Published in final edited form as:

Nat Med. 2024 August ; 30(8): 2121–2124. doi:10.1038/s41591-024-02988-7.

Revised criteria for the diagnosis and staging of Alzheimer's disease

Clifford R. Jack Jr.[1], **J. Scott Andrews**[2], **Thomas G. Beach**[3], **Teresa Buracchio**[4], **Billy Dunn**[5], **Ana Graf**[6], **Oskar Hansson**[7,8], **Carole Ho**[9], **William Jagust**[10], **Eric McDade**[11], **Jose Luis Molinuevo**[12], **Ozioma C. Okonkwo**[13], **Luca Pani**[14], **Michael S. Rafii**[15], **Philip Scheltens**[16], **Eric Siemers**[17], **Heather M. Snyder**[18], **Reisa Sperling**[19], **Charlotte E. Teunissen**[20], **Maria C. Carrillo**[18]

[1]200 1st ST SW, Department Radiology, Mayo Clinic, Rochester, MN, USA 55905

[2]500 Kendall Street, Global Evidence & Outcomes, Takeda Pharmaceuticals Company Limited, Cambridge, MA, USA 02142

[3]10515 W Santa Fe Drive, Civin Laboratory for Neuropathology, Banner Sun Health Research Institute, Sun City, AZ, USA 85351

[4]10903 New Hampshire Avenue, Office of Neuroscience, U.S. Food and Drug Administration, Silver Spring, MD, USA, 20993

[5]The Michael J Fox Foundation for Parkinson's Research, New York, NY, USA, 10163

[6]Novartis, Neuroscience Global Drug Development, Fabrikstrasse 2, CH-4056, Basel, Switzerland

[7]Clinical Memory Research Unit, Box 117, Department of Clinical Sciences Malmö, Faculty of Medicine, Lund University, 22100 Lund, Sweden.

[8]Clinical Research Centre, Box 50322, Memory Clinic, Skåne University Hospital, 202 13 Malmö, Sweden

[9]161 Oyster Point Bvld. Suite 200, Development, Denali Therapeutics, South San Francisco, CA, USA, 94080

[10]450 Li Ka Shing Biomedical Center, MC#3370, School of Public Health and Helen Wills Neuroscience Institute, University of California Berkeley, Berkeley, CA, USA 94720-3370

[11]660 Euclid Avenue, Department of Neurology, Washington University St Louis School of Medicine, St Louis, MO, USA 63108

[12]Ottiliavej 9, 2500Experimental Medicine, Department Global Clinical Development H. Lundbeck A/S, Copenhagen, Denmark

[13]2870 University Avenue, Department of Medicine, Division of Geriatrics and Gerontology, University of Wisconsin School of Medicine, Madison, WI, USA 53705-3611

[14]1600 NW 10th Ave #1140, University of Miami, Miami FL, 33136

Corresponding author: Jack C. R. Jr, jack.clifford@mayo.edu.

[15]9860 Mesa Rim Road, Alzheimer's Therapeutic Research Institute (ATRI), Keck School of Medicine at the University of Southern California, San Diego, CA USA 92121

[16]De Boelelaan 1117, 1081 HV Amsterdam University Medical Center (Emeritus), Neurology, The Netherlands, Amsterdam

[17]9546 Irishmans Run Lane, Clinical Research, Acumen Pharmaceuticals, Zionsville, IN, USA 46077

[18]225 North Michigan Avenue, Suite 1700 Medical & Scientific Relations Division, Alzheimer's Association, Chicago, IL, USA 60601

[19]60 Fenwood Road, 1st Floor, Department of Neurology, Brigham and Women's Hospital, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA 02115

[20]De Boelelaan 1117, 1081 HV Amsterdam, Department of Laboratory Medicine, Amsterdam UMC, Neurochemistry Laboratory, The Netherlands, Amsterdam.

Abstract

Alzheimer's disease can be treated by targeting amyloid-β plaques and diagnosed in vivo by biomarkers, prompting the revision of criteria for the diagnosis and staging of this disease.

A workgroup convened by the Alzheimer's Association recently published Revised Criteria for Diagnosis and Staging of Alzheimer's Disease [1]. Members of this committee (who also co-authored this comment) were selected to provide balanced representation of academia, clinical medicine, industry, the National Institute on Aging, the Food and Drug Administration, and included participants from the USA and Europe. The revised criteria [1] are an update to prior criteria published in 2011 and 2018 [2, 3]. Formulation of these revised criteria [1] was prompted by two major developments in this field that occurred after the 2018 research framework [3] was published: regulatory approval of the first disease targeted therapeutics for Alzheimer's disease (AD) [4, 5]; and development of accurate blood-based biomarkers of AD [6].

The 2024 Revised Criteria for Diagnosis and Staging of AD [1] are founded on several core principles. AD is defined as a biologic process that is first detectable by abnormal biomarkers of its defining neuropathologic features (β-amyloid plaques and tau neurofibrillary tangles) when an individual is asymptomatic. The disease progresses biologically during the preclinical period and when a sufficient pathologic burden is reached, symptoms appear and then progress. The entire disease course may span up to 30 years.

Categorization of biomarkers

In the revised criteria [1], biomarkers are categorized into those that are core biomarkers of AD neuropathologic change [7] (specific to AD), non-core biomarkers of processes (not specific to AD but still important in AD pathogenesis, such as biomarkers of inflammation or immune activation, and neurodegeneration), and biomarkers of common non-AD copathologies (such as cerebro vascular disease and neuronal α-synuclein disease). This commentary focuses on core AD biomarkers that fall into the following categories:

biomarkers of the amyloid-β (Aβ) proteinopathy pathway (labeled 'A'); biofluid biomarkers of phosphorylated and secreted AD tau, which become abnormal early in the disease process (labeled 'T_1'); and biomarkers of AD tau neurofibrillary pathology that become abnormal later in the disease process (labeled 'T_2'). We group biomarkers into Core 1 (A and T_1) and Core 2 (T_2) (Table 1).

Core 1 biomarkers define the initial stage of AD that is detectable in vivo. An abnormal Core 1 biomarker is sufficient to establish a diagnosis of AD and to inform clinical decision making (Table 2). Core 2 biomarkers are not typically used as standalone tests for the diagnosis of AD, but when combined with Core 1 may be used to stage biological disease severity and provide prognostic information (Table 2).

Diagnosis

An abnormal Core 1 biomarker test is diagnostic of AD. The following are currently considered fit for this purpose: amyloid positron emission tomography (PET); cerebrospinal fluid (CSF) Aβ42/40, CSF p-tau181/Aβ42, CSF t-tau/Aβ42; and accurate plasma assays (defined below). However, the revised criteria outline important caveats around diagnostics, especially using plasma biomarkers. Chief among these is a minimum diagnostic accuracy requirement (90% or greater) with respect to an accepted reference standard in the intended context of use (which includes a description of the intended use population). Amyloid PET ligands and CSF assays listed in Table 1 have received regulatory approval in the USA and EU; the former were validated against autopsy [8] and the latter validated against amyloid PET [9]. While presently no plasma assays have received regulatory approval, this is expected to change soon as some plasma assays (such as p-tau217) have demonstrated diagnostic accuracy equivalent to approved CSF assays [10]. The diagnostic accuracy of other plasma assays, however, do not meet the 90% standard [10] and would not be considered fit for the purpose of diagnosis.

A second important caveat centers on the role of the clinician. The biologically based diagnosis of AD is meant to assist, rather than supplant, the clinical evaluation of individuals with cognitive impairment. Biomarker testing should only be performed under the supervision of a clinician.

Staging

The revised criteria [1] describe separate schemes for staging biological AD severity and for staging the severity of clinical symptoms. Biological staging is based on ordering of biomarker events in the natural history of the disease from observational research. A 4-point staging scale (A-D) is outlined that can be accomplished by amyloid and tau PET, by Core 1 biofluids and tau PET, or a forward-looking conceptual staging approach based only on biofluids [11, 12]. Staging the severity of clinical symptoms is based on a 6-point numeric scale ranging from asymptomatic (stage 1) to severe dementia (stage 6). Integration of biological and clinical staging is described using an alphanumeric labeling scheme (for example, stage 1A, 4D, and so on).

While clinical stages generally worsen with increasing biological stages, the revised criteria recognize that mismatches between clinical and biological stage commonly occur. This is because AD is only one of several common pathologies that underlie cognitive decline and dementia in older individuals; the other 3 most common are cerebro vascular disease, neuronal α-synuclein disease, and limbic-predominant age-related TDP-43 encephalopathy (LATE) [13]. Individuals with one or more of these pathologies are likely to have worse clinical stage than expected for their biological AD stage. Conversely, individuals with exceptional resilience or cognitive reserve may have better clinical stage than expected for their biological AD stage.

Use of the name Alzheimer's disease

Two successive drafts of these criteria were presented at scientific meetings in 2023 and were also posted for public comment. It is our view that some of the comments or critiques offered contradict fundamental positions of the committee and so below we describe these critiques and the rational underlying the committee's decision to formulate the criteria as done.

The term AD is understood by many in the public and in general medicine to be synonymous with dementia. Many think of AD as a progressive impairment leading to loss of functional independence in older persons, irrespective of etiology. A common critique of the revised criteria [1] is that to avoid confusion on the part of the public, the term AD should be used to describe all-cause dementia and the distinction between etiology (pathobiology) and symptoms (the result of pathobiology) should be ignored.

The position of the committee is that not only is this scientifically inaccurate, but it is also harmful. The etiology or etiologies underlying clinical symptoms must be understood and accurately diagnosed to enable effective treatments. Although AD is the most common pathologic condition underlying progressive cognitive impairment in elderly persons, non-AD pathologies are also common [13]. The typical syndrome association with AD (a progressive memory impairment that progresses to other cognitive domains) can also be caused by common non-AD pathologies, most often in combination. For example, in early Aβ immunotherapy trials where eligibility was based on a traditional clinical diagnosis of AD without biological confirmation, 30% of individuals had normal amyloid PET scans [14], meaning that nearly one third of participants in these trials did not have the disease they were being treated for. The position of the committee is that therapy directed toward a biological target requires confirmation of that biology both in clinical trials and in clinical practice. Thus, AD must be defined by its biology for medical progress to be made; the public is readily able to grasp this concept with the proper educational effort.

Requiring symptoms for the diagnosis of AD

A second critique argues that a diagnosis of AD should require the presence of both abnormal AD biomarkers and the presence of clinical symptoms. The argument is that preclinical AD is not a valid concept and asymptomatic individuals with abnormal biomarkers should be labeled 'at risk' for AD. The reasoning is that many asymptomatic

individuals with abnormal biomarkers (preclinical AD) will not develop symptoms in their lifetime. The argument continues, labeling such individuals with a disease may cause psychological, financial, or social harm without potential for benefit, since at present, disease targeted treatments are not approved for preclinical AD.

The committee takes a different view [1]. First, diseases are routinely diagnosed in other areas of medicine while patients are asymptomatic. It is axiomatic throughout medicine that treatments are more effective when administered as early in the disease process as possible [2]. Therefore, conducting clinical trials in persons with preclinical AD is considered by the committee to be a forward-looking approach to identify the most effective means of slowing or preventing the onset of symptoms.

Second, while it is true that many asymptotic individuals with abnormal AD biomarkers will not experience symptoms in their lifetime, this is because of increasing all-cause mortality rates with advancing age, not because AD pathology is benign in the preclinical period. AD is characterized by a preclinical period of 15–20 years or more, which most often begins from age 60 [1]. Over half of individuals newly diagnosed in their mid-70s may not experience symptoms in their lifetime, but nearly half will. The position of the committee is that asymptomatic individuals who may experience symptoms deserve treatment once these are approved for the preclinical population. Mortality from unrelated diseases should not be interpreted to indicate that AD in asymptomatic persons is a benign condition. Individuals with Down syndrome have genetically determined AD (trisomy 21) and 95% of these individuals develop dementia in their lifetime, [15] because the average age of onset of clinical symptoms is mid-50s, at which age all-cause mortality rates are far lower than in older age. Remaining life expectancy is an important consideration in clinical management, but mortality from unrelated causes should not be a criterion used to define what is and what is not a disease [1].

Third, the revised criteria have been criticized for advocating screening of the general population with AD biomarkers, which could place asymptomatic persons who test positive in a position of potential harm without benefit. However, the criteria are very clear that since no treatment has yet been approved for asymptomatic persons, biomarker testing should not be performed in this population outside the context of observational or therapeutic research studies [1]. This may change in the future, however, pending results of ongoing trials.

Validation of plasma biomarkers

Criticism was raised that plasma biomarkers are too new to be used clinically and have not been adequately tested in all representative populations. While the committee recognizes that plasma biomarkers are a recent development, we also outline rigorous criteria that plasma biomarkers need to meet to be considered fit for the purpose of diagnosis [1]. The committee strongly endorses the need for testing and prospective evaluation of plasma biomarkers in more representative populations.

Neuropathological underpinnings of diagnosis by biomarkers

Some critics claim that defining AD by an abnormal Core 1 biomarker is a departure from the accepted neuropathological definition which requires the presence of both β-amyloid plaques and tau tangles [7]. Regulatory approval of amyloid PET ligands was based on their ability to detect moderate to frequent neuritic β-amyloid plaques at autopsy and not both plaques and tangles [8], whilst approval of CSF assays was based on their ability to differentiate normal from abnormal amyloid PET scans [9]. Thus, the argument of these critics is that defining AD by the presence of abnormal Core 1 biomarkers does not fully capture the neuropathologic standard that requires tau tangles in addition to β-amyloid plaques. However, amyloid PET scans (and thus biofluid surrogates) are not able to reliably detect mild levels of AD pathology; it can detect moderate to frequent neuritic plaques but not sparse plaques [8]. Given that nearly all (over 90%) of individuals with moderate to frequent neuritic plaques at autopsy (and therefore abnormal Core 1 biomarkers) will also have sufficient neurofibrillary tangle pathology to meet criteria for a pathological diagnosis of intermediate to high AD neuropathologic change,[7] diagnosing AD based on abnormal Core 1 biomarkers will nearly always be consistent with the accepted neuropathologic reference standard for AD.

Future

Many in the AD field are optimistic about the prospects for improving care of patients. Recent advances in the ability to diagnose and treat AD herald a virtuous cycle wherein improvements in diagnostic methods enable more sophisticated treatment approaches which in turn steer advances in diagnostic methods. An unchanging principle, however, is that effective treatment will always rely on the ability to diagnose and stage the biology driving the disease process. The committee recognizes that the feasibility of implementing criteria for biologically-based diagnosis and staging of AD in clinical practise varies across regions, even within high-income countries. We anticipate that the increasing availability and accuracy of blood-based biomarkers will make these criteria more widely deployable.

Acknowledgments:

Masliah, Eliezer.* and Ryan Laurie are contributing members of the committee and are acknowledged here.

*denotes members of the steering committee in the author list as well as above in acknowledgements.

Disclosures:

Clifford R. Jack Jr. is employed by Mayo Clinic. He receives grant funding from the National Institutes of Health, the Alexander family professorship and the GHR Foundation. Within the past 36 months, he served on a DSMB for Roche pro bono; no payments to the individual or institution were involved. He has received funding from the Alzheimer's Association for travel. In addition, he holds index funds.

Jeffrey Scott Andrews is employed by Takeda Pharmaceuticals and is a minor shareholder for the company. He has a leadership or fiduciary role in the Clinical Trials on AD (CTAD) Task Force – Clinical Meaningfulness and Optimizing Therapies, AD PACE Executive Steering Committee and UsAgainstAlzheimer's – Clinical Meaningfulness Forum. He is a former employee of Eli Lilly and Company and is a minor shareholder for the company.

Thomas G. Beach is employed by Banner Health. He has received grant funding from the National Institutes of Health, Veterans Administration, State of Arizona, Life Molecular Imaging, Michael J. Fox Foundation for

Parkinson's Research, Avid Radiopharmaceuticals/Eli Lilly, and Gates Foundation. He has received consulting fees from Aprinoia Therapeutics, and Acadia Pharmaceuticals. He consulted, not paid, for Biogen. He has received payment or honoraria from the World PD Coalition, Mayo Clinic Florida, Stanford University and the IOS Press-Journal of Parkinson's Disease and support for attending meetings from the Alzheimer's Association, AD/PD/Kenes Group, Mayo Clinic Florida and the Universitätsklinikum Hamburg-Eppendorf. He also has a leadership/fiduciary role and stock options with Vivid Genomics.

Teresa Burracchio is employed by the U.S. Food and Drug Administration and has no financial conflicts to disclose.

Billy Dunn is a consultant and has received consulting fees for his role as an advisor for Arch Venture Partners, Cerveau Technologies, Epilepsy Foundation, F-PRIME Capital, Loulou Foundation, and Michael J. Fox Foundation. He has held a past position of leadership or fiduciary role in the Virginia Neurological Society (past president) and Prothena Inc. (Director). He holds stock options with Prothena Inc.

Ana Graf is employed by Novartis Pharma AG and has stock options in the company.

Oskar Hansson is employed by Lund University. He has grants or contracts from ADx, AVID Radiopharmaceuticals, Biogen, Eli Lilly, Eisai, Fujirebio, GE Healthcare, Pfizer, and Roche. He also has been paid consulting fees by AC Immune, Amylyx, Alzpath, BioArctic, Biogen, Cerveau, Eisai, Eli Lilly, Fujirebio, Genentech, Merck, Novartis, Novo Nordisk, Roche, Sanofi, and Siemens.

Oskar Hansson is employed by Lund University. He has acquired research support (for the institution) from AVID Radiopharmaceuticals, Biogen, C2N Diagnostics, Eli Lilly, Eisai, Fujirebio, GE Healthcare, and Roche. In the past 2 years, he has received consultancy/speaker fees from AC Immune, Alzpath, BioArctic, Biogen, Bristol Meyer Squibb, Cerveau, Eisai, Eli Lilly, Fujirebio, Merck, Novartis, Novo Nordisk, Roche, Sanofi and Siemens.

Carole Ho is employed by Denali Therapeutics. She has stock options with Denali Therapeutics. Carole is also a Board Director for Beam Therapeutics and NGM Therapeutics and has stock options with both companies.

William Jagust is employed by University of California, Berkley and has received grants or contracts paid to his institution from the National Institute on Aging, Roche/Genentech, Alzheimer's Association, and BrightFocus Foundation. He has received consulting fees from Biogen, Clario, Eisai, Lilly, and Prothena and has stock with Optoceutics and Molecular Medicine.

Eric McDade is employed by Washington University, St Louis and has received grant funding from NIA, Eli Lilly, Hoffmann-La Roche, Alzheimer's Association and GHR Foundation all directly to his institution. He has received royalties for work on "Methods of diagnosing AD with phosphorylation changes" which is licensed to C2N with royalties to himself and Washington University. He has received consulting fees from Alzamend (SAB member), Sanofi, AstraZeneca, Roche, Grifols, Merck and Sage. He has also received payments from Neurology Live, Kaplan-Projects in Knowledge, and support for travel from Foundation Alzheimer, Alzheimer's Association, and Eisai. He has a patent planned, issued, or pending on "Methods of diagnosing AD with phosphorylation changes" and has participated on a Data Safety Monitoring Board or Advisory Board for Alector and Eli Lilly, both roles for which he was paid. He has a leadership/fiduciary role in Alzamend (paid).

Jose Luis Molinuevo is a full-time employee of H. Lundbeck A/S.

Ozioma Okonkwo is employed by University of Wisconsin School of Medicine & Public Health and has received support from the following grants, paid to his institution: R01AG062167, R01AG077507, U19AG024904, U19AG078109, U19AG073153, R01AG066203, R01AG070028, R01AG027161, RF1AG052324. He has received consulting fees from Mayo Clinic Rochester and IUPUI, and holds a leadership or fiduciary role in the International Neuropsychological Society (Board Member) and previously held an advisory role for Society for Black Neuropsychology.

Luca Pani is employed by the University of Miami and the University of Modena and Reggio Emilia and has no financial conflicts to disclose. In unrelated areas, he holds options/stocks from Relmada Therapeutics (US) and NetraMark (Canada).

Michael Rafii is employed by University of Southern California and the Alzheimer's Therapeutics Research Institute (ATRI) and has received grants or contracts from Eisai (AHEAD Study) and Eli Lilly (A4 Study), which were paid to his institution. He has received consulting fees from AC Immune and Ionis. He has participated on a Data Safety Monitoring Board or Advisory Board for Alzheon, Aptah Bio, Biohaven, Embic, Keystone Bio, Prescient Imaging and Positrigo.

Philip Scheltens is employed by Life Science Partners and is Professor Emeritus Amsterdam University Medical Center. He has received grants or contracts from Novo Nordisk, Toyama, UCB, AC Immune, and Alzheon, all paid

to his institution. He has an unpaid leadership position as Chair of World Dementia Council. He holds stock options in EQT AB.

Eric Siemers is employed by Acumen Pharmaceuticals, Inc. He has received consulting fees from Biogen Inc., Cogstate Ltd., Cortexyme Inc., Partner Therapeutics Inc., Pinteon Therapeutics Inc., Prothena Inc, Vaccinex Inc., Acumen, Pharmaceuticals Inc., Gates Ventures LLC, and Hoffman La Roche Ltd and payments were made to Siemers Integration LLC. He has participated on a Data Safety Monitoring Board for Hoffman La Roche Ltd. and has had a leadership or fiduciary role with the Alzheimer's Association and BrightFocus Foundation, both unpaid. He holds stock options and is a shareholder for Acumen Pharmaceuticals and is a shareholder for Eli Lilly and Company.

Heather Snyder is a full-time employee of the Alzheimer's Association, Chicago, IL and has a spouse who is employed by Abbott Laboratories in an unrelated area. She has no financial conflicts to disclose.

Reisa Sperling is employed by Brigham and Women's Hospital. She has received grants or contracts from National Institute on Aging, Eli Lilly (public-private partnership trial funding), Eisai (public-private partnership trial funding), Alzheimer's Association and GHR Foundation. She has received consulting fees from Abbvie, AC Immune, Acumen, Alector, Alnylam, Bristol-Myers Squibb, Cytox, Genentech, Ionis, Janssen, NervGen, Neuraly, Neurocentria, Oligomerix, Prothena, Roche, Shionogi, and Vaxxinity.

Charlotte E. Teunissen is employed by Amsterdam UMC. She has grants or contracts for Research of the European Commission (Marie Curie International Training Network, grant agreement No 860197 (MIRIADE), Innovative Medicines Initiatives 3TR (Horizon 2020, grant no 831434) EPND (IMI 2 Joint Undertaking (JU), grant No. 101034344) and JPND (bPRIDE), National MS Society (Progressive MS alliance), Alzheimer Drug Discovery Foundation, Alzheimer Association, Health Holland, the Dutch Research Council (ZonMW), including TAP-dementia, a ZonMw funded project (#10510032120003) in the context of the Dutch National Dementia Strategy, Alzheimer Drug Discovery Foundation, The Selfridges Group Foundation, Alzheimer Netherlands. She is recipient of ABOARD, which is a public-private partnership receiving funding from ZonMW (#73305095007) and Health~Holland, Topsector Life Sciences & Health (PPP-allowance; #LSHM20106). She is also a contract researcher for ADx Neurosciences, AC-Immune, Aribio, Axon Neurosciences, Beckman-Coulter, BioConnect, Bioorchestra, Brainstorm Therapeutics, Celgene, Cognition Therapeutics, EIP Pharma, Eisai, Eli Lilly, Fujirebio, Grifols, Instant Nano Biosensors, Merck, Novo Nordisk, Olink, PeopleBio, Quanterix, Roche, Siemens, Toyama, Vivoryon, and the European Commission. She has received payment or honoraria from Eli Lilly, Grifols, Novo Nordisk, Olink, and Roche, where all payments were made to her institution. She also serves on editorial boards of Medidact Neurologie/Springer; and in Neurology: Neuroimmunology & Neuroinflammation. She is editor of Alzheimer Research and Therapy.

Maria Carrillo is a full-time employee of the Alzheimer's Association and has a daughter in the neuroscience program at USC. She has no financial conflicts to disclose.

Eliezer Masliah and Laurie Ryan served as advisory members to the workgroup. They are employed by National Institute on Aging at the National Institutes of Health and has no financial conflicts to disclose.

REFERENCES

1. Jack CR Jr., Andrews S, Beach T, et al. Revised Criteria for Diagnosis and Staging of Alzheimer's Disease: Alzheimer's Alzheimer's dement 2024;accepted for publication.
2. Sperling RA, Aisen PS, Beckett LA, et al. Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 2011;7:280–292. [PubMed: 21514248]
3. Jack CR Jr., Bennett DA, Blennow K, et al. NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease. Alzheimers Dement 2018;14:535–562. [PubMed: 29653606]
4. van Dyck CH, Swanson CJ, Aisen P, et al. Lecanemab in Early Alzheimer's Disease. N Engl J Med 2023;388:9–21. [PubMed: 36449413]
5. Sims JR, Zimmer JA, Evans CD, et al. Donanemab in Early Symptomatic Alzheimer Disease: The TRAILBLAZER-ALZ 2 Randomized Clinical Trial. JAMA 2023;330:512–527. [PubMed: 37459141]
6. Hansson O, Blennow K, Zetterberg H, Dage J. Blood biomarkers for Alzheimer's disease in clinical practice and trials. Nat Aging 2023;3:506–519. [PubMed: 37202517]

7. Hyman BT, Phelps CH, Beach TG, et al. National Institute on Aging-Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease. Alzheimers Dement 2012;8:1–13. [PubMed: 22265587]
8. Clark CM, Pontecorvo MJ, Beach TG, et al. Cerebral PET with florbetapir compared with neuropathology at autopsy for detection of neuritic amyloid-beta plaques: a prospective cohort study. Lancet Neurol 2012;11:669–678. [PubMed: 22749065]
9. Administration. USFaD. FDA Permits Marketing for New Test to Improve Diagnosis of Alzheimer's Disease. In: FDA, ed.2022.
10. Janelidze S, Bali D, Ashton NJ, et al. Head-to-head comparison of 10 plasma phospho-tau assays in prodromal Alzheimer's disease. Brain 2023;146:1592–1601. [PubMed: 36087307]
11. Barthelemy NR, Li Y, Joseph-Mathurin N, et al. A soluble phosphorylated tau signature links tau, amyloid and the evolution of stages of dominantly inherited Alzheimer's disease. Nat Med 2020;26:398–407. [PubMed: 32161412]
12. Salvado G, Horie K, Barthelemy NR, et al. Novel CSF tau biomarkers can be used for disease staging of sporadic Alzheimer's disease. medRxiv 2023;Online Ahead of Print.
13. Beach TG, Malek-Ahmadi M. Alzheimer's Disease Neuropathological Comorbidities are Common in the Younger-Old. J Alzheimers Dis 2021;79:389–400. [PubMed: 33285640]
14. Doody RS, Thomas RG, Farlow M, et al. Phase 3 trials of solanezumab for mild-to-moderate Alzheimer's disease. N Engl J Med 2014;370:311–321. [PubMed: 24450890]
15. McCarron M, McCallion P, Reilly E, Dunne P, Carroll R, Mulryan N. A prospective 20-year longitudinal follow-up of dementia in persons with Down syndrome. J Intellect Disabil Res 2017;61:843–852. [PubMed: 28664561]

Table 1.

Categorization of Core AD imaging biomarkers and biofluid assays

Category	Modalities
Core 1	Amyloid PET and biofluid measures of Aβ proteinopathy (A)
	Biofluid measures of phosphorylated and secreted AD tau (T_1)
Core 2	Tau PET and biofluid measures of AD tau proteinopathy (T_2)

Table 2.

Intended uses of Core AD imaging biomarkers and biofluid assays

Category	Intended use	Details
Core 1	Diagnosis	Early detection of AD in asymptomatic individuals
		Confirmation that AD is an underlying pathology in symptomatic individuals
Core 2	Staging and prognosis	Provide information on the likelihood that symptoms are associated with AD
		Inform on the risk of and rate of progression