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

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Abstract (350 words)

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 this definition being applied clinically, the understanding of AD by society at large, and the translation of blood-based biomarkers into clinical practice prompt this IWG recommendation.

Objective: To critically review the revised AA criteria, outline their paradoxes and inherent risks. We offer an alternative definitional view, updating the 2021 IWG diagnostic criteria as being more appropriate for clinical consideration.

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 AA diagnostic criteria, AD is defined clinically as encompassing cognitively normal people having a core AD biomarker. However, recent literature shows that the majority of 'amyloid positive' cognitively normal individuals will not become symptomatic along a proximate timeline. Paradoxically, while these criteria address disease definition and diagnosis in cognitively normal individuals, the AA criteria recommend against biomarker testing in this setting. Requiring that biomarker testing needs clinical context for interpretation is another paradox of these pure biological AD criteria.

Conclusions and Relevance: We appreciate that the ultimate aim is to foster effective AD treatments, including preventing symptoms and dementia. We consider this approach of

diagnosing AD without a clinical and biological construct as being unwarranted and potentially harmful to people who may experience psychological distress from learning and living with a brain disorder without symptoms and without a clear idea of when or whether symptoms will ever develop. We recommend that amyloid-positive only cognitively normal individuals should not be labeled as having AD. Rather, they are 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 foreseeable symptoms in the near future.

The recently revised AA criteria for Alzheimer disease (AD)[1], which aim to inform both research and clinical care, propose that the AD diagnosis is extended to cognitively normal people with evidence of "core AD biomarkers," highlighting the incremental 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 diagnosis[2]. Since then, brain amyloid PET has been shown to correlate with the presence and density of beta-amyloid 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 research[5]. 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 symptoms[6]. 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 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-25[7].

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 2012[8], 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 decline[9]. Additionally, lesions of different pathological nature are frequently observed post-mortem due to the high prevalence of comorbidities and to the synergy between pathologies[10]: 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 studies[11] 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 construct[12]. Therefore, we argue that biomarkers alone should remain markers of pathological processes and not markers of a specific disease[8]. Furthermore, the contribution of biomarkers in the clinical setting depends on the context of use[3] and, importantly, should differ between the assessment of cognitively impaired and unimpaired individuals[4].

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 AD[4]. This association defines the clinical-biological entity of the disease, proposed by the IWG[4], in line with the clinical-pathological description by Alois Alzheimer[13,14] and the neuropathological consensus[8]. 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 individuals[18].

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 AD[19].

In the clinical setting, extending the diagnosis of AD to cognitively normal people with only core AD biomarkers, represents the most problematic implication of the revised AA diagnostic criteria. 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], despite the recent controversy surrounding prostate-specific-antigen[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 analogy 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 dementia[21].

This model cannot be transferred to cognitively normal individuals with sporadic Alzheimer pathologic changes, as their lifetime risk is much lower. Indeed, the lifetime risk of AD dementia in a 65-year-old man who is amyloid positive has been estimated at 21.9%, a mere 1.7 times higher than the risk of amyloid negative of similar age[22]. 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-up[23], 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 years[24]. Therefore, the revised AA criteria, proposing that a diagnosis of AD can be reduced to the sole presence of AD core biomarkers, may introduce major uncertainty and variability in the clinical prognosis of patients diagnosed with AD[1]. 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][26]). However, the risk of progression to AD dementia significantly increases when the aggregated forms of tau spread out in neocortical areas[24]. 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 imminence 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 to revise the traditional amyloid cascade, the probabilistic amyloid cascade model[27]. This model postulates decreasing penetrance of the phenotype from autosomal dominant mutations (almost complete penetrance) to *APOE*ε4 carrier status (intermediate penetrance) and *APOE*ε4 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 *APOE*ε4 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 impact of a biological vs. clinical-biological AD definition is not just semantics. First, 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 impacts 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. 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[30,31]. Second, recent findings show that high-dose gantenerumab achieved similar amyloid PET clearance as approved aducanumab despite its lack of clinical effectiveness.[32,33] This demonstrates the potential liability of the clinical and biological dissociation of AD definition regarding drug approval.

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 use[3]. In principle, 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.[34] Hence, interpreting biomarkers in the clinical context is crucial, as also emphasized by the AA criteria[1].

The harmful 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 diagnosis[35]. 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” according to the new AA criteria may be expected[36]. As a result, increasing societal pressure for anti-tau or anti-amyloid drugs to prevent cognitive decline is foreseeable, including treatment off-label in persons who are cognitively normal.

The AA's criteria have ambiguous statements regarding the use of biomarkers to identify AD. Paradoxically, while these criteria apply definition and diagnosis in cognitively normal individuals, they recommend that such diagnostic testing not be undertaken in this setting. Requiring that biomarker testing in cognitively normal subjects will need clinical judgment

for interpretation is another paradox, as the AA criteria claim to be purely biological. This underscores the inherent limitations of relying solely on a biological definition of AD in clinical practice.

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[37].

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[38]. 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 AD[14]. 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[39]. 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 effective[37]. 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, 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 (360 words)

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[40,41]. (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 regions[24].

Future studies from population-based cohort may identify distinct biomarker profiles including additional risk factors defining this subgroup.[42]

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 biomarkers[4]. 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.

Table 1: Main differences between AA and IWG new criteria

	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 for the diagnosis in clinical setting	Presence of any abnormal core AD biomarker (i.e., fluid Aβ42/40, pTau, etc) is sufficient. A biomarker-positive cognitively normal person can be diagnosed with AD	Presence of objective cognitive deficits and AD biomarkers is needed. A biomarker-positive cognitively normal person cannot be diagnosed with AD*
Implications in announcement of subject status	Cognitively normal persons with one positive 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 preventive clinical trials	Biomarkers can be primary endpoints in clinical trials. Demonstration of efficacy on clinical parameters is not necessary.	Biomarkers cannot be primary endpoints in clinical trials. 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)

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.
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
5. Hansson O, Blennow K, Zetterberg H, Dage J. Blood biomarkers for Alzheimer's disease in clinical practice and trials. *Nature aging*. 2023;3(5):506-519. doi:10.1038/S43587-023-00403-3
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. *Alzheimer's Research and Therapy*. 2023;15(1):1-13. doi:10.1186/S13195-023-01314-6/FIGURES/4
7. Ebenau 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
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. *Neurobiology of aging*. 1997;18(4):388-389. doi:10.1016/S0197-4580(97)00055-9
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
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
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
13. Alzheimer A. Über eine eigenartige Erkrankung der Hirnrinde. *Allgemeine Zeitschrift fur 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. *The New England journal of medicine*. 2023;388(1):9-21. doi:10.1056/NEJMoa2212948
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
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
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. *The Lancet Neurology*. 2021;20(11):930-942. doi:10.1016/S1474-4422(21)00245-3
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. *Nature Medicine*. 2022;28(11):2381-2387. doi:10.1038/s41591-022-02049-x
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
26. Hanseeuw BJ, Betensky RA, Jacobs HIL, et al. Association of Amyloid and Tau with Cognition in Preclinical Alzheimer Disease: A Longitudinal Study. *JAMA Neurology*. 2019;76(8):915-924. doi:10.1001/jamaneurol.2019.1424
27. Frisoni GB, Altomare D, Thal DR, et al. The probabilistic model of Alzheimer disease: the amyloid hypothesis revised. *Nature reviews Neuroscience*. 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
30. Schermer MHN, Richard E. On the reconceptualization of Alzheimer's disease. *Bioethics*. 2019;33(1):138-145. doi:10.1111/bioe.12516

31. 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
32. 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
33. 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
34. 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 Network Open*. 2019;2(12):e1917363-e1917363. doi:10.1001/JAMANETWORKOPEN.2019.17363
35. 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
36. 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
37. 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
38. Global pharmaceutical industry - statistics & facts | Statista. Accessed January 7, 2024. https://www.statista.com/topics/1764/global-pharmaceutical-industry/#topicOverview
39. 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
40. 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
41. 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 medicine*. 2022;14(1). doi:10.1186/S13073-022-01070-6
42. Andronie-Cioara FL, Ardelean AI, Nistor-Cseppento CD, et al. Molecular Mechanisms of Neuroinflammation in Aging and Alzheimer's Disease Progression. *International journal of molecular sciences*. 2023;24(3). doi:10.3390/IJMS24031869