criteria are for research, but throughout there are numerous references to clinicians. The expert panel is not representative of the field and includes biased industry and (regulatory captured) FDA input. The proposed puzzling dual Core measurements, the uncertainty about the reliability, validity, and utility of the various mentioned biomarkers, and the expanded theoretical model underlying the staging framework lead are unclear. These confusing criteria may serve some who wish to profit from them, but not patients, families, researchers, clinicians or and society at large. No wonder former and current Alzheimer Research Center Directors and the NIA are distancing themselves from them.

The draft revised guidelines endorse a broader use of blood-based biomarkers in clinical settings. In section 10, the authors state that there is a need for more representative samples and that the biomarkers described in the guidelines have not been extensively tested in diverse populations. These statements are accurate and cause for significant concern if blood-based biomarkers will be used in clinical settings without further validation. Biomarkers in many disease areas have been developed and optimized on predominantly White populations. Any systematic phenotypic differences even as seemingly unrelated to the biology of dementia (R1) may compromise the performance of biomarkers in unanticipated ways. Differential accuracy across racial and ethnic groups could affect access to care and exacerbate health disparities in dementia, as it has in other domains. Furthermore, more detail needs to be provided on why the predictive ability biomarkers or treatment efficacy may differ by population. Genetic differences and effects of social determinants of health without specificity as to how and why they affect biomarker performance are cited in the document as potential causes in unequal performance across racial groups. However, we already know what factors are likely the primary drivers of differences between groups and do not need to appeal to untested genetic explanations or vaguery. We should, in fact, anticipate the unequal performance of blood based biomarkers across racial groups due to racially patterned comorbidities, notably differences in impaired hepatic and renal function, BMI, and vascular burden of disease. These factors are downstream of social determinants of health and are all known to affect blood-based biomarker performance. Failure to account for these factors, in addition to impacting individual care, could exacerbate health disparities in dementia. In addition, it is stated that cut points for biomarkers will not be provided but will be determined empirically by clinicians and researchers, without details on how this should be done rigorously. In addition to issues with unequal predictive performance across groups, more attention ought to be paid to the following issues that receive only limited attention in the document: lack of clear gold standard for blood-based biomarkers; dynamic range, i.e. blood-based

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biomarkers may vary more at a different stage of disease than PET markers; test-retest reliability of blood-based biomarkers; and factors not directly measuring brain disease, such as kidney and liver function or fasting status, that are known to impact performance. These issues are further detailed in the recent publication Considerations for use of blood-based biomarkers in epidemiologic dementia research (R2). Finally, it is incorrectly stated that APOE-e4 prevalence is lower in Black populations than in White populations (line 799; non-US: R3, R4, US: R5-7). It would also be more precise to specify this is in comparison to non-Latino White populations. References: R1: Lee CM, Jacobs HI, Marquiã© M, Becker JA, Andrea NV, Jin DS, Schultz AP, Frosch MP, Gomez-Isla T, Sperling RA, Johnson KA. 18F-flortaucipir binding in choroid plexus: related to race and hippocampus signal. *Journal of Alzheimer's disease*. 2018 Jan 1;62(4):1691-702. R2: Hayes-Larson E, Ackley SF, Turney I, La Joie R, Mayeda ER, Glymour MM, Alzheimer's Disease Neuroimaging Initiative FT. Considerations for use of blood-based biomarkers in epidemiologic dementia research. *American Journal of Epidemiology*. 2023 Oct 16:kwad197. R3: Sepehrnia B, Kamboh MI, Adams-Campbell LL, Bunker CH, Nwankwo M, Majumder PP, Ferrell RE. Genetic studies of human apolipoproteins. X. The effect of the apolipoprotein E polymorphism on quantitative levels of lipoproteins in Nigerian blacks. *American journal of human genetics*. 1989 Oct;45(4):586. R4: Hallman DM, Boerwinkle E, Saha N, Sandholzer C, Menzel HJ, Csazar A, Utermann G. The apolipoprotein E polymorphism: a comparison of allele frequencies and effects in nine populations. *American journal of human genetics*. 1991 Aug;49(2):338. R5: Weuve J, Barnes LL, de Leon CF, Rajan KB, Beck T, Aggarwal NT, Hebert LE, Bennett DA, Wilson RS, Evans DA. Cognitive aging in black and white Americans: cognition, cognitive decline, and incidence of Alzheimer disease dementia. *Epidemiology (Cambridge, Mass.)*. 2018 Jan;29(1):151. R6: Evans DA, Bennett DA, Wilson RS, Bienias JL, Morris MC, Scherr PA, Hebert LE, Aggarwal N, Beckett LA, Joglekar R, Berry-Kravis E. Incidence of Alzheimer disease in a biracial urban community: relation to apolipoprotein E allele status. *Archives of neurology*. 2003 Feb 1;60(2):185-9. R7: Barnes LL, Bennett DA. Alzheimer's s disease in African Americans: risk factors and challenges for the future. *Health affairs*. 2014 Apr 1;33(4):580-6.

I commend the working group for its transparency in releasing the original draft criteria, publicly posting commentary, and providing an opportunity to comment on the revised draft criteria. I am glad to see some changes to the revised version, including the following: Clarification of the exact biomarkers that provide evidence sufficient to diagnose Alzheimer's disease (now called Core 1 biomarkers). Taking a stance that biomarker testing should only be performed under the supervision of a physician. Taking a stance that cognitively unimpaired individuals should not receive biomarker testing until an approved intervention emerges for this group. Clarifying limitations of currently available biomarkers in Text Box 3. Highlighting that the research literature surrounding fluid markers and relevant cutpoints is in flux, such that clinician judgment is required for use. Using the term cognitively unimpaired to describe individuals in clinical Stages 1 and 2, as the term preclinical was an inaccurate description of Stage 2. â€ Creating an easy-to-follow clinical-biological staging schema with numbers for clinical stage and letters for biological stage. There remain additional ways this manuscript could be improved. There are two broad points I would like to raise about the framing of the document. First, there continues to be a mixed message being sent regarding the intent of these criteria. On the one hand, the authors describe the document as including criteria for diagnosis and staging that are intended to inform both research and clinical care. On the other hand, the authors admit that these are not intended to be specific clinical practice guidelines. Given these conflicting statements, it is unclear whether this document represents consensus criteria for use in research or clinical practice or not. The authors seemed to capture the true spirit of the document in this sentence: Finally, we point out that these are not intended to be specific clinical practice guidelines, but rather

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criteria to inform diagnosis and staging of AD that reflect current science. The manuscript could be revised to remove statements that conflict with this stated purpose. Second, I continue to believe that the document would benefit from a stronger statement regarding the real-world applicability of these criteria. Very few hospital systems have access to adequate specialists, biomarker technologies, and clinical support resources necessary to rigorously implement these criteria. It would be helpful to place these diagnostic criteria in the context of the realities of the current healthcare environment and provide guidance to individuals working in situations in which the available resources would not support application of these criteria. In addition to these broad points, I have a two more specific issues to raise. First, in the current version, the criteria no longer allow for clinical Stage 2 to be diagnosed based on objective test data at an isolated time point. This approach was allowed in the 2018 NIA-AA research framework, and it is supported by evidence from several studies: â€¢ Thomas KR, Bangen KJ, Weigand AJ, Edmonds EC, Wong CG, Cooper S, Delano-Wood L, Bondi MW; Alzheimer's Disease Neuroimaging Initiative. Objective subtle cognitive difficulties predict future amyloid accumulation and neurodegeneration. *Neurology*. 2020 Jan 28;94(4):e397-e406. doi: 10.1212/WNL.0000000000008838. Epub 2019 Dec 30. PMID: 31888974; PMCID: PMC7079691. â€¢ Kiselica AM, Kaser AN, Bengtson JF. An Initial Empirical Operationalization of the Earliest Stages of the Alzheimer's Continuum. *Alzheimer Dis Assoc Disord*. 2021 Jan-Mar 01;35(1):62-67. doi: 10.1097/WAD.0000000000000408. PMID: 33009036; PMCID: PMC7904575. â€¢ Thomas, K.R., Weigand, A.J., Edwards, L.C. et al. Tau levels are higher in objective subtle cognitive decline but not subjective memory complaint. *Alz Res Therapy* 14, 114 (2022). <https://doi.org/10.1186/s13195-022-01060-1> â€¢ Kiselica AM; Alzheimer's Disease Neuroimaging Initiative. Empirically defining the preclinical stages of the Alzheimer's continuum in the Alzheimer's Disease Neuroimaging Initiative. *Psychogeriatrics*. 2021 Jul;21(4):491-502. doi: 10.1111/psyg.12697. Epub 2021 Apr 22. PMID: 33890392; PMCID: PMC8819647. Second, the authors state that individuals may only be diagnosed with clinical Stage 3 if there is cognitive impairment present. This requirement does not give adequate weight to the possible presence of mild behavioral impairment (MBI). For example, in one study of 348 patients referenced below, there were separable MBI (27.5%), MCI (25%), and psychiatric symptom (47.4%) groups, and the MBI group had highest rate of progression to dementia. As a result, it would seem to make sense to allow for diagnosis of Stage 3 based on either the presence of cognitive or behavioral impairment. â€¢ Taragano, F. E., Allegri, R. F., Heisecke, S. L., Martelli, M. I., Feldman, M. L., SÃ¡nchez, V., ... & Dillon, C. (2018). Risk of conversion to dementia in a mild behavioral impairment group compared to a psychiatric group and to a mild cognitive impairment group. *Journal of Alzheimer's Disease*, 62(1), 227-238.

I appreciate all of the hard work that is going into this proposal. A few comments for our consideration. Throughout the document, I would suggest changing "asymptomatic" to "preclinical AD" and "asymptomatic" to "cognitively unimpaired persons. When we developed the 2011 criteria, I had originally proposed "asymptomatic" or "presymptomatic" myself, and the group wisely suggested that it wanted to cover everyone who did not yet meet criteria for MCI, even if they subjective concerns or more modest neuropsychological signs or symptoms. Furthermore, I see no reason to abandon the "preclinical AD" concept as different stakeholders which want to further this "preclinical" stage of AD for a range of reasons in the research and clinical setting, even if the diagnosis should be biological. To make the diagnosis of AD based on biomarker evidence of amyloid plaques alone, it would be helpful to not only cite the two smallish studies in unimpaired persons to show that CU and impaired persons who are A+ have greater subsequent declines than those who do not regardless of whether they have tau tangles or neurodegeneration. I suggesting calling for the need to confirm that

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"prognostic" value in additional studies. When I was a psychiatrist who was at Washington University when its "research diagnostic criteria" for several psychiatric disorders was being considered in the development of DSM-III, I recall my colleagues trepidation at the move to such widespread clinical diagnoses. In the absence of disease mechanisms or pathology, the criteria they used for a diagnosis included a) reproducibility by different evaluators and locations, such that we can communicate with each other and compare findings, and b) prognostic value. Regarding reliability, I think we not only need biomarkers that are accurate but robust/repeatable over time. (I think you've articulated that well). But I also think the staging, while a nice aspirational goal is far from established in terms the ability to accurately and reliably distinguish some of those stages (including the earlier tau tangle stages even with PET), and should be confined to research criteria until reliability and perhaps further prognostic or therapeutic value is clarified. Regarding prognostic value, I think the additional confirmatory data about impact of A+ (with or without T+) on subsequent rates of cognitive decline and, indeed, progression from preclinical AD to MCI due to AD would be very important, especially given some of the pushback you're already receiving. So my general suggestion would be to consider more incremental changes based on compelling evidence, make distinctions when relevant between what meets the threshold for research or clinical criteria, and note more precisely what is needed to go from your aspirational goals to reducing these criteria to practice in the research and clinical settings. For instance, I would propose using A+ alone as research diagnostic criteria for AD--and call for additional analyses of data from studies to confirm its prognostic value with reliable PET and blood tests before quickly extended its use to the clinical setting. Shouldn't take long and would make your argument more compelling. I would also suggest confining the staging to "research staging criteria," since their reliability, accuracy and prognostic or therapeutic value hasn't been established yet. I think that would help with credibility and also give the field more specific direction about what will be needed to make those criteria clinically relevant. (BTW, I do see the potential for the tau staging (e.g., with the donanemab findings, but even there, the tau measurements are not fully consistent with your proposed tau staging. Needs some more work.) Thank you again for your efforts and the chance to provide input.

I thank the authors and the AA for the opportunity to submit my comments to this second round of revision (first revision number was 34). In this new version of the criteria, the authors have included important new statements about preclinical diagnosis and the role of clinicians and syndromes. - PRECLINICAL DIAGNOSIS. In particular, I am very satisfied that the authors pointed out that diagnostic testing for AD is not suggested for asymptomatic patients at present (We emphasize that, in the absence of approved interventions in asymptomatic individuals, we do not advocate routine diagnostic testing in this population currently.....however at present we do not see how results of AD diagnostic testing in asymptomatic individuals would produce medically actionable information) I could not check whether the sentence in box 1 - Symptoms are not necessary to diagnose AD - that suggested the possibility of preclinical diagnosis, was removed or changed, because the figures and tables file does not open. - CLINICAL CONTEXT AND CLINICIANS. In addition, I am pleased with how the authors emphasized the priority role of clinical context and clinician on decision-making and managing the diagnostic pathway. (.we recommend that biomarkers testing should only be performed under the supervision of a physician. we do not advocate initiating treatments targeting core AD pathology in all symptomatic persons with biologically confirmed AD without regard to clinical context. 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) Another area where clinical judgment is essential is when a Core biomarker is

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discordant with the clinical impression. Clinical judgement is also required to assess potential effects of confounding conditions on biomarker results. - CLINICAL PRESENTATION AND SYNDROMES. I also find it positive that the authors have included two mentions (albeit very limited) on the importance of clinical presentation and syndromes and their recognition in the diagnostic pathway (The nature of the syndromic presentation may indicate the likelihood that AD is or is not a dominant contributor to symptoms. For example, a negative test result in a patient in whom the clinical presentation suggests a high probability of AD). - DISEASE AND ILLNESS. Remaining unheeded, however, is my comment regarding the statement the authors propose in theoretical support of the biological definition of AD. (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 is an unusual and untenable theoretical position. A solid and broad epistemological tradition considers ILLNESS as the disease from the patient's perspective, while DISEASE as the disease in an objective sense, studied scientifically. Signs and symptoms studied objectively, scientifically, are part of disease on the same conceptual level as proteinopathies. They are not the illness. Accordingly, the sentence in box 1 should also be changed (Symptoms are a result of the disease process, not its definition). However, I could not check because the figures and tables file does not open. - LABORATORY AGAINST CLINICAL CRITERIA. Last but not least, I find enlightening the statement the authors added about the purpose of these new criteria, which are not intended to be specific clinical guidelines (Finally, we point out that these are not intended to be specific clinical practice guidelines, but rather criteria to inform diagnosis and staging of AD that reflect current science.). In accordance, the previous title (NIA-AA Revised Clinical Criteria for Alzheimer's Disease) has been changed and the word clinical has been dropped (Revised Criteria for Diagnosis and Staging of Alzheimer's Disease: Alzheimer's Association Workgroup). These changes greatly reduce the scope of the work done, but at the same time make it much more acceptable. In simple words these are the diagnostic criteria we could say laboratory criteria of Alzheimer's. In analogy to the neuropathological criteria, today we also have laboratory criteria. As a researcher I cannot but perceive this as an important advance for science. However, as a clinician engaged daily in detecting the early signs and symptoms of dementia I wonder at this point how and how much exactly will these criteria help clinicians? My preliminary answer to this question is rather negative unfortunately. Indeed, the part devoted to the clinic in the criteria seems to me very weak. It introduces a new classification and staging, for which I find no need and which certainly creates confusion with the already known staging; it ignores terminology well known from decades of studies on clinical-radiological syndromes in dementias (e.g., there is no mention of PCA syndrome, logopenic, etc.); it appears incomplete in mentioning syndromic variants (e.g., corticobasal syndrome is missing); it appears ill-defined in some passages (In particular, stage 2 is absolutely undefined); furthermore, and most importantly, it does not really help the clinician to relate the symptom study that occurs first (sincerely hoping that the preclinical diagnosis of AD will be banned for much longer), with the laboratory study that occurs second. On the contrary, far from being a guide on how best to integrate clinical diagnosis (syndrome diagnosis) with the new laboratory diagnosis that certifies etiology (etiological diagnosis), it seems to introduce a dangerous split between the two (we distinguish between clinical staging and biological disease staging. These are regarded as quasi-independent variables....) not at all agreeable even on a purely scientific level. What is certain is that clinicians will have to study a lot! But this is always a good thing.

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In observing the development and evolution of these new criteria, as well as the controversy they have generated, one can clearly appreciate the diversity of viewpoints that arise from differing approaches to the practice of medicine. This is perhaps amplified in the care of older patients with and without cognitive impairment. As a department chair who has assembled a breadth of specialties into a multidisciplinary clinic for memory disorders, and as a faculty member jointly appointed in Neurology and Radiology Departments, I view the discussions between the radiologist, neurologist, geriatrician, psychiatrist, pathologist and those in laboratory medicine (returning lab results to clinicians) as highly influenced by their very different training backgrounds and their resultant specialty cultures. Its part of the beauty of medicine and brings excellent cross-fertilization to the care of our patients but it is also part of the reason why I don't think these criteria are going to catch on very widely, at least in their current form. The panel and its recommendations appear skewed toward a radiologist approach to clinical care, which (please excuse the oversimplification) is to call it like they see it, quite literally in black and white, with some caveats that clinical correlation is suggested. The panelists who are active in clinical care, seeing patients at the bedside, are likely aware that so much of medicine is too complicated to conform to such a viewpoint, no matter how attractive. Indeed, attractive as it would be to the research community, the clinician who is experienced sitting in the room with elderly patients and families- whether neurologist, geriatrician, psychiatrist, or primary care doctor- recognizes that diagnosis and care is as personal as it gets. This is why I believe that the bulk of clinicians will not permit such an algorithmic approach to meaningfully alter their sacrosanct doctor-patient relationship. That is not to say that they will not allow the algorithm into their sanctuary at all. It just cannot be as prescriptive within the diagnostic process as these new criteria aim to be. The practicing physician, I predict, will reject any such attempt to take full control of the diagnostic process in this set of diseases. My suggestion is that the criteria effort swallows a dose of humility and restricts itself and the ambitious project to creating A Revolutionary Change in Laboratory Medicine and in the Return of Laboratory and Imaging Results with Respect to ADRD. Toward this end, a missing specialist on the panel is one skilled in Laboratory Medicine (often from pathology departments) who can inform the return of an integrated set of relevant lab and imaging results with maximal use to clinicians who are dealing directly with the patients. This would permit the beautiful and diverse cultures of medical subspecialties to continue with their own interpretations of how to apply such results and interpretations at the bedside, but would provide them, for the first time, with an integrated set of complementary measures with which to improve their diagnosis and staging of disease. Often, I expect, they will agree with the returned results and the desired impact on the field will be achieved, but only after giving due attention to the loaded caveat that clinical correlation is suggested.

The tau PET staging can be replicated using plasma P-tau217 with very similar hazard ratios. It is not clear why it is not a staging marker? The association of plasma P-tau217 with NFT Braak Stage is very similar to that of tau PET with NFT Braak Stage. I am not sure what data is driving the decision to have different suggested uses for tau PET and plasma P-tau217?

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Thank you for this thorough update for clinical criteria. As part of these criteria that serve as a bridge between research and clinical use, a conceptual framework for staging based on fluid markers is also suggested, with the explicit mention that this should not be used in the clinic. We agree, because the literature to support such staging mentioned in the paper is minimal and based on 3 recent papers, two from the same groups, and one on medRxiv. Such a staging framework should be thoroughly validated. We appreciate that the text states that this concept needs to be used carefully and not in the clinic. However, this manuscript has an explicit objective to aid the use of biomarkers for clinical use in the abstract. As such, it is confusing to introduce a conceptual framework that is not to be used in the clinic within this paper. Possibly it would be better to remove table 4, and other suggestions for staging based on fluid markers and instead mention in a text box that there is a need for staging based on fluid markers, which requires more work. To illustrate the difficulty of using fluid markers for staging, we would like to point out the literature on CSF vs pathology that indicates that up to 30% of individuals with AD pathology at post mortem had normal CSF tau levels (Shaw et al., 2009; Vromen et al., 2023). Thus, in those individuals CSF ptau 181 could not be seen as an early marker (such as suggested on p15 line 450 in the manuscript). Other work has also demonstrated only a moderate correlation of tangle burden as measured in a continuous way (Tapiola et al., 2009). This suggests that CSF measures for tau may also reflect other aspects than only tangle pathology, and that normal levels do not exclude tangle pathology.

Regarding the need for biomarkers to be interpreted under the supervision of a physician line- I am a PA by training and I am confident that because I have worked with the experts, I am heavily dedicated to this and have been exposed to proper interpretation that I am more capable of interpreting these biomarkers in the clinical setting than many physicians. This should be changed to clinicians with experience in interpreting these biomarkers. There is nothing in medical school or even most neurology residencies that would've better equipped someone for this, it takes very specific and niche training and is a bit daft to generalize that any physician/MD/DOs would know how to properly interpret these biomarkers in a clinical setting.

The current guidelines state Biomarkers should be ordered under the supervision of a physician. I am a dementia specialist (PA) and I have worked on over 20 AD trials and treated thousands of patients. I do not think this statement should be included. States have their own guidance for supervising physicians however there may be independent NPs or PAs that will be comfortable ordering and analyzing Biomarkers under the clinical section. Thank you

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1) In the sentence "plasma assays where accurate is defined as equivalent accuracy to approved CSF assays in detecting abnormal amyloid PET in the intended use population", it is unclear how the IP/LC MS MS ABeta 40/42 approach proposed by Quest can reasonably be excluded if amyloid PET is set as the gold standard. This approach has an AUC of 0.86 (doi:10.1002/alz.064182; doi:10.1002/alz.13443). Furthermore, a study by Mila-Aloma et al. (Nat Med, 2022 ; DOI: 10.1038/s41591-022-01925-w) showed that plasma pTau 217 and Abeta40/42 had comparable performances when amyloid PET was set as the gold standard. It is worth noting that the study used an immunoassay for ABeta40/42 measurement, not the IP/LC MS MS approach, which has better performance (doi:10.1001/jamaneurol.2021.3180). 2) In the "Clinical judgment" section, when referring to the likelihood of AD being a dominant contributor to symptoms, it may be useful to cite the IWG 2021 framework (DOI: 10.1016/S1474-4422(21)00066-1), which has a dedicated Table 2 for interpreting this kind of presentation. This table could also be generally useful in this section.

Page 6. Line 160. Please comment on the interpretation of stand alone CSF Ab42 (no Ab40) low concentration. Is this neurochemical change also considered part of the AD pathophysiological process? This question is prompted by data from longitudinal studies in which A+/T-/N- individuals defined by CSF AD biomarkers have low risk of progression to dementia. Also isolated CSF Amyloid abnormalities are non-specific and common in a number of neurological disorders. For example, we and others have observed that patients with behavioral variant frontotemporal dementia show decrease CSF values, which correlates with faster brain atrophy in typical FTD patterns, without necessarily developing typical Alzheimer's disease phenotypes. See figure 2 of: Skillbäck T, Farahmand BY, Rosén C, Mattsson N, Nånberg K, Kilander L, Religa D, Wimo A, Winblad B, Schott JM, Blennow K, Eriksdotter M, Zetterberg H. Cerebrospinal fluid tau and amyloid- β 1-42 in patients with dementia. *Brain*. 2015 Sep;138(Pt 9):2716-31. doi: 10.1093/brain/awv181. Epub 2015 Jun 30. PMID: 26133663. See Figure 1 of: Soldan A, Pettigrew C, Fagan AM, Schindler SE, Moghekar A, Fowler C, Li QX, Collins SJ, Carlsson C, Asthana S, Masters CL, Johnson S, Morris JC, Albert M, Gross AL. ATN profiles among cognitively normal individuals and longitudinal cognitive outcomes. *Neurology*. 2019 Apr 2;92(14):e1567-e1579. doi: 10.1212/WNL.0000000000007248. Epub 2019 Mar 6. PMID: 30842300; PMCID: PMC6448449. See figure 2 of: Ljubenkov PA, Staffaroni AM, Rojas JC, Allen IE, Wang P, Heuer H, Karydas A, Kornak J, Cobigo Y, Seeley WW, Grinberg LT, Spina S, Fagan AM, Jerome G, Knopman D, Boeve BF, Dickerson BC, Kramer J, Miller B, Boxer AL, Rosen HJ. Cerebrospinal fluid biomarkers predict frontotemporal dementia trajectory. *Ann Clin Transl Neurol*. 2018 Sep 20;5(10):1250-1263. doi: 10.1002/acn3.643. PMID: 30349860; PMCID: PMC6186942.

Page 12. Line 341. "at present we do not see how results of AD..." I disagree. There is evidence showing that those cognitively healthy individuals who receive a positive AD biomarker result are more likely to modify their attitudes towards healthy lifestyles. Observational evidence also suggest that cognitively healthy individuals who have positive amyloid PET and engage in higher physical activity have lower risks of cognitive decline and brain atrophy. The only caveat is the vulnerability a positive tests creates for a patient who may be discriminated in diverse realms. This sentence should be changed to reflect this promising horizon and its challenges. See: Largent EA, et al, REVEAL-SCAN Team. Family members' perspectives on learning cognitively unimpaired older adults' amyloid- β PET scan results. *J Am Geriatr Soc*. 2021 Jul 12. Largent EA, et al. Cognitively unimpaired adults' reactions to disclosure of amyloid PET scan results. *PLoS One*. 2020 Feb 13;15(2):e0229137. Rabin JS, et al. Associations of Physical Activity and β -Amyloid With Longitudinal Cognition and Neurodegeneration in Clinically Normal Older Adults. *JAMA Neurol*. 2019 Oct 1;76(10):1203-1210.

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Page 18. Line 526. This sentence may be misleading. These symptoms are common in the general population, but they are also very common in neurodegenerative disease. See: Okura T, Plassman BL, Steffens DC, Llewellyn DJ, Potter GG, Langa KM. Prevalence of neuropsychiatric symptoms and their association with functional limitations in older adults in the United States: the aging, demographics, and memory study. *J Am Geriatr Soc.* 2010 Feb;58(2):330-7. doi: 10.1111/j.1532-5415.2009.02680.x. Epub 2010 Jan 26. PMID: 20374406; PMCID: PMC2875937.

Page 18. Line 536. "Five characteristic AD phenotypes are recognized". There is also corticobasal syndrome. See: Ossenkopp R, Schonhaut DR, Schöll M, Lockhart SN, Ayakta N, Baker SL, O'Neil JP, Janabi M, Lazaris A, Cantwell A, Vogel J, Santos M, Miller ZA, Bettcher BM, Vossel KA, Kramer JH, Gorno-Tempini ML, Miller BL, Jagust WJ, Rabinovici GD. Tau PET patterns mirror clinical and neuroanatomical variability in Alzheimer's disease. *Brain.* 2016 May;139(Pt 5):1551-67. doi: 10.1093/brain/aww027. Epub 2016 Mar 8. PMID: 26962052; PMCID: PMC5006248. Lee SE, Rabinovici GD, Mayo MC, Wilson SM, Seeley WW, DeArmond SJ, Huang EJ, Trojanowski JQ, Growdon ME, Jang JY, Sidhu M, See TM, Karydas AM, Gorno-Tempini ML, Boxer AL, Weiner MW, Geschwind MD, Rankin KP, Miller BL. Clinicopathological correlations in corticobasal degeneration. *Ann Neurol.* 2011 Aug;70(2):327-40. doi: 10.1002/ana.22424. PMID: 21823158; PMCID: PMC3154081.

Page 15. Line 444. There's a typo.

My comment is regarding the designation of Alzheimer's disease label to individuals with normal cognition and positive amyloid. Appreciating the fact that these individuals are at increased risk of developing Alzheimer's disease, my suggestion is to use a different terminology such as cerebral amyloidosis to define this group. The analogy is that in someone with significant carotid stenosis, we do not use the label "stroke" to define them just due to increased risk of developing the condition in the future.

The shift towards an exclusively biological diagnosis of Alzheimer's disease proposed for research purposes since 2018 would now be a fact. This approach could be acceptable, if there were the proper diagnostic tools to make this shift convincingly, but from the document this does not yet appear to be the case. In conclusion, my general impression is that the paper is rushed. The explanation of the initiative is in box 2: allow widespread use of anti-beta amyloid drugs. The work appears as an attempt to model the disease around new drugs: since they don't work very well clinically, the definition of the disease needs to be changed. Among the contradictions is the definition of core biomarkers which would be identified on the basis of their validity in relation to a gold standard (page 4) 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. This gold standard is not specified, as also explained in the chapter Rigorous validation (For both PET and fluid assays this would include validation against an accepted gold standard. Ideally the standard would be large biomarker to autopsy correlation studies, but this may not always be possible given the challenges with obtaining biomarker and autopsy sampling close in time in representative samples). So we don't have a gold standard to test the biomarkers. This needs to be clarified: is PET the gold standard of a blood biomarker? If this were the case, PET would be sufficient, but the authors clearly distinguish the two categories, considering them "not interchangeable for many use cases". Furthermore: we do not know when biomarkers become positive over the course of life and how they

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change over time (also in relation to therapies). We do not have defined, standardized and shared cutpoints to define the positivity of a biomarker. Among the statements that go too far is the definition of a biological diagnosis (substantially presence of A+) as an ETIOLOGICAL diagnosis. I would propose to change etiology to NEUROPATHOLOGY The authors write that "People with amyloidosis, who by definition have AD" (page 16, line 461): we might as well call the disease "cerebral amyloidosis". Ultimately, it is not clear who should be tested for beta amyloid (with PET and/or blood biomarkers). And I believe this should be made explicit in this document. I propose the following changes: 1. Change the wording biological (etiological) diagnosis to biological (neuropathological) diagnosis. 2. Define the population to screen/test for the presence of beta amyloid.

The addition of the Vascular Component is very Wellcome as this is a major contributor to the disease pathology and manifesting symptoms. It would be helpful , particularly given the emergence of new DMD, to further differentiate vascular amyloid pathology increasing risk of ARIA, (eg V1 subtype) from other vascular pathologies (eg V2 for infarcts and WMH in absence of evidence of macro/ micro haemorrhage).

The BBB vision is excellent. I conducted a survey of 500 US and EU physicians that found 74% would order blood tests if they were accurate for diagnosis or staging. Patients and the field would benefit due to low cost and ready point of care access. However as you imply all this depends on the accuracy. There are no clear binary cut-offs established for any blood marker for diagnosis or prognosis. None are FDA approved for diagnosis in practice. With 4 core BBB markers, there would be 16 possible permutations of positive/negative or high/low. It would be useful to know how doctors in the real world would interpret such results. Also there are >50 BBB tests in development. Cancer staging blood markers are tested in large field trials before launching widely. e.g. the NCI is doing a field trial of cancer blood markers in 240000 people as part of the cancer moonshot. In addition to research validation studies, I recommend the committee consider doing a field trial of BBBs for AD in general practice and neurology settings to understand real world performance. Such a trial will help determine how blood test results for AD/MCI should be interpreted, and determine a standard approach to patient screening as companies flood the field with new tests.

EMAIL BODY: We are contacting you on behalf of the EU-funded AI-Mind research project, which focuses on the utilization of Artificial Intelligence for analyzing electromagnetic brain signals (EEG/MEG) in conjunction with clinical, neuropsychological, and genetic/protein data. The project, identified as RIA H2020-SC1-BHC-06-2020, No. 964220, is financially supported from 2021 to 2026 (www.ai-mind.eu). In AI-Mind, we are developing two new artificial intelligence (AI) based digital tools, the AI-Mind Connector and the AI-Mind Pre-dictor, to analyse existing and routinely collected data in an innovative manner. By extracting salient features from EEG data and more modern MEG, we will convert EEG from an easily accessible with rather restricted analytical power to an easily accessible low-cost global health tool with a much higher potential and predictive power. The AI-Mind Connector will fully automate the identification of early brain network disturbances. After enriching data from AI-Mind Connector with genetic, protein and cognitive information, AI-Mind Predictor will provide an early marker of risk for de-mentia in people with MCI with high sensitivity and specificity (>90%). We have integrated these two digital clinical decision-making tools into a cloud-based diagnostic support platform. We are interested in contributing a concise document to the 'DRAFT Body Text as of October 9, 2023 Workgroup Title/Name as of October 25, 2023 Public Comment at alz.org/Diagnostic Criteria Revised Criteria for Diagnosis and Staging of Alzheimer's Disease: Alzheimer's Association Workgroup' that you recently circulated within the scientific

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community and among disease stakeholders. Of note (to include in N biomarkers): EEG may be one of the synaptic measures since it provides insight into synaptic connectivity. Functional connectivity measures have shown to be related both to cognitive performance and to AD pathophysiology; LETTER FOLLOWS:
Present diagnostic practices lack the necessary screening tools to identify those at risk of such progression.
This is where the AI-Mind project comes into play, introducing an innovative approach to early risk assessment by harnessing advanced artificial intelligence (AI) on multimodal data. The AI-Mind initiative's cutting-edge tools, namely the Connector and Predictor, aim not only to expedite the diagnostic process but also to provide highly accurate predictions concerning an individual's risk of developing dementia in the future, when preventive measures and interventions are still viable.
Current treatment options focus on late symptom management, but not on early intervention when synaptic pathology is beginning to show. Most state-of-the-art biomarkers (CSF, fMRI, PET, SPECT) are unevenly distributed and the European and Global health service need to offer a more equitable method to meet the aging challenge.
The AI-Mind Connector automates the identification of dysfunctional brain networks by leveraging DeepLearning-Artificial Intelligence based recognition of pathological features derived from high-density electromagnetic brain signal recordings. Meanwhile, the AI-Mind Predictor employs the information from the Connector, enhanced by digitalized cognitive testing, genetic and protein biomarkers, sociodemographic, and clinical variables, to predict dementia risk. These procedures are fully automated.
Collaborating with Roche Diagnostic and Pharma, the AI-Mind project ensures the subsequent steps of industrialization and global distribution. Notably, this groundbreaking concept was introduced at the Alzheimer Europe conference in October 2023 in Helsinki by Eli Lilly.
Although reliable and clinically applicable procedures will soon be introduced worldwide only through AI-Mind, earlier studies have already shown promising results. Various techniques such as recurrent neural network classifiers, random forest classifiers, SVM, and ANN have demonstrated high accuracies in distinguishing between different stages of cognitive impairment and healthy controls. Moreover, innovative deep learning methods for resting-state EEG signals analysis have showcased impressive accuracy in classifying AD, MCI, and HC.
In conclusion, modern fully automated, DL AI-based EEG analysis is poised to serve as a population-based screening method for neurodegenerative dementias. This low-cost and widely accessible tool can effectively demonstrate the degradation of brain network architecture due to synaptopathy in the initial

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stages of these conditions. Furthermore, the algorithm, supplemented with additional protein, genetic, and cognitive digitalized data, can effectively predict an individual's risk profile. With the growing recognition from industry leaders, the AI-Mind Connector and Predictor are anticipated to make a significant impact on global health, and we hope that future guidelines will reflect this breakthrough advancement.

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from unprocessed electroencephalograms by using robust invariant features. *Artif Intell Med.* 2015 May;64(1):59-74.

Summary:

We welcome the AA Revised Criteria for Diagnosis and Staging of Alzheimer's Disease, in which the workgroup has carefully considered feedback from a broad array of stakeholder groups. The revised draft has taken important feedback into consideration and has been developed in a very open and collaborative way. In the updated draft, the workgroup has clearly considered the feedback and incorporated a number of important changes, including clarifications on the way biomarkers are categorized (eg. as individual or hybrid ratios), as well as acknowledging the importance that clinical validation and regulatory approvals play in bringing biomarker assays into routine clinical practice.

While these changes are well received, we welcome the opportunity to contribute and would like to bring the below considerations to the workgroup prior to publication. We hope that our feedback is of value and will help ensure that this document is comprehensive and will support the transition from research to future clinical guidelines in Alzheimer's Disease (AD).

Our feedback focused on:

- I. A framework for clinical use should be clearly presented, and the document should be consistent about the regulatory status of the assays being discussed, for example blood-based biomarkers (BBBM) which are validated and approved for a specific intended use. It is important to convey that for currently approved hybrid ratios, the regulatory approval is against a reference standard (e.g. Amyloid PET).
- II. The authors should consider including total-Tau and sTREM in table 1.
- III. For biomarker assays with an indeterminate zone, the workgroup should clarify that it is not a requirement and provide guidance on what further testing may be needed in patients falling in an indeterminate zone of plasma or CSF biomarker tests. This will reduce the potential for unnecessary testing and diagnostic delay.
- IV. The workgroup proposes that these guidelines form a basis for the separation of biological and syndromic diagnosis of Alzheimer's disease and neurocognitive disorders. It should be acknowledged that there is no consensus on this.
- V. Lastly, due to the complexity and rapid changes in the field of Alzheimer's disease, we ask that a brief synopsis is made available alongside the full publication.

I. Framework for clinical use:

A. The fact that no blood-based biomarker has yet received formal approval by regulatory entities should be consistent throughout the text.

1. Along the main text (Line 26, 68-69), it is mentioned that "some (but not all) [blood-based biomarkers] demonstrate excellent diagnostic performance". Consider acknowledging in the text that while there are studies demonstrating excellent diagnostic performance for blood-based biomarkers, additional prospective studies which better reflect their real-world performance are needed for clinical implementation, such as their use in clinical practice in different settings (primary vs secondary), and on diverse populations (e.g. race, comorbidities), along with their regulatory approval/clearance which underscores their safety and effectiveness.

2. Line 69-71 "[blood-based biomarkers' diagnostic performance] now makes the biological diagnosis

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of AD (which previously required PET or CSF assays) generally accessible and is projected to revolutionize clinical care and research”. The focus, here, is on the use of blood-based biomarkers to replace CSF/PET confirmatory testing. However, blood-based biomarkers are expected to streamline the AD diagnostic pathway and show clinical value through several intended uses. They may be used in clinical practice as a triage test to rule out patients without amyloid pathology, rule in, or replace CSF/PET confirmatory testing in some patients, monitor disease progression or monitor treatment, among others.

1 Each intended use needs to be validated in the appropriate intended use population and the specific BBBM needs to be approved by the regulatory entities. Therefore, although they hold the promise to make AD diagnosis more accessible and are projected to revolutionize clinical care and research, we strongly suggest to make it clear throughout the text that none of these assays (except plasma Sysmex Ab42/40, which has received regulatory approval in Japan 2) have yet received formal approval as an in vitro diagnostic (IVD). Moreover, it should be noted that currently, CSF and amyloid PET are the only two recommended methods to qualify patients for the amyloid targeting therapies 3.

3. Line 242 states “In contrast plasma p-tau is used as a standalone assay”. We suggest replacing it with “[...] in contrast, plasma p-tau demonstrated very good clinical performance in clinical trials and studies as a standalone biomarker.”.

B. Table 2 shows intended uses for imaging, CSF and plasma biomarker assays. The first intended use is defined as “Diagnosis” where, instead of focusing on proteinopathies, a classification more useful for research purposes than for clinical practice, this table should group assays by their ability to identify amyloid or tau pathology based on how they correlate with either amyloid, or with tau PET scans. This will also clarify the use of the “hybrid ratios” for amyloid pathology detection based on their clinical performance and concordance with amyloid PET scan (see paragraph C). This classification will therefore include all ratios concordant with amyloid PET, as well as pTau217 (and pTau181 as per paragraph D). The tau pathology category would include biomarkers which correlate well with tau PET, which might also include pTau217 and pTau181, as per recent literature 4,5.

Please see a suggestion for Table 2 below:

Identification of pathology
(Triage testing - rule in/out,
Confirmatory testing)

*Plasma **CSF Imaging

Amyloid pTau181, pTau217,
pTau217/np-tau 217

Abeta42/40,
pTau181/Abeta42,

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tTau/Abeta42

Amyloid PET

Tau pTau181, pTau217,
pTau217/np-tau 217

Tau PET

*No FDA approved/cleared assays at this time

**FDA approved/cleared assays concordant with amyloid PET scan available.

The same approach for the A/T1/Hybrid ratios could be applied for the Staging, prognosis and as an indicator of

biological treatment effect intended use in Table 2.

C. The classification used for the hybrid ratios is impractical and confusing. If the focus currently is on detecting amyloid

pathology using fluid biomarkers, by the way of amyloid PET concordance, then, it would be more useful to split it into

assays which detect amyloid positivity and include all ratios listed here, as well as pTau217

6

, and pTau181 as per table 2

suggestion and comment below.

D. Plasma pTau181 is not included in Table 2, as per the argument that it has “not yet demonstrated diagnostic accuracy

equivalent to approved CSF assays” (Line 146-148). Based on recent literature, we suggest to include pTau181 as a

plasma assay that can be used both for identifying amyloid pathology, as well as tau pathology

5,7,8,9

. Studies have shown

that plasma pTau181 differentiated AD dementia from non-AD neurodegenerative diseases with data from one study

showing an accuracy similar to that of CSF p-tau181 and Tau PET (AUC = 0.94-0.98)

10

; another study showed that plasma

pTau181 is an excellent predictor of both amyloid PET and tau PET, validating these findings in two large cohorts

11

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E. It is important to emphasize that accuracies demonstrated in the current literature may not reflect the diagnostic

accuracy in routine clinical use, as currently, the high clinical performance of many of these assays is only demonstrated

in retrospective batch measurements in research cohorts for specific disease stage populations,

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which may not be representative of the real-world scenario (e.g. in terms of minorities/comorbidities and preanalytical handling, both of which can have an impact on biomarker levels and thus potentially also clinical performance).

II. Biomarker categorization:

A. Following on our feedback on the first version of this document, we reiterate our advise toward the inclusion of total Tau (tTau) as a non-specific marker of neurodegeneration in Table 1, as it is elevated in a range of conditions associated with neuroaxonal injury and the results of plasma tTau studies suggest that its role is akin to CSF tTau’s as a non-specific biomarker of neurodegeneration

12

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B. Additionally in Table 1, we suggest to include soluble TREM2 together with GFAP in the I (inflammation) category, since it is becoming increasingly studied in the field, and it is described in the text as “another I biomarker that received recent attention in research [...] which reflects microglial reactivity” (Line 646-648).

III. Clinical performance of the FDA approved/cleared biomarkers:

A. Line 208-211 : “Accordingly, regulatory approval of CSF assays (Supplemental Table 1) was anchored to positive/negative visual reads of amyloid PET: sensitivity/specificity (or positive % agreement/negative % agreement) of approved CSF assays ranged from 97%/84% to 91%/89% to 88%/92% against this reference standard.

50-52

”. We would

like to ask for these values to be corrected as per their respective Decision Summaries and references updated as needed:

1. For the first assay, the 97%/84% for sensitivity/specificity data do not represent the clinical performance at the same cutoff; as the assay has two cutoffs and an indeterminate zone, sensitivity and specificity for each of the two cutoffs should be included for clarity

13

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2. The performance for the other two assays should be listed as: 88%/93%

14 and 85%/94%

15

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IV. Certified reference materials:

A. In Text Box 3, the first limitation of biomarkers lists “Lack of certified reference methods and materials (except for CSF A β 42/40, where these are available)”. This is inaccurate as the Certified Reference Materials is only available for A β 42, not for A β 40

16

. Buolo et al describes the first amyloid β 1-42 certified reference material for re-calibrating commercial

immunoassays

17

V. Indeterminate zone:

A. Regarding the section “3.5) Conservative treatment of values near a cutpoint; the indeterminate zone”, and based on our previous feedback on the first version of this document, “Most available clinical assays are able to provide a single validated cutpoint that optimizes sensitivity and specificity for the clinical intended use, without the need for two cutoffs and an indeterminate zone in between”. We would like to highlight that the presence of an intermediate zone versus a unique cut point is based not only on analytical capabilities of the assay, but also on its clinical performance (i.e. separation of normal vs abnormal) and biomarker characteristics (disease specificity, biological variability, renal excretion, etc). Moreover, the presence of an indeterminate zone implies the pursuit of confirmatory testing, and we suggest for that to be explained in the main text. In case an indeterminate zone exists for an assay there should be clear recommendations on how the clinicians should handle the patients with results in this zone.

VI. Alzheimer’s Disease diagnosis definition:

A. Regarding the AD diagnosis definition presented in this document, Line 10 states that “These include, AD should be defined biologically, not based on a clinical syndrome(s).” The fact that there is currently no consensus on this ought to be acknowledged

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B. We would like to reiterate again from the last feedback provided that AD diagnosis should be made

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in the clinical context, no diagnosis should be made only with biomarkers, and that imperative should be made clearer throughout the text. In concordance, the current FDA/IVDR approved/cleared assays include in their insert packages, in the Intended Use section:

I. "The Lumipulse G β -Amyloid Ratio (1-42/1-40) results must be interpreted in conjunction with other patient clinical information. This test is not intended as a screening or stand-alone diagnostic test."

II. "A positive result does not establish a diagnosis of AD or other cognitive disorder. The pTau181/Abeta42 ratio result is used as an adjunct to other clinical diagnostic evaluations."

This is contradictory with the framework presented where the authors propose biological parameters sufficient to diagnose the disease, "In this update we propose that abnormality on specific Core 1 biomarkers is sufficient to diagnose AD." (L 160-161). We strongly suggest for this to be clarified.

VII. How the document is to be used remains unclear:

A. Please clarify that these criteria are a bridge between research and clinical practice. The document states "First, no treatments that target core disease pathology had received regulatory approval in 2018 but since then several have. In response, the present document has progressed from a framework for research, to criteria for diagnosis and staging that are intended to inform both research and clinical care" but then it also states "Finally, we point out that these are not intended to be specific clinical practice guidelines, but rather criteria to inform diagnosis and staging of AD that reflect current science".

B. Finally, given the broader scope of the present document, it feels necessary to add a synopsis or summary of the criteria, as part of the document, to make its interpretation clearer.

Final considerations:

In summary, we continue to welcome the timely and appropriate proposed revisions of the AA research framework and transition to a research and clinical framework. These updates will be an important step forward for the AD field, in an important and transformative

moment for the patients. We encourage the Working Group to, once more, consider our comments and feedback carefully to ensure that clear recommendations are made, and to make sure they bring a positive impact on the diagnosis and

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management of AD patients in the future.

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Use of blood biomarker nomenclature - Line 24 and Line 72 and Line 114 throughout document

We suggest the use of the term “blood biomarker (BBM)” over the term of “blood-based biomarker (BBB)” throughout the document. This term is consistent with the 2022 CTAD/EU Task Force document with the term blood biomarker of BBM. We note that there are no references to CSF-based or CBB and PET-based biomarkers or PBB in the document.

We suggest the use of the terms as outlined in Line 114 – “...the imaging, CSF, or plasma biomarker...” and favor the use of blood biomarker (BBM) throughout the document. Such standardization would help with communicating the messages of the document to the core intended readers.

Use of more than one biomarker

Furthermore, the 2022 EU/US CTAD Task Force report highlights the potential use of combination

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biomarkers in the evaluation of patients with cognitive impairment. (Reference: Angioni D, Delrieu J, Hansson O, et al. Blood Biomarkers from Research Use to Clinical Practice: What Must Be Done? A Report from the EU/US CTAD Task Force. J Prev Alzheimers Dis. 2022;9(4):569-579. doi:10.14283/jpad.2022.85)

For example, the PrecivityAD blood test quantifies plasma concentrations of amyloid beta 42 and 40 (A β 42 and A β 40) and determines the presence of apolipoprotein E (ApoE)-specific peptides to establish the APOE genotype. The A β 42/40 Ratio + APOE genotype + patient's age are used to calculate the Amyloid Probability Score (APS) by way of a validated regression model. The APS reflects the likelihood that a patient, on a scale of 0-100, will be amyloid positive on an amyloid PET scan.

This test has published analytic validity, clinical validity, and clinical utility.

For example, the PrecivityAD2 blood test is an analytically and clinically validated blood test that aids healthcare providers in ruling in or ruling out AD in patients presenting with mild cognitive impairment or dementia. In a clinical validation study of 583 patients with cognitive impairment using amyloid PET as the reference standard, the PrecivityAD2 blood test has achieved 88% sensitivity, 89% specificity and 88% overall accuracy (West et al., CTAD 2023; manuscript under review).

The PrecivityAD2 blood test simultaneously quantifies specific plasma amyloid beta and tau peptide concentrations to calculate the A β 42/40 Ratio and p-tau217/np-tau217 (%p-tau217). Inclusion of plasma analyte ratios has been shown to mitigate the effects of confounding factors such as chronic kidney disease. The ratios are combined into a proprietary statistical algorithm to calculate the Amyloid Probability Score 2 (APS2), a numerical value ranging from 0-100, that determines whether a patient is Positive (has high likelihood) or Negative (has low likelihood) for the presence of brain amyloid plaques by amyloid PET scan.

Further evidence to the value of combining analytes to improve early amyloid pathology detection, Rissman et al., on behalf of the AHEAD 3-45 investigators, recently published data from a large sample set of 1080 cognitively unimpaired individuals (Rissman et al., Alz Dem Nov 6 2023 online edition. <https://alz-journals.onlinelibrary.wiley.com/doi/10.1002/alz.13542>). The investigators demonstrated that the combination of the plasma %p-tau217 along with A β 42/40 Ratio into screening algorithms results in highly accurate amyloid status prediction (AUC 0.95, accuracy of 88% - 90%, with or without age and ApoE in the model, respectively) in individuals with Centiloid >20. This performance was statistically superior to the performance of single analyte measures of p-tau181/np-tau181 (AUC 0.77), A β 42/40 (AUC 0.87), p-tau217/np-tau217 (AUC 0.92).

Mention of comorbidities – Line 319

There are no specific mentions to clinical comorbidities such as renal and hepatic impairment and their effect on biomarker levels. Confounding variables require that biomarkers need to be normalized for renal function. We also believe such information on confounding should be included in the Future Directions section of the manuscript.

β -amyloid proteinopathy pathway – Line 123 and Line 129-138

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Category A denotes biomarkers of the β -amyloid proteinopathy pathway...”

We do have some concerns about the classification of p-tau181 & p-tau217 as T1, due to the potential for creating clinical confusion as to what p-tau181 & p-tau217 best measure. A large body of evidence demonstrates that these analytes correlate most strongly with amyloid burden, with more modest correlations with tau tangle pathology. In addition, it is possible for p-tau217 to be present; however, for tau tangle pathology on tau PET to be absent. One potential alternative to the T1 classification for these p-tau analytes could be to list them as A2, emphasize that A2 reflects more advanced amyloid pathology and the beginning of tau proteinopathy with a hyperphosphorylated tau pattern, and to consider shifting the T2 analytes to T.

Furthermore, we believe that A-T1-N is not the same as A-T2-N. The latter would indicate a later stage of disease. A1-A2-N would make it clear that a T is missing. For this reason, we offer the idea of creating two A subgroups as opposed to two T subgroups.

In addition, we suggest that the core biomarkers should also be separated by their correlation with changes in neurocognitive status, as Core 1 fluid biomarkers related to amyloid do not often correlate with changes in neurocognitive status by themselves unlike Core 2. (reference on MTBR-tau243 is a specific biomarker of tau tangle pathology in Alzheimer’s disease, Nature Medicine, 29, pages1954–1963 (2023))

Considerations when defining accurate biomarkers - Line 162

In this document, accurate plasma assays are defined as equivalent accuracy to approved CSF assays in detecting abnormal amyloid PET in the intended use population (Text box 2).

We suggest that the criteria document must be very clear on how the performance of blood biomarker is statistically compared to address substantial equivalence with the approved CSF/Imaging. This should include the method of comparison, whether it's binary or intermediate (small percentage in the intermediates vs. large intermediates) cut points.

Additionally, we suggest that the criteria should describe the risk-benefit analysis of using a blood test, even though the blood test may have slightly lower PPV and NPV relative to the predicate, especially when the intermediate zone for the predicate is eliminated.

Biofluids and PET and interchangeable nature – Line 194

In this update, biofluids and PET are no longer considered interchangeable, and the T category has been split into T1 and T2. This statement suggests that a BBM is not and cannot be equivalent to PET, but rather a complementary tool. We believe that such a statement moves away from the first version of the NIA-AA document and sets the stage for underuse of blood biomarkers, which are critically needed to address the need for a safe and scalable method for measuring brain amyloid as well as facilitate the use of anti-amyloid disease modifying treatment.

Anchoring biomarkers for AD diagnosis to reference standards – Line 198

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The document states that the amyloid PET visual reading scale on which regulatory approval of florbetapir was based is highly accurate (sensitivity 96%, specificity 100%) at discriminating CERAD none/sparse vs moderate/frequent plaques in individuals who came to autopsy within 1 year of the PET scan 47. Quantification of amyloid PET is also accurate at distinguishing intermediate/high vs none/low AD neuropathological change (ADNPC) (in one example, 203 sensitivity 84%, specificity 88%) 9.

We suggest that it is important to mention the inter-reader variability in visual reads, which is approximately 8-10%. Theoretically, any CSF or blood test compared against visual reads cannot achieve an accuracy greater than 92%. Furthermore, we believe that the high performance (sensitivity 96%, specificity 100%) of amyloid PET is overstated due to the study definition used in the reference trial and thus does not represent a reliable figure as a reference standard.

Plasma assays and regulatory approval – Line 212

The document states “Currently, no plasma assays have received regulatory approval although this is expected 212 to change soon.” C2N Diagnostics has regulatory approval from CLIA and CAP to perform the PrecivityAD and PrecivityAD2 tests. There are no other regulatory approvals necessary for a clinical laboratory to perform LDTs.

Biofluid assay development transparency – Line 249

We suggest that the paragraph describing regulations and assay performance on lines 256-269 should include analytical and clinical validation requirements that are also required by clinical laboratories performing LDTs.

PET Visual read – line 223

“Thus, our definition of plasma assays that may suffice as standalone diagnostic tests for AD are those with accuracy of approximately 90% to detect abnormal amyloid PET by visual read ...”

We suggest consideration of the mention of PET by itself without designation of visual read or Centiloid.

Enhanced description around p-tau217 ratios and plasma A β 42/40 assays – Line 250

There have been several recent studies proving enhanced description of the role of p-tau217 and the usefulness of looking at hybrid ratios. There references include the following:

Janelidze S, Barthélemy NR, He Y, Bateman RJ, Hansson O. Mitigating the Associations of Kidney Dysfunction With Blood Biomarkers of Alzheimer Disease by Using Phosphorylated Tau to Total Tau Ratios. *JAMA Neurol* 2023;80:516. doi:10.1001/jamaneurol.2023.0199;

Barthélemy NR, Horie K, Sato C, Bateman RJ. Blood plasma phosphorylated-tau isoforms track CNS change in Alzheimer's disease. *J Exp Med* 2020;217:e202008611. doi:10.1084/jem.20200861;

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Janelidze S, Bali D, Ashton NJ, Barthélemy NR, Vanbrabant J, Stoops E, et al. Head-to-head comparison of 10 plasma phospho-tau assays in prodromal Alzheimer's disease. *Brain* 2023;146:1592–601. doi:10.1093/brain/awac333

Based on this evidence, we suggest the following modifications to the text:

In many cases, plasma p-tau is used as a standalone assay 18, 59, 64-72, but recent evidence suggests that the plasma concentration (hybrid) ratio p-tau217/non-phosphorylated-tau217 has better diagnostic performance than standalone plasma p-tau measures. The percent difference between individuals with vs without β -amyloid pathologic change is around 50% for CSF A β 42/40 but only 10%-15% for plasma A β 42/40. 16, 54, 73-75. This percent difference along with non-specific, less sensitive analytical assays accounts for the generally worse accuracy of some plasma A β 42/40 assays compared to CSF assays or plasma p-tau 217 assays 53, 54.

Quantification of the terms moderate SUVR and high SUVR would be helpful (line 415)

Therefore, for biological staging with amyloid and tau PET, we propose the following staging scheme (Tables 3a, 3b): stage A (initial) – abnormal amyloid PET with no uptake on tau PET (A+T-). Stage B (early) – abnormal amyloid PET plus tau PET uptake that is restricted to medial temporal areas (A+TMTL+). Stage C (intermediate) - abnormal amyloid PET plus tau PET uptake in the moderate SUVR range on a neocortical ROI (A+TMOD+). Stage D (advanced) - abnormal amyloid PET plus tau PET uptake in the high SUVR range in the same neocortical ROI (A+THIGH+).

Addition of fluid A β 42/40 to list of treatment effects as measured by biomarkers:

Given the results of the CLARITY AD study, we suggest that the addition of fluid A β 42/40 (which has been observed to be the most dynamic measure of amyloid changes in response to therapy) to list of treatment effects as measured by biomarkers:

Anti A β immunotherapy can dramatically reduce the load of amyloid plaque in a time and dose dependent manner and also change downstream biomarkers in the direction of normalization, including fluid A β 42/40, ptau and total tau (CSF and plasma) 130, 206-208, plasma GFAP 130, 207, and also reduce the level of or slow accumulation on tau PET 130, 206.

We suggest addition of the following reference:

van Dyck, C. H., Swanson, C. J., Aisen, P., Bateman, R. J., Chen, C., Gee, M., Kanekiyo, M., Li, D., Reyderman, L., Cohen, S., Froelich, L., Katayama, S., Sabbagh, M., Vellas, B., Watson, D., Dhadda, S., Irizarry, M., Kramer, L. D., & Iwatsubo, T. (2023). Lecanemab in Early Alzheimer's Disease. *New England Journal of Medicine*, 388(1), 9–21. <https://doi.org/10.1056/NEJMoa2212948>

Core 1 fluid biomarkers and Ab42/40 - Line 436

We suggest that a sentence should be added stating the likelihood of staging based off Core1 fluid biomarkers as a first approach (plasma Abeta ratio predicts a positive Amyloid PET years in advance)

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Future directions – Line 818

We suggest that a topic for future directions should include globalization of sample collections for fluid biomarkers. If harmonization of the many assays, both CSF & plasma, is ever going to be on the table, sample collection standardization should be a key priority.

Use of a multi-analyte algorithm to incorporate multiple modalities in the evaluation of cognitive impairment – Line 822

Starting on Line 822, the document states that “We envision creating a comprehensive system to stratify risk of progression by incorporating all biomarkers (core AD, non-core, and biomarkers of non-AD pathology) along with demographics and genetics”

There is a general lack of acknowledgement of algorithms/computer modeling that incorporates other risk factors (even though plenty of it is done in research). The incorporation of biometrics has been shown to be valuable.

For example, the PrecivityAD blood test quantifies plasma concentrations of amyloid beta 42 and 40 (A β 42 and A β 40) and determines the presence of apolipoprotein E (ApoE)-specific peptides to establish the APOE genotype. The A β 42/40 Ratio + APOE genotype + patient’s age are used to calculate the Amyloid Probability Score (APS) by way of a validated regression model. The APS reflects the likelihood that a patient, on a scale of 0-100, will be amyloid positive on an amyloid PET scan.

This test has published analytic validity, clinical validity, and clinical utility.

For example, the PrecivityAD2 blood test is an analytically and clinically validated blood test that aids healthcare providers in ruling in or ruling out AD in patients presenting with mild cognitive impairment or dementia. In a clinical validation study of 583 patients with cognitive impairment using amyloid PET as the reference standard, the PrecivityAD2 blood test has achieved 88% sensitivity, 89% specificity and 88% overall accuracy.

The PrecivityAD2 blood test simultaneously quantifies specific plasma amyloid beta and tau peptide concentrations to calculate the A β 42/40 Ratio and p-tau217/np-tau217 (%p-tau217). Inclusion of plasma analyte ratios has been shown to mitigate the effects of confounding factors such as chronic kidney disease. The ratios are combined into a proprietary statistical algorithm to calculate the Amyloid Probability Score 2 (APS2), a numerical value ranging from 0-100, that determines whether a patient is Positive (has high likelihood) or Negative (has low likelihood) for the presence of brain amyloid plaques by amyloid PET scan.

Further evidence to the value of combining analytes to improve early amyloid pathology detection, Rissman et al., on behalf of the AHEAD 3-45 investigators, recently published data from a large sample set of 1080 cognitively unimpaired individuals (Rissman et al., Alz Dem Nov 6 2023 online

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edition. <https://alz-journals.onlinelibrary.wiley.com/doi/10.1002/alz.13542>). The investigators demonstrated that the combination of the plasma %p-tau217 along with AB42/40 Ratio into screening algorithms results in highly accurate amyloid status prediction (AUC 0.95, accuracy of 88% - 90%, with or without age and ApoE in the model, respectively) in individuals with Centiloid >20. This performance was statistically superior to the performance of single analyte measures of p-tau181/np-tau181 (AUC 0.77), AB42/40 (AUC 0.87), p-tau217/np-tau217 (AUC 0.92).

GENERAL COMMENTS

Line 95: We suggest modification to "Fluid biomarkers reflect net production/clearance of analytes in near real time."

Line 111: Suggest rephrasing ratios to reflect the calculation of a combination of individual analyte concentrations.

Line 113: Suggest abbreviation of LDT

Line 113: Suggest abbreviation of RUO

Line 129 and 132: Suggest spelling change to "phosphorylated"

Line 133: Suggest rewording to "In contrast to other tau fragment analytes, MTBR-tau243 phosphorylated and non-phosphorylated tau fragments ..."

Line 146: Suggest rewording to "Because of the onset timing, these analytes and their combination ratios have been proposed as biomarkers of amyloid plaques, ..."

Line 149: Suggest rewording to "Core 2 biomarkers are those in the T2 category in Tables 1 and 2 and include tau PET, p-tau205, MTBR-tau243, and non-phosphorylated tau fragments."

Suggest rewording Tables 1 and 2 to reflect this changes.

Line 194: Suggest "update biofluids and PET biomarkers.."

Line 237: Suggest change to roman numerals -"Braak stages I-IV"

Line 276: Suggest rewording to "The definition of an abnormal test value requires creating a cut point within the analytical measurement range of values for a biomarker."

Line 280: Suggest striking the word "study": "When using a CSF, blood-based, or PET biomarker quantitatively 280 for diagnosis, a useful approach would be to report results with three elements."

Line 448: Suggesting adding the word "abnormal": The onset of abnormal fluid Core 1 biomarkers occurs around the time of an abnormal amyloid PET and much earlier than neocortical tau PET abnormalities

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Line 454: Suggest use of p-tau205 versus pT205 throughout document

Comment on the Revised Guidelines

The new orientation adopted by the revised AD guidelines is a welcome paradigm shift towards more tangible, biological definitions of the disease and potentially less invasive approaches to document them.

A comment on serum biomarkers of neurodegeneration and overlapping biology between COVID-19 and Alzheimer's disease. 1 Our current knowledge on COVID-19 indicates that older survivors may be susceptible to subsequent cognitive impairment 2 , as well as radiologically evident neurodegeneration along the olfactory-limbic pathway. 3 Several studies indicate that fluid biomarkers of neurodegeneration , including tau species 4, 5 , are affected by COVID-19 and may be a manifestation of is shared biology with AD, particularly innate immune dysregulation 6-8 – to a currently unknown extent.

A point to consider and the nucleus of this comment is whether older adults exposed to COVID-19 fulfil the criteria for Alzheimer's disease due to that very exposure. While viral illness is a recognized susceptibility factor for neurodegenerative disease, 9 COVID-19 so far appears to affect several parameters considered by clinicians and by the revised criteria in ruling in AD, with biomarkers being perhaps a worrying prospect and a direct perturbator.

Reference

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4. Boutajangout A, Frontera J, Debure L, Vedvyas A, Faustin A, Wisniewski T. Plasma biomarkers of neurodegeneration and neuroinflammation in hospitalized COVID-19 patients with and without new neurological symptoms. *Alzheimers Dement* 2021;17.
5. Frontera JA, Boutajangout A, Masurkar AV, et al. Comparison of serum neurodegenerative biomarkers among hospitalized COVID-19 patients versus non-COVID subjects with normal cognition, mild cognitive impairment, or Alzheimer's dementia. *Alzheimers Dement* 2022;18:899-910.
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7. Di Primio C, Quaranta P, Mignanelli M, et al. Severe acute respiratory syndrome coronavirus 2 infection leads to Tau pathological signature in neurons. *PNAS Nexus* 2023;2:pgad282.
8. Ramani A, Muller L, Ostermann PN, et al. SARS-CoV-2 targets neurons of 3D human brain organoids. *EMBO J* 2020;39:e106230.

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9. Levine KS, Leonard HL, Blauwendraat C, et al. Virus exposure and neurodegenerative disease

MELODEM asked experts to share opinions about the draft of the AAIC biomarker criteria for AD diagnosis. Comments below and will be added as shared with MELODEM.

DRAFT comments regarding the proposed 2023 Alzheimer’s disease diagnostic criteria

When the 1984 NINDS/ADRDA criteria were updated to address the then newly available in vivo biomarkers in new 2011 research/clinical criteria for Alzheimer’s disease (Jack et al., 2011), the addition of a research diagnosis of preclinical AD (Sperling et al., 2011) was a critical turn for the field. In 2018, the field moved further along this new road to a research staging system that ignored clinical symptoms altogether (Jack et al., 2018). While some hailed this as a new medical era for AD, others—including a MELODEM-affiliated group (Glymour et al., Eur J Epidemiol, 2018) raised concerns, notably setting aside exactly what matters to families and patients and premature closure for etiologic and mechanistic research. These concerns are brought to higher relief in the present document, which elevates this staging system to diagnostic criteria in the setting of more widely available plasma biomarkers, new marginally effective and potentially risky therapies, and increasing evidence that dementias of mixed pathology are the most common among older adults. Redefining the pathology as the disease has some advantages but is problematic for a number of reasons. The term “Alzheimer’s disease” is widely used by physicians and the general public to indicate what may have surpassed cancer as our most dreaded disease. Using the same term to refer to the underlying pathology irrespective of symptoms will introduce potential misunderstandings among physicians, their patients, and the broader public. To avoid confusion, fear, and anxiety that could be an unintended consequence of the proposed criteria, many of us would prefer a term like brain amyloidosis or the neuropathologists’ Alzheimer disease neuropathologic changes (ADNC; Hyman et al, Alzheimer’s & Dementia, 2011) to stress the difference, i.e., using a term that specifically refers to the detected neuropathological phenomena rather than the clinical correlates of those changes. More broadly, since this confusion is likely here to stay and can have significant emotional consequences, I suggest that clinicians and researchers alike now avoid using Alzheimer disease alone, and instead either refer to Alzheimer disease neuropathologic changes (for the pathology) or to Alzheimer dementia ([or MCI due to AD] for the clinical syndrome). Another major problem is the current lack of clarity about when and even whether someone with

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positive biomarkers might develop the clinical syndrome, which makes the distinction between the pathology and clinical disease more critical. We have long seen pathology without a history of symptoms in post-mortem studies, and in vivo measurement confirms that pathology can be present for a long time without clinical disease. Because we’ve only had biomarkers available during life for a limited time, and we can’t know how long pathology has been present at baseline, along with limited observation times due to mortality and loss to follow up, it is difficult to characterize the true duration of pathology before symptoms arise, and whether everyone eventually would become impaired if they lived long enough.

We do know, however, that predictive value is limited as to whether an individual will develop dementia, and very poor for when (for this, imaging is a bit better). Indeed, the disease trajectory is heterogenous, and the manifestation of clinical syndromes at a given level of pathology is ultimately a function of multiple other factors such as genetics, life experiences, and comorbid conditions. Larger studies with diverse representation will be required to fully estimate person-specific risk. Notably, current samples are heavily biased toward the white and highly educated, those with family history, and those with symptoms (recognized or not); all of these may bias estimates toward greater risk sooner. When we move from CSF biomarkers to plasma, where analyte concentrations are much lower, the problems can be more complex. Plasma biomarkers have improved greatly, but still have issues with technical reliability, day-to-day variability, changes with renal and other physiologic measures, and other unknown factors. Lack of reference standards for plasma biomarkers combined with fuzzy “indeterminate zones” further complicates matters. More critically, perhaps, like the more established CSF and imaging biomarkers, their ability to predict future cognitive status—the issue of relevance to patients and their families—is limited, and data are particularly lacking on persons from racially and ethnically minoritized communities. Moreover, the major advantage of plasma biomarkers is their potential widespread availability, a double-edged sword given the complex issues in interpretation. With respect to treatment implications, the new criteria do not advocate early intervention, in keeping with current indications for anti-amyloid therapies, but they do pave the way. The hoped-for scenario is therapy early, before symptoms, with a blood test and FDA-approved treatment with appealing potential to center initial dementia screening and care in primary care, which is probably a logistical and economic necessity. However, at present, too little is known about amyloid’s role in the pathological cascade and

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how it plays out over time to allow risk-benefit discussions about the use of anti-amyloid therapeutics in those without symptoms. This pre-clinical designation of Alzheimer's disease is being presented as carcinoma in situ, but we don't know whether the biomarkers' performance will compare to screening colonoscopies (which extensive evidence suggests saves lives) or to the prostate-specific antigen test ([PSA] which extensive evidence suggests does more harm than good). The confusion of a test that claims to detect Alzheimer's disease (rather than serving as a marker of future risk) and a therapy with complex adverse effects could lead to false hopes, and costly, potentially dangerous off-label use. Such use is unlikely at present given cost and insurance reimbursement limits but seems invited by the diagnostic framework itself. I believe that a more circumspect title and more cautious framework is in order.

"I support the above statement prepared by Dr. Blacker In addition to the issues raised in the statement, I would like to add that the issues around the lack of clear and accepted cut-points for plasma biomarkers are compounded by evidence of a lack of agreement on the absolute value of biomarkers measured with different assays or measured using assays conducted in different labs. These challenges with cross-lab consistency and harmonization only serve to further complicate the use of these biomarkers to define Alzheimer's disease in clinical practice."

HRS-HCAP has plasma biomarkers and LASI-DAD in India has also measured the same plasma biomarkers, using either comparable or harmonizable assays. These data are set to be released publicly eventually. I think this is a scientifically useful comparison as we consider about the importance of including diverse samples; the US and India provide uniquely contrasting contexts with diverse populations with distinct socioeconomic factors, lifestyle practices, healthcare systems, and even genetic profiles. Our group recently submitted a research proposal to conduct cross-national comparisons in these plasma biomarkers, and in their associations with cognition. Our preliminary findings did suggest cross-national consistency in inter-correlations among these biomarkers. However, we expect differences in associations of these biomarkers with cognitive outcomes because of the different social/economic/behavioral circumstances in these populations. Among other things, we think we do know that cognitive impairment due to nutritional deficiencies is uncommon in the US and other HIC but more common in India.

This is the kind of research across populations that I hope is consistent with the MELODEM position. I have no interest in clinical diagnosis using biomarkers from plasma or CSF; it isn't that such diagnosis

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is
wrong so much as I think it is entirely premature at this time.

The draft revised criteria endorse a broader use of blood-based biomarkers in clinical settings. In section 10, the authors state that there is a need for more representative samples and that the biomarkers described in the guidelines have not been extensively tested in diverse populations. These statements are accurate and cause for significant concern if blood-based biomarkers will be used in clinical settings

without further validation.

Biomarkers in many disease areas have been developed and optimized on predominantly White populations. Any systematic phenotypic differences—even as seemingly unrelated to the biology of dementia (1)—may compromise the performance of biomarkers in unanticipated ways. Differential accuracy across racial and ethnic groups could affect access to care and exacerbate health disparities in

dementia, as it has in other domains.

Furthermore, more detail needs to be provided on why the predictive ability biomarkers or treatment efficacy may differ by population. Genetic differences and effects of social determinants of health—without specificity as to how and why they affect biomarker performance—are cited as potential

causes in unequal performance across racial groups. However, we already know what factors are likely

the primary drivers of differences between groups and do not need to appeal to untested genetic explanations or vaguery. We should, in fact, anticipate the unequal performance of blood based

biomarkers across racial groups due to racially patterned comorbidities, notably differences in impaired

hepatic and renal function, BMI, and vascular burden of disease. These factors are downstream of social

determinants and are all known to affect blood-based biomarker performance. Failure to account for these factors, in addition to impacting individual care, could exacerbate existing disparities in dementia

diagnosis, care, and treatment.

In addition, it’s stated that cut points for biomarkers will not be provided but will be determined empirically

by clinicians and researchers, without details on how this should be done rigorously. In addition to issues

with unequal predictive performance across groups, more attention ought to be paid to the following issues that receive at most limited attention in the document: lack of clear gold standard for blood-based

biomarkers; dynamic range, i.e., blood-based biomarkers may vary more at a different stage of disease

than PET markers; test-retest reliability of blood-based biomarkers; and factors not directly measuring

brain disease, such as kidney and liver function or fasting status, that are known to impact

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performance.

These issues are further detailed in the recent publication “Considerations for use of blood-based biomarkers in epidemiologic dementia research” (2).

Finally, it is incorrectly stated that APOE-e4 prevalence is lower in Black populations than in White populations (line 799; non-US: citations 3, 4; US: citations 5-7). APOE-e4 prevalence is, in fact, higher.

It

may also be more precise to specify this is in comparison to non-Latino White populations.

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I. Considerations for public and patient engagement in labels that carry significant personal and societal meaning and consequence

Up to 60% of individuals with probable dementia do not know or understand their (clinical) diagnosis (Amjad et al., 2018). Contributing to this startling figure are a number of contextual factors including ageism, the highly stigmatized nature of Alzheimer’s disease related dementias, and inadequate training

and capacity within the healthcare system to facilitate early, reliable, and equitable diagnosis. Serious consideration must be given to the consequences of substantial changes in the use of labels and underlying biological framework that the public and patients associate with the 1:1 presence of a

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disease

with clinical consequences. Stewarding an era of use of plasma biomarkers and revised staging into clinical care will necessitate communication that is responsive to the realities of the how patients and families generally understand links between underlying disease biology and clinical disease; not how scientists may like them to. Feedback from patients and families on labeling is feasible and critically necessary at this juncture.

II. Lack of specificity and consistency with AD as biologically defined, and clinical utility of staging model

The 2023 Alzheimer’s disease diagnostic criteria state that “AD is defined by its biology” yet present multiple internally inconsistencies by conflating these biological states with “clinical staging” despite identifying that this definition does not relate to “appearance and progression of clinical syndromes.”

It is

thus unclear why biological staging is being introduced as an anchor for clinical staging (which is, again, purportedly not definitionally relevant), particularly whilst noting the significant individual variability. In this

mislabeling the new diagnostic criteria risk perpetuating significant public mistrust and confusion; as well

as confusion among clinicians through a staging model (Table 6) that is explicitly not reflective of or relevant to clinical impairment – which is what most end users both need and desire from a model for disease staging. It is unclear how this will be useful to families making decisions regarding care such as advanced directives and complex treatment decisions – if the stage of disease they are presented as having is not actually relevant to their human condition.

Many of these challenges could be better navigated by actually advancing the stated framework for diagnostic criteria as “AD as defined by its biology” through use precise biological terminology to facilitate

diagnostic labeling. For example, it may be much clearer to the public and clinicians to describe the state

of elevated cerebral beta amyloidosis and/or tauopathy (and associated staging) as a biological disease

state, with associated staging, and to separate this terminology from labels that the public and patient

communities associate with disease (understood by the public as having observable health consequences); such as Alzheimer’s and dementia. This will also support clearer and more accurate scientific communication for non-AD co-pathologies through garnering use of accurate and specific terms

rather than general labels with diverse connotations among end users. Minimally rather than stating Alzheimer’s disease, the term “Alzheimer’s disease biology” could be used to enhance clarity among all

affected parties regarding what is meant by “disease” in this specific context.

II. Additional Considerations

There are a number of internal consistencies in the documents stated objectives and scope of proposed

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criteria which are not explained to the reader. As one example, the document states that new criteria are not intended to be used to inform diagnosis and staging, yet state that they should be used to inform diagnosis and staging— in which case they would functionally serve as a guideline for practice. Another example is recognition that the same AD biology results in different phenotypic presentations; yet presentation of clinical staging that is tied to AD biology. Opportunities for earlier recognition and diagnosis of disease, alongside prevention and appropriate treatments are extremely important for alleviating the societal burden of Alzheimer’s disease and dementia. There is generally an assumption that these efforts are generally targeted towards individuals likely to experience health effects due to this underlying disease. There remains inadequate attention to the ethical implications of diagnosing many individuals with a disease for which they may never develop clinical symptoms (based on their age at discovery, other risk and protective factors, etc.) In addition to the personal ethical challenges this poses, there are also societal implications associated with allocation of finite resources for the care of persons at risk for and with the clinical syndrome of dementia – many of whom already do not receive adequate care. It is important that these risks are identified, so that unintended consequences can be anticipated and mitigated. There is also a lack of attention to the reality that the proposed criteria are inaccessible to many health care settings, and the populations they serve.

My comments address the designation of a “pre-clinical” (asymptomatic) stage of Alzheimer’s disease diagnosis. Dementia is unquestionably devastating to the individuals who live with it, their families and communities, and dementia demands much from social safety nets, health care systems, and social services. Thus, it is of critical interest to be able to identify people without cognitive symptoms who will go on to develop dementia—if it is possible to safely intervene to alter their trajectory so that their cognitive symptoms are minimal if present at all. The use of plasma biomarkers for this purpose has appeal, as it fits with the model of continuum of Alzheimer’s disease from pathology-only phenomenon to dementia. It must be true that people who develop the clinical syndrome of dementia have passed through a sequence of pathologic and mild symptom phases, even if those passages were not measured when they occurred. Moreover, extensive evidence indicates that, at the population aggregate, biomarker concentrations in CSF or plasma correspond to higher dementia risk. However, as a raft of evidence suggests, the presence of

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Alzheimer’s pathology—whether in the brain or in CSF or blood—is not a guarantee that a specific person will subsequently develop cognitive symptoms, including those of the most feared degree, dementia. The quality of individual-level prediction is critical for diagnostic and treatment decisions about individuals. The distinction here is similar to the contrast between observing an adverse association between smoking and cardiovascular disease in a population, and using smoking status to diagnose an individual with early-stage cardiovascular disease. For example, a large clinicopathologic study found that of people who did not have dementia upon death, more than 40% had Alzheimer’s brain pathology upon autopsy (Kapasi et al., 2017). Likewise, other evidence suggests that the sequence and timing of pathologic and clinical events in Alzheimer’s disease progression, at least as marked by CSF biomarkers, is far from uniform (Lespinasse et al., 2023). There is still limited evidence as to what cut-points of biomarkers would be used to make diagnoses and clinical decisions. Although some research groups have attained what seems to be reasonable predictive accuracy as indicated by the “area under the curve” index, three features of this evidence stand out: (1) blood biomarkers offer little value in predicting dementia risk beyond cognitive testing and other traditional measures (Planche et al., 2023); (2) the specificity of some proposed cut-points, while “high,” remain low enough to generate a non-trivial number of “false-positives” and therefore mistaken diagnoses (e.g., Janelidze et al., 2023); and (3) sparse evidence on the accuracy of the plasma biomarkers in subgroups of the population, defined, for example, by chronic disease status and racialization. The possibility of identifying people as having “stage 1” or “stage 2” Alzheimer’s disease who never go on to develop symptoms deserves our attention, especially in light of well-intended attempts to designate pre-clinical stages of other conditions or use of screening test to identify persons who likely have an early stage of a condition. Whereas as some of these efforts, such as the pap smear for screening for cervical cancer, have yielded clear benefits and little harm to individuals, other efforts have resulted in wasted resources and even potential harm to individuals, such as with osteopenia (as an early stage of osteoporosis), or biomarker-based tests of prostate cancer for older men. At issue is that imperfect specificity means that many of the “positive” biomarker tests will result in mislabeling people, subject them to further testing, and/or subject them to inappropriate and potentially risky treatment. Assuming that 1 in 4 adults will develop dementia during their lives, a cut-point sensitivity of 0.9, and a specificity of 0.85, 1 in 3 of all positive tests will be in people who never go on to develop dementia. This is a

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staggering burden to those testing positive, their families, and health care systems. It also represents a

diversion of resources from those who truly will go on to develop dementia.

Finally, there is a notable lack of evidence about the performance of plasma biomarkers among persons

living with chronic disease (notably renal illness, which could affect plasma concentrations), and among

person in racialized communities. This is especially concerning given that persons with these characteristics bear disproportionately high risks of dementia.

A definition and diagnosis of pre-clinical Alzheimer's disease will serve us well when approaches are available that do not burden people who are truly not at risk for dementia, and that result in better dementia outcomes among people who truly are. With the measures on hand, we are not there yet.

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Dear Dr. Jack,

We would like to share with you some comments/suggestions from our Community of more than 100 clinicians/researchers collaborating since 2018 within the frame of the INTERCEPTOR project.

This project is a Public Health-oriented initiative funded by the Italian Health Ministry and Agency for Drugs aiming to recruit and follow-up for 3 years a population of nearly 400 MCI subjects enrolled in 20 Centres in a hub-&Spoke nationwide organization. At time 0 besides the neuropsychological tests for the MCI condition diagnosis, various biomarkers have been collected including PET-FDG, volumetric MRI, EEG for connectivity, CSF for amyloid/tau metabolites, blood for ApoE genetic testing. Every biomarker has been centrally evaluated by an Expert center.

Along the follow-up about 100 subjects reached the threshold for dementia diagnosis. The accuracy/specificity/sensitivity of individual biomarkers and of their different combinations as well as the costs/benefits ratio will be evaluated in the next weeks/months. Follow-up just finished on

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October 31 st and all the statistical analysis is actually going-on.

Within the frame of the experience we developed during this 5 years study we would like to share with you some comments on the draft guidelines of the Alzheimer's Association.

We hope this contribution will help in improving the final document under you guidance.

Nowadays, worldwide Health systems and scientific societies are focusing on identifying the preclinical and prodromal phases of Alzheimer's disease. An early AD diagnosis is essential for improving patient's quality of life as well as reducing the healthcare and social costs associated with dementia management.

Considering the updated criteria for AD, we point out some critical issues and starting points for future considerations.

Firstly, according to this proposal, neuropsychological tests and brain MRI are not anymore essential in the diagnostic workflow of AD. However, up to date, a complete neuropsychological assessment represents the most indicative method to evaluate the cognitive status of an individual complaining cognitive disturbances. In this update, the Authors propose that abnormality on specific Core 1 biomarkers are sufficient to diagnose AD, without performing comprehensive neuropsychological tests. Specifically, they propose that amyloid PET, CSF A β 42/40, CSF p-tau181/A β 42 and CSF t-tau/A β 42 are diagnostic for identifying the disease. Therefore, in this perspective, also asymptomatic individuals can be directly considered as affected by AD even if they might potentially never develop symptoms; meanwhile, in the immediate, such a 'suspected diagnosis' might determine adverse consequences on the psychosocial functioning of those individuals and their families.

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Additionally, due to their high costs, limited availability, and invasiveness, PET and CSF tests cannot be readily applied on a large scale, as at a national level, for a first-level diagnostic workup. For instance, tau-PET is an expensive technique which is not available in all clinical centers.

The novel proposal should also take into account that the general measurements of amyloid or tau might be influenced by some demographic variables, such as individual age. Indeed, the burden of these proteins, which reflects the disease severity, can differently impact on individuals functioning and quality of life at different age levels.

A further consideration is addressed to the Author proposal of including the EEG study into N biomarker category. EEG may be one of the 'early stage' measures since it provides insight into synaptic connectivity. However, EEG measurements should be not considered as specific marker of an etiological diagnosis, but as a first level screening method also in consideration of its low-cost, total harmlessness and widespread availability with also the easy-to-perform signal transfer via web-based technological platforms to Expert centers for advanced (i.e. Artificial Intelligence) signal analysis.

To conclude, in the context of Public Health-oriented research (and not of clinical trials for innovative drugs), it is essential to consider the challenges associated with the need of standardizing analytical procedures for biomarkers. Normative values and biomarker cut points are also mandatory to harmonize clinical procedures among all clinical sites.

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Response from International Federation of Clinical Neurophysiology to Alzheimer's Association's paper, 'Criteria for Diagnosis and Staging of Alzheimer's Disease: Alzheimer's Association 2 Workgroup,' to which public responses were sought. Clifford Jack, coordinator of the initiative; jack.clifford@mayo.edu

I write on behalf of the IFCN executive committee to respond to your document on diagnosis and staging of Alzheimer's Disease. We were gratified that in the section on non-specific biomarkers you cited the important paper of Gouw et al from 2017.

'EEG may be one of the synaptic measures since it provides insight into synaptic connectivity. Functional connectivity measures have shown to be related both to cognitive performance and to AD pathophysiology.'

May we also bring to your attention some more recent work employing complex EEG analysis in this field? While differentiating those with healthy controls and those with Alzheimer's is not difficult, the need is for a reliable biomarker for the earliest stages. EEG has shown promise here. Gouw et al have shown that it can distinguish those healthy amyloid positive subjects who are more likely to convert to MCI and then Alzheimer's. (For overviews see Ferreri et al and Dubois et al). EEG can also contribute later in Alzheimer's. Those with the condition with more abnormal EEGs go onto have more rapid deterioration of their pathology, (Briels et al). EEG is also very sensitive in detecting Lewy Body pathology in the dementia stage, as well as in the precursor "MCI" state, (van der Zande et al). A very recent paper showed that analysis of both whole brain and regional power in resting state EEGs could distinguish Alzheimer's from mild cognitive impairment, (Scheijbeler et al). Since Alzheimer's is primarily a disease of neuronal function and connectivity, advanced EEG analysis, which looks at these in real time, non-invasively and relatively cheaply, seems well placed to become part of the investigative toolkit used in the diagnosis, assessment of severity, and of progression and response to treatment in Alzheimer's and other neurodegenerative and conditions of cognitive impairment. Beyond excluding non-convulsive status epilepticus as a cause for cognitive decline, EEG may prove a useful first step diagnostic procedure for populations at risk, allowing further investigation to be more targeted.

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