



Published in final edited form as:

JAMA Neurol. 2024 December 01; 81(12): 1304–1311. doi:10.1001/jamaneurol.2024.3770.

Alzheimer disease is a clinical-biological construct: An IWG recommendation

Bruno Dubois, MD, MSc^{1,2}, Nicolas Villain, MD, PhD^{1,3}, Lon Schneider, MD, MSc⁴, Nick Fox, MD, MA⁵, Noll Campbell, PharmD, MSc^{6,7,8}, Douglas Galasko, MD, MSc⁹, Miia Kivipelto, MD, PhD^{10,11}, Frank Jessen, MD^{12,13,14}, Bernard Hanseeuw, MD, PhD^{15,16,17}, Mercè Boada, MD, PhD^{18,19}, Frederik Barkhof, MD, PhD^{20,21,22}, Agneta Nordberg, MD, PhD^{23,24}, Lutz Frolich, MD, PhD²⁵, Gunhild Waldemar, MD, DMSc^{26,27}, Kristian Steen Frederiksen, MD, PhD^{26,27}, Alessandro Padovani, MD, PhD^{28,29}, Vincent Planche, MD, PhD^{30,31}, Christopher Rowe, MD³², Alexandre Bejanin, PhD^{33,34}, Agustin Ibanez, PhD^{35,36}, Stefano Cappa, MD^{37,38}, Paulo Caramelli, MD, PhD³⁹, Ricardo Nitrini, MD, PhD⁴⁰, Ricardo Allegri, MD, PhD^{41,42}, Andrea Slachevsky, MD, PhD^{43,44,45}, Leonardo Cruz de Souza, MD, PhD³⁹, Andrea Bozoki, MD⁴⁶, Eric Widenra, MD^{47,48}, Kaj Blennow, MD, PhD^{49,50}, Craig Ritchie, MD, PhD^{51,52}, Marc Agronin, MD⁵³, Francisco Lopera, MD⁵⁴, Lisa Delano-Wood, PhD^{55,56,57}, Stéphanie Bombois, MD, PhD¹, Richard Levy, MD, PhD^{1,2}, Madhav Thambisetty, MD, DPhil⁵⁸, Jean Georges, BA⁵⁹, David T. Jones, MD^{60,61}, Helen Lavretsky, MD, MSc^{62,63}, Jonathan Schott, MD, BSc⁶⁴, Jennifer Gatchel, MD, PhD^{65,66,67,68,69}, Sandra Swantek, MD⁷⁰, Paul Newhouse, MD^{71,72,73}, Howard H Feldman, MD^{74,75}, Giovanni B Frisoni, MD^{76,77}

¹AP-HP Sorbonne Université, Pitié-Salpêtrière Hospital, Department of Neurology, Institute of Memory and Alzheimer's Disease, Paris, France

²Sorbonne Université, INSERM U1127, CNRS 7225, Institut du Cerveau - ICM, 'FrontLab', Paris, France

³Sorbonne Université, INSERM U1127, CNRS 7225, Institut du Cerveau - ICM, 'Maladie d'Alzheimer, Maladies à prions', Paris, France

⁴Keck School of Medicine of the University of Southern California, Los Angeles, USA

⁵Dementia Research Centre, Department of Neurodegenerative Disease, and the UK Dementia Research Institute, UCL Queen Square Institute of Neurology, London WC1N 3AR, UK

⁶Purdue University College of Pharmacy, West Lafayette, Indiana, USA

⁷Purdue University Center for Aging and the Life Course, West Lafayette, Indiana, USA

⁸Indiana University Center for Aging Research, Indianapolis, Indiana, USA

⁹Department of Neurosciences, University of California, San Diego, La Jolla, CA, USA

¹⁰Center for Alzheimer Research, Karolinska Institutet, Department of Geriatric Medicine, Karolinska University Hospital, Stockholm, Sweden

¹¹Institute of Clinical Medicine/ Neurology, University of Eastern Finland, Kuopio, Finland

Corresponding author: Bruno Dubois, Département de Neurologie, Groupe Hospitalier Pitié-Salpêtrière, 47-83 boulevard de l'Hôpital 75651 PARIS Cedex 13, FRANCE, bruno.dubois@aphp.fr.

- ¹².Department of Psychiatry, Medical Faculty, University of Cologne, Cologne, Germany.
- ¹³.German Center for Neurodegenerative Diseases (DZNE), Bonn, Germany.
- ¹⁴.Excellence Cluster on Cellular Stress Responses in Aging-Associated Diseases (CECAD), University of Cologne, Cologne, Germany.
- ¹⁵.Department of Neurology, Cliniques Universitaires Saint-Luc, Brussels, Belgium.
- ¹⁶.Institute of Neurosciences, UCLouvain, Brussels, Belgium.
- ¹⁷.Department of Radiology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA Institute of Neuroscience, UC Louvain, Brussels, Belgium
- ¹⁸.Ace Alzheimer Center Barcelona – Universitat Internacional de Catalunya, Barcelona, Spain
- ¹⁹.Networking Research Center on Neurodegenerative Diseases (CIBERNED), Instituto de Salud Carlos III, Madrid, Spain
- ²⁰.Centre for Medical Image Computing (CMIC), Department of Medical Physics and Bioengineering, University College London, London, United Kingdom
- ²¹.Amsterdam UMC, location VUmc, Department of Radiology and Nuclear Medicine, Amsterdam, The Netherlands
- ²².Queen Square Institute of Neurology, University College London, UK
- ²³.Department of Neurobiology, Care Sciences and Society, Center for Alzheimer Research, Karolinska Institutet, Stockholm, Sweden
- ²⁴.Theme Inflammation and Aging, The Aging Brain, Karolinska University Hospital. Stockholm, Sweden
- ²⁵.Department of Geriatric Psychiatry, Central Institute of Mental Health, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany.
- ²⁶.Danish Dementia Research Centre, Department of Neurology, Copenhagen University Hospital - Rigshospitalet, Copenhagen, Denmark
- ²⁷.Dept. of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Denmark.
- ²⁸.Director Neurology and Neurophysiology Section, Department Clinical and Experimental Sciences, University of Brescia
- ²⁹.Director of the Hospital Department of “Continuità di Cura e Fragilità”, ASST Spedali Civili di Brescia
- ³⁰.Univ. Bordeaux, CNRS, Institut des Maladies Neurodégénératives, UMR 5293, Bordeaux, France
- ³¹.Pôle de Neurosciences Cliniques, Centre Mémoire de Ressources et de Recherche, CHU de Bordeaux, France
- ³².Department of Molecular Imaging and Therapy, Austin Health, The University of Melbourne, Melbourne, VIC, Australia

33. Sant Pau Memory Unit, Department of Neurology, Hospital de la Santa Creu i Sant Pau, Biomedical Research Institute Sant Pau, Universitat Autònoma de Barcelona, Barcelona, Spain
34. Center of Biomedical Investigation Network for Neurodegenerative Diseases (CIBERNED), Madrid, Spain
35. Latin American Institute for Brain Health (BrainLat), Universidad Adolfo Ibanez, Santiago, Chile
36. Global Brain Health Institute (GBHI), Trinity College Dublin, Dublin, Ireland
37. University School for Advanced Studies (IUSS), Pavia, Italy
38. RCCS Mondino Foundation, Pavia, Italy
39. Behavioral and Cognitive Neurology UNit, Faculdade de Medicina, Universidade Federal de Minas Gerais, Belo Horizonte (MG), Brazil
40. Department of Neurology, Faculdade de Medicina, Universidade de São Paulo, Brazil
41. Department of Cognitive Neurology, Fleni Neurological Institute, Buenos Aires, Argentina.
42. Department of Cognitive Neurosciences, Universidad de la Costa (CUC), Barranquilla, Colombia.
43. Geroscience Center for Brain Health and Metabolism (GERO), Santiago, Chile
44. Memory and Neuropsychiatric Center (CMYN) Neurology Department, Hospital del Salvador and Neuropsychology and Clinical Neuroscience Laboratory (LANNEC), Institute of Biomedical Sciences (ICBM), Faculty of Medicine, University of Chile.
45. Neurology and Psychiatry Department, Clínica Alemana-Universidad Desarrollo, Santiago, Chile
46. Department of Neurology, University of North Carolina, Chapel Hill, North Carolina, USA
47. Division of Geriatrics, University of California San Francisco
48. Hospice & Palliative Care, San Francisco Veterans Affairs Health Care System
49. Institute of Neuroscience and Physiology, Department of Psychiatry and Neurochemistry, The Sahlgrenska Academy at the University of Gothenburg, Mölndal, Sweden
50. Clinical Neurochemistry Laboratory, Sahlgrenska University Hospital, Mölndal, Sweden
51. Professor of Brain Health and Neurodegenerative Medicine, University of St Andrews, Scotland. UK
52. Scottish Brain Sciences, Edinburgh, Scotland. UK
53. Medical Office for MIND Institute (MEA), Miami
54. Grupo de Neurociencias de Antioquia (GNA), Facultad de Medicina, Universidad de Antioquia, Medellín, Colombia
55. Veterans Affairs San Diego Healthcare System, San Diego, CA, USA.
56. Department of Psychiatry, University of California San Diego Health, La Jolla, CA, USA.
57. Center for Stress and Mental Health, VA San Diego Healthcare System, San Diego, CA, USA

- ⁵⁸.Clinical and Translational Neuroscience Section, Laboratory of Behavioral Neuroscience, National Institute on Aging, National Institutes of Health Baltimore, MD 21224
- ⁵⁹.Alzheimer Europe, Luxembourg
- ⁶⁰.Department of Neurology, Mayo Clinic, Rochester, MN, USA
- ⁶¹.Department of Radiology, Mayo Clinic, Rochester, MN, USA
- ⁶².Semel Institute for Neuroscience and Human Behavior, Department of Psychiatry and Biobehavioral Sciences
- ⁶³.David Geffen School of Medicine, University of California, Los Angeles (UCLA)
- ⁶⁴.Dementia Research Centre, UCL Queen Square Institute of Neurology, UCL, London, UK.
- ⁶⁵.Massachusetts General Hospital Department of Psychiatry, Boston MA
- ⁶⁶.McLean Hospital, Belmont MA
- ⁶⁷.Harvard Medical School, Boston MA
- ⁶⁸.Baylor College of Medicine Department of Psychiatry, Houston TX USA
- ⁶⁹.Michael E. DeBakey VA Medical Center, Houston TX USA
- ⁷⁰.Pt American Association for Geriatric Psychiatry
- ⁷¹.Vanderbilt University, 2301 Vanderbilt Place, Nashville, TN, 37235, USA.
- ⁷².Center for Cognitive Medicine, Department of Psychiatry, Vanderbilt University Medical Center, Nashville, TN, USA.
- ⁷³.VA-TVHS Geriatric Research Education and Clinical Center, Nashville, TN, USA.
- ⁷⁴.Department of Neurosciences University of California, San Diego, La Jolla, CA, USA
- ⁷⁵.Shiley-Marcos Alzheimer's disease Research Center, University of California, San Diego, La Jolla, CA, USA
- ⁷⁶.Laboratory of Neuroimaging of Aging (LANVIE), University of Geneva, Geneva, Switzerland
- ⁷⁷.Memory Clinic, University Hospital of Geneva, Geneva, Switzerland

Abstract

Importance: Since 2018, a movement has emerged to define Alzheimer disease (AD) as a purely biological entity based on biomarker findings. The recent revision of the Alzheimer Association (AA) criteria for AD furthers this direction. However, concerns about a purely biological definition of AD being applied clinically, the understanding of AD by society at large, and the translation of blood-based biomarkers into clinical practice prompt this International Working Group (IWG) updated recommendations.

Objective: To consider the revised AA criteria and to offer an alternative definitional view of AD as a clinical-biological construct for clinical use. We update recommendations of the 2021 IWG diagnostic criteria for further elaborating at risk and presymptomatic states.

Evidence Review: We searched PubMed for articles published between Jul 1, 2020, and March 1, 2024, using the terms “biomarker” OR “amyloid” OR “tau” OR “neurodegeneration” OR “preclinical” OR “CSF” OR “PET” OR “plasma” AND “Alzheimer’s disease”. We also searched the references of relevant articles.

Findings: In the new AA diagnostic criteria, AD can be defined clinically as encompassing cognitively normal people having a core 1 AD biomarker. However, recent literature shows that the majority of biomarker positive cognitively normal individuals will not become symptomatic along a proximate timeline. In the clinical setting, disclosing a diagnosis of AD to cognitively normal people with only Core 1 AD biomarkers, represents the most problematic implication of a purely biological definition of the disease.

Conclusions and Relevance: the ultimate aim is to foster effective AD treatments, including preventing symptoms and dementia. We consider that the approach of diagnosing AD without a clinical and biological construct as being unwarranted and potentially concerning without a clear knowledge of when or whether symptoms will ever develop. We recommend that amyloid-positive only and more generally most of biomarker positive cognitively normal individuals should not be labeled as having AD. Rather they should be considered as being at risk. We see the expansion of presymptomatic AD as being a better diagnostic construct for those with a specific pattern of biomarkers, indicating that they are proximate to the expression of symptoms in the near future.

The recently revised AA criteria for Alzheimer disease (AD)¹ propose to define AD on biological evidence only. The diagnosis of AD can be provided to cognitively normal people with evidence of “core 1 AD biomarkers” encompassing CSF ABeta and Tau ratios and plasma phosphoTau217 validated against amyloid PET, even though these new criteria do not recommend testing for these biomarkers in cognitively normal individuals. This raises the question of the role and influence of biomarkers in the diagnostic workup.

The value of biomarkers

In 2007, the International Working Group (IWG) revised the 1984 diagnostic criteria for AD and were the first to propose that the diagnosis of AD in patients with cognitive deficits could be anchored around the presence of biomarkers to support more accurate and earlier disease diagnosis². Since then, brain amyloid PET has been shown to correlate with the presence and density of beta-amyloid plaques in autopsy-derived brain tissue samples. CSF and plasma amyloid and phospho-tau biomarkers have been validated against amyloid PET. These validations justify the inclusion and reimbursement of biomarkers in diagnostic work-ups in different countries. However, the clinical value and utility of these biomarkers or tests differ depending on the context, e.g., research or clinical settings, in which they are used^{3,4}.

The availability of these biomarkers has radically changed both observational and clinical trial research⁵. They are regularly used to identify and confirm the presence of AD pathology with a strong emphasis on amyloid, to study the natural history of disease biology, to evaluate pharmacodynamic effects of treatment candidates, and as surrogate clinical outcomes in clinical trials. At variance with post-mortem investigation, which provides the final definitive but static information about lesions in the brain, these biomarkers allow

dynamic in-vivo monitoring of pathological changes and inform about their relationships to the onset and progression of symptoms⁶. Each biomarker provides information about a type of pathological lesion or a process that has its own weight and contribution to the natural history of the disease. However, the so-called “AD core 1 biomarkers” are individually insufficient to account for the many mechanisms and interactions underlying the disease process. In turn, selected tau and amyloid biomarkers should be conceptualized as AD risk factors with different/specific weights and synergies across the disease continuum. The potential of many other biological markers is currently being actively investigated including markers of glial activation and neuroinflammation, such as GFAP and YKL-40; neurodegeneration, such as neurofilament light chain (NfL); as well as synaptic dysfunction and degeneration, such as neurogranin and SNAP-25⁷.

In the clinical setting, amyloid and tau biomarkers are used to support or refute a clinically suspected diagnosis. As acknowledged by neuropathologists in a National Institute of Aging conference consensus in 2012⁸, Alzheimer neuropathologic changes are necessary but not sufficient for establishing the diagnosis of AD. They concluded, aligned with its historical definition, that ‘Alzheimer disease’ is a clinico-pathological entity that should be disentangled from Alzheimer pathological changes, which are frequently observed in post-mortem brains of aged individuals who died without any cognitive or functional decline⁹. Additionally, lesions of different pathological nature are frequently observed post-mortem due to the high prevalence of comorbidities and to the synergy between pathologies¹⁰: combinations of alpha-synuclein aggregates (Lewy bodies), insoluble aggregates of TAR DNA-binding protein 43 (TDP-43), non-AD tauopathies, and vascular pathologies commonly exist alongside with amyloidopathy and AD tauopathy. These are more the norm than the exception in pathological studies¹¹ on sporadic cases.

The inherent logic of the new AA criteria leads to the conclusion that the development of emerging biomarkers of co-pathologies, e.g., alpha-synuclein, TDP-43, and others in the future, could result in the diagnosis of two, three, or more different neurodegenerative diseases in a cognitively normal person, as a norm.¹¹ While multiple diagnoses are common in elderly patients, it took decades of studies to demonstrate the superiority of the comorbidity-based versus the additive single-disease approach, now accepted as a valid clinical construct¹². Therefore, we argue that biomarkers alone should remain markers of pathological processes and not markers of a specific disease⁸. Furthermore, the contribution of biomarkers in the clinical setting depends on the context of use³ and, importantly, should differ between the assessment of cognitively impaired and unimpaired individuals⁴.

Contribution of biomarkers in cognitively impaired patients

The combination of common (amnestic syndrome of the hippocampal type, logopenic aphasia, posterior cortical atrophy) or uncommon (cortico-basal syndrome, behavioral and dysexecutive variants) clinical phenotypes and the positivity of pathophysiological amyloid and tau biomarkers establishes the diagnosis of AD⁴. This association defines the clinical-biological entity of the disease, proposed by the IWG⁴, in line with the clinical-pathological description by Alois Alzheimer^{13,14} and the neuropathological consensus⁸. This scenario also enables a clinical-biological diagnosis at an early prodromal stage, i.e., once mild

but definite symptoms are in place. The concept of AD as a clinical-biological entity has played a vital role in the FDA's approval of anti-amyloid monoclonal in prodromal AD^{15–17}. The clinical implications and associated diagnostic narrative of the IWG and AA criteria are similar in the case of such cognitively impaired biomarker-positive patients, but very different in cognitively normal individuals¹⁸.

Contribution of biomarkers in asymptomatic at-risk and presymptomatic AD

Many cognitively normal people, with or without cognitive complaints, seek expert advice for their memory concerns, subjective perception of cognitive decline, positive family history of AD, or simply the wish to know their risk of AD. These persons can present with normal objective memory and cognitive performance and ask for evidence-based and clinically meaningful answers. Here, it is again necessary to distinguish between research and clinical settings.

In the research setting, there is major interest in developing effective drugs or other interventions at the earliest point in time possible in persons with an increased risk of progression to AD dementia. Functional recovery as a treatment outcome is highly unlikely once the degeneration in neural networks has reached a threshold of severity. We are in support of all research efforts in the field to move towards the goal of decreasing the incidence of cognitive impairment in cognitively normal persons at risk. As brain β -amyloidosis is an acknowledged risk factor for the onset of clinical symptoms, we endorse the view that clearing amyloid burden may possibly reduce the risk of future cognitive impairment—under certain conditions— analogous to treating vascular risk factors to prevent myocardial infarction or stroke. The vascular analogy has been endorsed by the international Dominantly Inherited Alzheimer Network, which has used the hypercholesterolemia/heart disease analogy to interpret their results on biomarker changes in autosomal dominant AD¹⁹.

In the clinical setting, extending the diagnosis of AD to cognitively normal people with only core 1 AD biomarkers, represents the most problematic implication of diagnostic criteria that have a purely biological definition of the disease. The argument invoked by the AA workgroup is the analogy with cancer, where less severe stages, such as in situ gastric or breast cancer, allow the earliest possible diagnosis and the most favorable outcomes^{1,20}. In these cancer scenarios, an asymptomatic incubation period is followed by gradual and steady growth resulting in the occurrence of the clinical symptoms over a fairly predictable time course. This scenario is fitting for the autosomal dominant form of AD, where fully penetrant monogenic mutations in the *APP*, *PSEN-1*, and *PSEN-2* genes identify persons who will almost invariably develop symptoms during their normal lifespan and to Down syndrome where the abnormal production of β -amyloid is responsible for the almost universal development of AD dementia²¹.

The model cannot be transferred to cognitively normal individuals with sporadic Alzheimer pathologic changes, as their lifetime risk of becoming symptomatic is much lower. Indeed, the lifetime risk of AD dementia in a 65-year-old man who is amyloid-biomarker positive has been estimated at 21.9%, a mere 1.7 times higher than the risk of amyloid negative of similar age²². Other reports have confirmed these estimates, with a lack of significant

clinical progression in the ADNI cohort in cognitively normal individuals with isolated abnormal amyloid biomarker after an 8-year follow-up²³, while in research cohorts, only 17% of these individuals of cognitively normal individuals with isolated abnormal amyloid biomarker progressed to mild cognitive impairment over six years²⁴. Therefore, the revised AA criteria, proposing that a diagnosis of AD can be reduced to the sole presence of one AD core 1 biomarkers, may introduce major uncertainty and variability in the clinical prognosis of patients diagnosed with AD¹. The risk of progression of those who have abnormal amyloid biomarker is marginally increased, including in those with combined abnormal amyloid and tau biomarkers (i.e., soluble AD Tau biomarkers [“T1” biomarkers according to the AA framework: HR = 1.08–1.31]²⁵, and unstratified Tau PET positivity [35% of progression after 7 years of follow-up])^{25,26}. However, the risk of progression to AD dementia significantly increases when the aggregated forms of tau spread out in neocortical areas²⁴. This biomarker profile, together with other specific conditions (Panel 1), suggests that the underpinning pathological processes are active and that the development of clinical symptoms in the near future may be virtually inevitable. We do foresee the evolution of the diagnostic construct we have introduced previously of presymptomatic AD as applying well within the diagnostic lexicon. In its initial iteration, it was introduced within the IWG framework for monogenic fully penetrant AD mutations. We foresee being able to add new biomarker profiles within this presymptomatic grouping. Currently, long-term evidence for clinical progression remains limited and estimates are based on non-representative convenience cohorts of relatively small group size.

To summarize, the IWG approach allows the identification of two different categories of cognitively normal biomarker-positive subjects with different specific management strategies (Panel 1). First, individuals who are (A+) and (A+ and T1+) have an increased but far from a convincing benchmark of certainty of developing clinical AD within their expected lifetimes. These subjects should be labeled “at-risk,” and their follow-up in longitudinal cohorts will identify the modulating factors increasing/decreasing the risk of dementia and the likely emergence of symptoms. Second, individuals who are cognitively normal but are already on the path to clinical disease. We anticipate a realistic future where more and more of these individuals could be considered presymptomatic AD on the basis of models that incorporate a multiplicity of predictive biomarkers. (Panel 1)

The pathophysiological framework

The above classification derives from a theoretical pathophysiological framework recently developed as a revision of the traditional amyloid cascade, the probabilistic amyloid cascade model²⁷. This model postulates decreasing penetrance of the phenotype from autosomal dominant mutations (almost complete penetrance) to *APOEε4* carrier status (intermediate penetrance) and *APOEε4* non-carrier status (lowest penetrance) due to the increasing effect of stochastic factors (non-*APOE* genes, environmental exposures, co-pathology). It further implies that brain amyloidosis in cognitively normal persons is a risk factor for cognitive impairment and dementia, and that the risk is higher in *APOEε4* carriers.

The model further implies that the risk of progression to cognitive impairment in the asymptomatic at-risk can be estimated by considering both markers of Alzheimer pathology

(amyloid and tau), other pathologies including TDP 43, vascular and Lewy body, resilience, lifetime and environmental factors, genetics, and other biomarker risk factors^{10,28}. The model is consistent with the view that amyloid and tau biomarkers can be used in combination to diagnose AD in cognitively impaired patients.²⁹

The societal impact

the consideration of whether cognitively normal persons with positive biomarkers for Alzheimer pathology should be labeled as asymptomatic at risk or already affected by AD, is not “just semantics”, because behind the different concepts and semantic differences lie different strategies of management of these persons (Table 1). There is a need to acquire detailed personalized risk knowledge and to be able to communicate this effectively in clinical practice.

A rich literature is available on the safety of disclosure of amyloid status to cognitively normal people^{30,31}. The disclosure narrative and the way results are communicated have a significant impact on patient experience and involve clarifying that amyloid status does not equal AD^{32,33}.

We cannot see any benefit in providing a diagnosis of AD to those who are cognitively normal with positive biomarker subjects with a high chance of never developing cognitive impairment in their lifetime. The resulting psychological and societal consequences of being diagnosed with AD and never developing symptoms can be consequential^{34,35}. In addition, recent findings show that high-dose gantenerumab achieved similar amyloid PET clearance as approved aducanumab despite its lack of clinical effectiveness.^{36,37} This demonstrates the potential liability of the clinical and biological dissociation of AD definition regarding drug approval. This decision becomes particularly challenging when dealing with biomarker-positive cognitively normal individuals, as the clinical effects may be more delayed in this population. There is a greater inclination to depend on a surrogate biomarker to account for the delayed clinical effect when evaluating this group³⁸, which adds to the uncertainty in determining treatment efficacy, especially if the biomarker is definitory, as proposed by the AA.

Last, the potential for diagnostic error should not be underestimated, considering realistic statistical parameters of the respective biomarkers in real-world clinical practice, e.g., PPV and NPV, that are, by definition, influenced by the disease prevalence in a given context of use³. In principle, a protein biomarker always delivers a probabilistic distinction of groups as opposed to genetic biomarkers, which may offer a deterministic separation of groups. As an example, cut-off points for AD biomarkers extrapolated from White North American and European population samples to more diverse populations have uncovered significant differences.³⁹ Hence, interpreting biomarkers in the clinical context is crucial, as also emphasized by the AA criteria. This underscores the inherent limitations of relying solely on a biological definition of AD in clinical practice.¹

The potential consequences are easily understandable for patients consulting for a benign memory complaint due to attention disorders or age-related changes and the biomarker

positivity representing a false positive diagnosis⁴⁰. These risks will be amplified when testing is done directly to the consumer as it is currently becoming available commercially and through online sources without physician or clinician involvement. Given the current availability of blood-based biomarkers for amyloid and tau, an explosion of cognitively normal persons who are labeled as having “Alzheimer disease” on a purely biological definition of the disease may be expected⁴¹. As a result, increasing societal pressure for anti-tau or anti-amyloid drugs to prevent cognitive decline is foreseeable, including treatment offlabel in persons who are cognitively normal.

The AA’s criteria do not endorse having the use of biomarkers to identify AD in those who are cognitively normal. Unfortunately, there may be no realistic way to control access to these biomarkers or diagnosis or treatment when a biomarker only diagnosis is made according to these criteria. Considering the concerns raised above, we believe that it is necessary to provide a clearer message on this critical issue. We recommend that routine diagnostic testing should not be performed in cognitively normal individuals outside of research purposes at this time. In this population, biomarkers of amyloid pathology are not diagnostic markers but risk markers. Risk assessment differs from diagnostic assessment, which can be done in the context of non-diagnostic patient journeys^{41,42}.

Diagnostic criteria for AD can have far-reaching societal, political, organizational, and economic implications. We want to restrict the focus in this position paper to the scientific evidence and clinical impact on healthcare practice of these proposed revised criteria. Considering AD as a purely biological entity may be useful for research studies in cognitively normal individuals. However, the IWG’s approach of considering biomarker positivity in the absence of cognitive impairment as a risk condition rather than a disease, in most cases, increases the motivation for secondary prevention treatments. It also enhances the societal relevance of AD, similar to the impact of risk factors for cardiovascular diseases^{42,43}. Instead, it will help better assess the risk/benefit ratio of drugs according to each context of use. Moreover, communicating a risk condition may stimulate these individuals to control their risk factors and change their lifestyle, as well as prompting public health policymakers to foster initiatives and programs for reducing dementia risk at the population level.

The future: defining the risk in cognitively normal individuals.

The conceptual approach proposed by the IWG is to maintain the essential clinical-pathological concept of AD¹⁴. We separate asymptomatic at-risk individuals from those who already have the disease. Persons who are asymptomatic at-risk deserve full research interest and engagement since current estimates of their cumulative risk of progression to cognitive impairment are undetermined and need to be defined according to their genetic and biomarker profile, factors of risk or prevention, lifestyle and potential mechanism of resilience. Individual cumulative risk profiling will drive strategies for risk reduction, including treatments with acceptable risk/benefit/cost ratio. The need is urgent to better estimate the risk of progression in the asymptomatic at-risk and the presymptomatic at large, from well-designed observational representative population-based studies with long follow-up and accurate measurements of baseline modifiable risk factors and biomarkers of

Alzheimer pathology^{43,44}. The study of groups for whom this information is lacking (e.g., non-white and ethnic minorities and populations from low and middle-income countries) is of utmost importance, as their dementia risk factors may differ.

There are task forces actively engaged in devising practical solutions for the asymptomatic at-risk and the presymptomatic persons. In particular, Brain Health Services for the Prevention of Dementia (dBHS) will offer: i) evaluation of risk; ii) communication of risk; and iii) risk reduction interventions targeting modifiable risk factors and disease modifiers when these will be shown effective⁴². Over time, the scenario might further evolve when well-tolerated drug treatments are developed. In such cases, a lower threshold of risk could be proposed for a preventive treatment in asymptomatic at-risk individuals.

To conclude, IWG continues to advocate for AD as is a clinical-biological entity.

In a clinical setting, a diagnosis of AD is made in the presence of established clinical phenotype with supportive pathophysiological biomarkers of AD pathology (CSF biomarkers, amyloid or Tau PET, or plasma biomarkers such as p-tau 217 pending their approval in clinical practice). The AD diagnosis encompasses the prodromal AD (predementia) and AD dementia stages, as these are just stages of the same disease.

The IWG discourages the use of biomarker investigation in cognitively normal individuals with or without complaints (e.g. in the so-called subjective cognitive decliners) to diagnose AD. Biomarker investigations in cognitively normal individuals can be done in the context of *ad hoc* non-diagnostic patient journeys aiming to evaluate the risk of future cognitive impairment, to communicate it, and to put in place risk reduction interventions. Pilot experiences of such patient journeys are currently in a research phase services, and might move into the clinic after due validation. Studies of cognitively normal subjects with positive AD biomarkers are important for defining predictive algorithms and risk estimates of progression to clinical symptoms. A very limited number of these subjects will be considered presymptomatic because of a genetic autosomal dominant mutation or because of a very high risk for imminent cognitive impairment due to a particular biomarker profile. All the other biomarker-positive individuals, much more numerous, should be considered as asymptomatic at-risk.

Future research should study cognitively normal persons in two main directions: i) observational longitudinal studies with long follow-up where lifestyle risk factors and biomarkers are simultaneously assessed to accurately estimate the independent weight of each on the incidence of cognitive impairment and dementia. ii) interventional clinical trials, to test the efficacy of drugs against Alzheimer pathology and other risk reduction strategies in reducing the incidence of cognitive impairment and assess the therapeutic risk/benefit profiles.

Panel 1- The 2024 IWG lexicon

We encourage the use of the following terms “at-risk for Alzheimer disease”, “presymptomatic Alzheimer disease” and “Alzheimer disease” according to the following definitions.

1. Asymptomatic at-risk for AD:

- Refers to cognitively normal individuals at increased risk of developing cognitive impairment because of uncertain/undetermined risk associated with a given biomarker profile.
- With currently available data, the biomarker profile corresponds to brain amyloidosis either isolated or associated with tauopathy limited to the medial temporal regions or a positive phospho-tau fluid biomarker.
- The lifetime risk of progression to cognitive impairment is increased compared to biomarker-negative individuals but remains far from a deterministic rate for clinical progression.
- They should not be defined as having Alzheimer disease.

2. Presymptomatic AD:

- Refers to cognitively normal subjects with a specific pattern of biomarkers associated with an almost deterministic and very high lifetime risk of progression.
- Examples of biomarker profiles associated with presymptomatic conditions:
 - Highly penetrant autosomal dominant genetic mutations associated with a close to 100% lifetime risk of clinical AD: APP, PSEN1, PSEN2
 - Persons affected with Down syndrome
 - Persons homozygous for the *APOE* e4 allele 4 with SORL1 loss of function^{4,45}. (For these profiles, age and parental age is an additional factor to take into account for the determination of the age at onset of the clinical expression of AD).
 - Sporadic AD pathology biomarker changes (+/- genetic background) associated with a very high lifetime risk of clinical AD such as amyloid PET(+) with tau PET(+) in neocortical regions²⁴.

Future studies from population-based cohort may identify distinct biomarker profiles including additional risk factors defining this subgroup.⁴⁶

3. Alzheimer disease:

- Refers to cognitively impaired individuals with:
 - Specific clinical phenotypes: common (amnestic syndrome of the hippocampal type, logopenic aphasia, posterior cortical atrophy) or uncommon (cortico-basal syndrome, behavioral and dysexecutive variants)

- And a positivity of CSF or PET pathophysiological AD biomarkers⁴. Plasma biomarkers such as p-tau 217 may soon enter the routine clinical workup.

This includes the prodromal (mild cognitive impairment and no loss of function) and dementia (with loss of function) stages.

References

1. Jack CR, Andrews JS, Beach TG, et al. Revised criteria for diagnosis and staging of Alzheimer's disease: Alzheimer's Association Workgroup. *Alzheimers Dement*. 2024;(April):1–27. doi:10.1002/alz.13859
2. Dubois B, Feldman HH, Jacova C, et al. Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS-ADRDA criteria. *Lancet Neurol*. 2007;6(8):734–746. [PubMed: 17616482]
3. Schindler SE, Galasko D, Pereira AC, et al. Acceptable performance of blood biomarker tests of amyloid pathology — recommendations from the Global CEO Initiative on Alzheimer's Disease. *Nature Reviews Neurology* 2024. Published online June 12, 2024:1–14. doi:10.1038/s41582-024-00977-5
4. Dubois B, Villain N, Frisoni GB, et al. Clinical diagnosis of Alzheimer's disease: recommendations of the International Working Group. *Lancet Neurol*. 2021;20(6):484–496. doi:10.1016/s1474-4422(21)00066-1 [PubMed: 33933186]
5. Hansson O, Blennow K, Zetterberg H, Dage J. Blood biomarkers for Alzheimer's disease in clinical practice and trials. *Nat Aging*. 2023;3(5):506–519. doi:10.1038/S43587-023-00403-3 [PubMed: 37202517]
6. Dubois B, von Arnim CAF, Burnie N, Bozeat S, Cummings J. Biomarkers in Alzheimer's disease: role in early and differential diagnosis and recognition of atypical variants. *Alzheimers Res Ther*. 2023;15(1):1–13. doi:10.1186/S13195-023-01314-6/FIGURES/4 [PubMed: 36597138]
7. Ebnau JL, Pelkmans W, Verberk IMW, et al. Association of CSF, Plasma, and Imaging Markers of Neurodegeneration With Clinical Progression in People With Subjective Cognitive Decline. *Neurology*. 2022;98(13):e1315–e1326. doi:10.1212/wnl.0000000000200035 [PubMed: 35110378]
8. Hyman BT, Phelps CH, Beach TG, et al. National Institute on Aging-Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease. *Alzheimer's and Dementia*. 2012;8(1):1–13. doi:10.1016/j.jalz.2011.10.007
9. Morris JC. The challenge of characterizing normal brain aging in relation to Alzheimer's disease. *Neurobiol Aging*. 1997;18(4):388–389. doi:10.1016/S0197-4580(97)00055-9 [PubMed: 9330969]
10. Robinson JL, Richardson H, Xie SX, et al. The development and convergence of co-pathologies in Alzheimer's disease. *Brain*. 2021;144(3):953–962. doi:10.1093/brain/awaa438 [PubMed: 33449993]
11. Spina S, La Joie R, Petersen C, et al. Comorbid neuropathological diagnoses in early versus late-onset Alzheimer's disease. *Brain*. 2021;144(7):2186–2198. doi:10.1093/BRAIN/AWAB099 [PubMed: 33693619]
12. Cohen HJ, Feussner JR, Weinberger M, et al. A Controlled Trial of Inpatient and Outpatient Geriatric Evaluation and Management. *New England Journal of Medicine*. 2002;346(12):905–912. doi:10.1056/NEJMSA010285/ASSET/AA9ED3BC-E8B2-4799-A18A-3905756042AD/ASSETS/IMAGES/LARGE/NEJMSA010285_T4.JPG [PubMed: 11907291]
13. Alzheimer A Über eine eigenartige Erkrankung der Hirnrinde. *Allgemeine Zeitschrift für Psychiatrie und Psychisch-gerichtliche Medizin*. 1907;64:146–148.
14. Villain N, Michalon R. What is Alzheimer's disease? An Analysis of Nosological Perspectives from the 20th and 21st Centuries *Journal: European Journal of Neurology*. *Eur J Neurol*. Published online 2024. doi:DOI: 10.1111/ene.16302
15. Budd Haeberlein S, Aisen PS, Barkhof F, et al. Two Randomized Phase 3 Studies of Aducanumab in Early Alzheimer's Disease. *The Journal of Prevention of Alzheimer's Disease* 2022. Published online March 18, 2022:1–14. doi:10.14283/JPAD.2022.30

16. van Dyck CH, Swanson CJ, Aisen P, et al. Lecanemab in Early Alzheimer's Disease. *N Engl J Med*. 2023;388(1):9–21. doi:10.1056/NEJMoa2212948 [PubMed: 36449413]
17. Sims JR, Zimmer JA, Evans CD, et al. Donanemab in Early Symptomatic Alzheimer Disease: The TRAILBLAZER-ALZ 2 Randomized Clinical Trial. *JAMA*. Published online 2023. doi:10.1001/jama.2023.13239
18. Frisoni GB, Ritchie C, Carrera E, et al. Re-aligning scientific and lay narratives of Alzheimer's disease. *Lancet Neurol*. 2019;18(10):918–919. doi:10.1016/S1474-4422(19)30323-0 [PubMed: 31526751]
19. Bateman RJ, Xiong C, Benzinger TLS, et al. Clinical and Biomarker Changes in Dominantly Inherited Alzheimer's Disease. *New England Journal of Medicine*. 2012;367(9):795–804. doi:10.1056/NEJMOA1202753/SUPPL_FILE/NEJMOA1202753_DISCLOSURES.PDF [PubMed: 22784036]
20. Tikkinen KAO, Dahm P, Lytvyn L, et al. Prostate cancer screening with prostate-specific antigen (PSA) test: a clinical practice guideline. *BMJ*. 2018;362. doi:10.1136/BMJ.K3581
21. Fortea J, Zaman SH, Hartley S, Rafii MS, Head E, Carmona-Iragui M. Alzheimer's disease associated with Down syndrome: a genetic form of dementia. *Lancet Neurol*. 2021;20(11):930–942. doi:10.1016/S1474-4422(21)00245-3 [PubMed: 34687637]
22. Brookmeyer R, Abdalla N. Estimation of lifetime risks of Alzheimer's disease dementia using biomarkers for preclinical disease. *Alzheimer's and Dementia*. 2018;14(8):981–988. doi:10.1016/j.jalz.2018.03.005
23. Bieger A, Brum WS, Borelli WV, et al. The impact of different diagnostic criteria on Alzheimer's disease clinical research. *Neurology*. Published online 2024.
24. Ossenkoppele R, Pichet Binette A, Groot C, et al. Amyloid and tau PET-positive cognitively unimpaired individuals are at high risk for future cognitive decline. *Nat Med*. 2022;28(11):2381–2387. doi:10.1038/s41591-022-02049-x [PubMed: 36357681]
25. Mielke MM, Aakre JA, Algeciras-Schimnich A, et al. Comparison of CSF phosphorylated tau 181 and 217 for cognitive decline. *Alzheimers Dement*. 2022;18(4):602–611. doi:10.1002/ALZ.12415 [PubMed: 34310832]
26. Hanseeuw BJ, Betensky RA, Jacobs HIL, et al. Association of Amyloid and Tau with Cognition in Preclinical Alzheimer Disease: A Longitudinal Study. *JAMA Neurol*. 2019;76(8):915–924. doi:10.1001/jamaneurol.2019.1424 [PubMed: 31157827]
27. Frisoni GB, Altomare D, Thal DR, et al. The probabilistic model of Alzheimer disease: the amyloid hypothesis revised. *Nat Rev Neurosci*. 2022;23(1). doi:10.1038/S41583-021-00533-W
28. Dhana K, Agarwal P, James BD, et al. Healthy Lifestyle and Cognition in Older Adults With Common Neuropathologies of Dementia. 2024;60612. doi:10.1001/jamaneurol.2023.5491
29. Frisoni GB, Altomare D, Ribaldi F, et al. Dementia prevention in memory clinics: recommendations from the European task force for brain health services. *The Lancet Regional Health - Europe*. 2023;26:100576. doi:10.1016/j.lanepe.2022.100576 [PubMed: 36895446]
30. Caprioglio C, Ribaldi F, Visser LNC, et al. Analysis of Psychological Symptoms Following Disclosure of Amyloid-Positron Emission Tomography Imaging Results to Adults With Subjective Cognitive Decline. *JAMA Netw Open*. 2023;6(1):E2250921. doi:10.1001/JAMANETWORKOPEN.2022.50921 [PubMed: 36637820]
31. Couch E, Ashford MT, Zhang W, Prina M. Psychosocial and Behavioral Outcomes for Persons With Cognitive Impairment and Caregivers Following Amyloid- β PET Scan Disclosure: A Systematic Review. *Alzheimer Dis Assoc Disord*. 2023;37(3):246–258. doi:10.1097/WAD.0000000000000569 [PubMed: 37561950]
32. Couch E, Zhang W, Belanger E, et al. "There has to be more caring": patient and care partner experiences of the disclosure of amyloid- β PET scan results. *Aging Ment Health*. Published online 2024. doi:10.1080/13607863.2024.2371471
33. Kim JE, Tamres LK, Orbell SL, et al. "And Does That Necessarily Mean Absolutely Alzheimer's?" An Analysis of Questions Raised Following Amyloid PET Results Disclosure. *Am J Geriatr Psychiatry*. 2024;32(1):45–54. doi:10.1016/J.JAGP.2023.08.005 [PubMed: 37634955]
34. Schermer MHN, Richard E. On the reconceptualization of Alzheimer's disease. *Bioethics*. 2019;33(1):138–145. doi:10.1111/bioe.12516 [PubMed: 30303259]

35. Largent EA, Harkins K, Van Dyck CH, Hachey S, Sankar P, Karlawish J. Cognitively unimpaired adults' reactions to disclosure of amyloid PET scan results. *PLoS One*. 2020;15(2):e0229137. doi:10.1371/JOURNAL.PONE.0229137 [PubMed: 32053667]
36. Bateman RJ, Smith J, Donohue MC, et al. Two Phase 3 Trials of Gantenerumab in Early Alzheimer's Disease. *New England Journal of Medicine*. 2023;389(20):1862–1876. doi:10.1056/nejmoa2304430 [PubMed: 37966285]
37. Budd Haeberlein S, Aisen PS, Barkhof F, et al. Two Randomized Phase 3 Studies of Aducanumab in Early Alzheimer's Disease. *The Journal of Prevention of Alzheimer's Disease* 2022. Published online March 18, 2022:1–14. doi:10.14283/JPAD.2022.30
38. Early Alzheimer's Disease: Developing Drugs for Treatment | FDA. Accessed August 20, 2024. <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/early-alzheimers-disease-developing-drugs-treatment>
39. Garrett SL, McDaniel D, Obideen M, et al. Racial Disparity in Cerebrospinal Fluid Amyloid and Tau Biomarkers and Associated Cutoffs for Mild Cognitive Impairment. *JAMA Netw Open*. 2019;2(12):e1917363–e1917363. doi:10.1001/JAMANETWORKOPEN.2019.17363 [PubMed: 31834392]
40. Brum WS, Ashton NJ, Simrén J, et al. Biological variation estimates of Alzheimer's disease plasma biomarkers in healthy individuals. *Alzheimer's & Dementia*. 2023;12:22. doi:10.1002/ALZ.13518
41. Gustavsson A, Norton N, Fast T, et al. Global estimates on the number of persons across the Alzheimer's disease continuum. *Alzheimer's and Dementia*. 2022;(November 2021). doi:10.1002/alz.12694
42. Frisoni GB, Altomare D, Ribaldi F, et al. Dementia prevention in memory clinics: recommendations from the European task force for brain health services. *The Lancet Regional Health - Europe*. 2023;26:100576. doi:10.1016/j.lanepe.2022.100576 [PubMed: 36895446]
43. Global pharmaceutical industry - statistics & facts | Statista. Accessed January 7, 2024. <https://www.statista.com/topics/1764/global-pharmaceutical-industry/#topicOverview>
44. Malzbender K, Barbarino P, Ferrell PB, et al. Validation, Deployment, and Real-World Implementation of a Modular Toolbox for Alzheimer's Disease Detection and Dementia Risk Reduction: The AD-RIDDLE Project. *Journal of Prevention of Alzheimer's Disease*. 2024;11(2):329–338. doi:10.14283/JPAD.2024.32/TABLES/1
45. Schramm C, Charbonnier C, Zaréa A, et al. Penetrance estimation of Alzheimer disease in SORL1 loss-of-function variant carriers using a family-based strategy and stratification by APOE genotypes. *Genome Med*. 2022;14(1). doi:10.1186/S13073-022-01070-6
46. Andronie-Cioara FL, Ardelean AI, Nistor-Cseppento CD, et al. Molecular Mechanisms of Neuroinflammation in Aging and Alzheimer's Disease Progression. *Int J Mol Sci*. 2023;24(3). doi:10.3390/IJMS24031869

Table 1:
Differentiating Diagnostic Approaches to AD

	AA 2024	IWG 2024
Definition of Alzheimer disease	Biological (“AD should be defined biologically, not based on a clinical syndrome”)	Clinical-biological (“AD is a clinical-biological construct”)
Implications diagnosis setting in for the clinical	Presence of any abnormal Core A AD biomarker (i.e., fluid Aβ42/40, pTau, etc) is sufficient.	Presence of objective cognitive deficits and AD biomarkers is needed.
	A biomarker-positive cognitively normal person can be diagnosed with AD	A biomarker-positive cognitively normal person cannot be diagnosed with AD *
Implications in diagnostic disclosure of subject status	Cognitively normal persons with one positive core 1 AD biomarker can be told they have AD	Cognitively normal persons with positive AD biomarker can be told they are at-risk for AD *
Implications for phase 3 preventive clinical trials	Biomarkers could be primary endpoints in clinical trials.	Biomarkers cannot be primary endpoints in clinical trials.
	Demonstration of efficacy on clinical parameters may not be necessary.	Demonstration of efficacy on clinical parameters is necessary.

AA= Alzheimer Association; IWG= International Working Group
BM= biomarker;
* except in the rare cases fulfilling the requirements for presymptomatic AD (see text)