Medical Coverage Policy | Evaluation of Biomarkers for Alzheimer's Disease

EFFECTIVE DATE: 11|01|2025
POLICY LAST REVIEWED: 07|02|2025

OVERVIEW

Biochemical changes associated with the pathophysiology of Alzheimer's disease (AD) are being evaluated to aid in the diagnosis of the disease. This includes the potential use of biomarkers, such as amyloid beta peptide 1-42 and total or phosphorylated tau protein, in cerebrospinal fluid (CSF), urine, and blood. Additionally, the potential correlation between CSF biomarkers and positron emission tomography (PET) amyloid scans has been proposed as useful in selecting appropriate patients for the initiation or discontinuation of amyloid beta plaque targeted therapy. This policy documents whether testing cerebrospinal fluid and urinary biomarkers improves outcomes in individuals with mild cognitive impairment or Alzheimer's disease.

The following test(s) are addressed in this policy:

- Lumipulse® G ß-Amyloid Ratio (1-42/1-40) (Fujirebio Diagnostics, Inc) – CPT code 0358U
- Neurofilament Light Chain (NfL) (Mayo Clinic) – CPT code 0361U (Code Deleted Effective 12/31/2025)
- PrecivityAD® blood test (C2N Diagnostics, LLC.) – CPT code 0412U
- Neurofilament Light Chain (NfL) by (Washington University in St. Louis School of Medicine-Neuromuscular Laboratory) – CPT code 0443U
- Elecsys® Phospho-Tau (181P) CSF (pTau181) and β-Amyloid (1-42) CSF II (Abeta 42) Ratio (Roche Diagnostics) – CPT code 0445U
- Elecsys® Total Tau CSF (tTau) and B-Amyloid (1-42) CSF II (Abeta 42) Ratio (Roche Diagnostics Operations, Inc) – CPT code 0459U

MEDICAL CRITERIA

Medicare Advantage Plans and Commercial Products

The following CPT code(s)/test(s) follow the medical necessity criteria below for Medicare Advantage Plans and Commercial Products:

- 82233
- 82234
- 84393
- 84394
- Lumipulse® G ß-Amyloid Ratio (1-42/1-40) (Fujirebio Diagnostics, Inc) – CPT code 0358U
- Elecsys® Phospho-Tau (181P) CSF (pTau181) and β-Amyloid (1-42) CSF II (Abeta 42) Ratio (Roche Diagnostics) – CPT code 0445U
- Elecsys® Total Tau CSF (tTau) and B-Amyloid (1-42) CSF II (Abeta 42) Ratio (Roche Diagnostics Operations, Inc) – CPT code 0459U

The use of cerebrospinal fluid biomarker testing of amyloid beta proteins and tau proteins may be considered medically necessary in individuals with mild cognitive impairment or mild dementia due to Alzheimer disease when:

- Used as part of an evaluation for the initiation of amyloid beta targeting therapy, and
- Not used as an adjunct to clinical diagnosis, and
- Not as part of an evaluation for the continuation of amyloid beta targeting therapy

PRIOR AUTHORIZATION

Medicare Advantage Plans and Commercial Products

Prior authorization is required for Medicare Advantage Plans and recommended for Commercial Products for the following CPT codes/tests:

- 82233
- 82234
- 84393
- 84394
- Lumipulse® G ß-Amyloid Ratio (1-42/1-40) (Fujirebio Diagnostics, Inc) – CPT code 0358U
- Elecsys® Phospho-Tau (181P) CSF (pTau181) and β-Amyloid (1-42) CSF II (Abeta 42) Ratio (Roche Diagnostics) – CPT code 0445U
- Elecsys® Total Tau CSF (tTau) and B-Amyloid (1-42) CSF II (Abeta 42) Ratio (Roche Diagnostics Operations, Inc) – CPT code 0459U

POLICY STATEMENT

Medicare Advantage Plans and Commercial Products

The following CPT code(s)/test(s) may be considered medically necessary for Medicare Advantage Plans and Commercial Products when the medical criteria above are met:

- 82233
- 82234
- 84393
- 84394
- Lumipulse® G ß-Amyloid Ratio (1-42/1-40) (Fujirebio Diagnostics, Inc) – CPT code 0358U
- Elecsys® Phospho-Tau (181P) CSF (pTau181) and β-Amyloid (1-42) CSF II (Abeta 42) Ratio (Roche Diagnostics) – CPT code 0445U
- Elecsys® Total Tau CSF (tTau) and B-Amyloid (1-42) CSF II (Abeta 42) Ratio (Roche Diagnostics Operations, Inc) – CPT code 0459U

When cerebrospinal fluid biomarker testing of neural thread proteins is used in individuals with mild cognitive impairment or mild dementia due to Alzheimer disease as an:

- Adjunct to clinical diagnosis, or
- As part of an evaluation for the initiation of amyloid beta targeting therapy, or
- As part of an evaluation for the continuation of amyloid beta targeting therapy, as

the evidence is insufficient to determine the effect of the technology on health outcomes.

Therefore, the following tests are not covered for Medicare Advantage Plans and not medically necessary for Commercial Products (See Coding section for details):

- Neurofilament Light Chain (NfL) (Mayo Clinic) – CPT code 0361U (Code Deleted Effective 12/31/2025)
- Neurofilament Light Chain (NfL) by (Washington University in St. Louis School of Medicine-Neuromuscular Laboratory) – CPT code 0443U

Measurement of urinary and blood biomarkers as an adjunct to clinical diagnosis in individuals with mild cognitive impairment or mild dementia due to Alzheimer disease is not covered for Medicare Advantage Plans and not medically necessary for Commercial Products as the evidence is insufficient to determine the effect of the technology on health outcomes. Therefore, the following tests are not covered for Medicare Advantage Plans and not medically necessary for Commercial Products:

- PrecivityAD® blood test (C2N Diagnostics, LLC.) – CPT code 0412U

Note: Laboratories are not allowed to obtain clinical authorization or participate in the authorization process on behalf of the ordering physician. Only the ordering physician shall be involved in the authorization, appeal or other administrative processes related to prior authorization/medical necessity.

In no circumstance shall a laboratory or a physician/provider use a representative of a laboratory or anyone

with a relationship to a laboratory and/or a third party to obtain authorization on behalf of the ordering physician, to facilitate any portion of the authorization process or any subsequent appeal of a claim where the authorization process was not followed and/or a denial for clinical appropriateness was issued, including any element of the preparation of necessary documentation of clinical appropriateness. If a laboratory or a third party is found to be supporting any portion of the authorization process, BCBSRI will deem the action a violation of this policy and severe action will be taken up to and including termination from the BCBSRI provider network. If a laboratory provides a laboratory service that has not been authorized, the service will be denied as the financial liability of the participating laboratory and may not be billed to the member.

Commercial Products
Some genetic testing services are not covered and a contract exclusion for any self-funded group that has excluded the expanded coverage of biomarker testing related to the state mandate, R.I.G.L. §27-19-81 described in the Biomarker Testing Mandate policy. For these groups, a list of which genetic testing services are covered with prior authorization, are not medically necessary or are not covered because they are a contract exclusion can be found in the Coding section of the Genetic Testing Services or Proprietary Laboratory Analyses policies. Please refer to the appropriate Benefit Booklet to determine whether the member's plan has customized benefit coverage. Please refer to the list of Related Policies for more information.

COVERAGE
Benefits may vary between groups and contracts. Please refer to the appropriate Benefit Booklet, Evidence of Coverage or Subscriber Agreement for not medically necessary/not covered services.

BACKGROUND
Alzheimer's Disease (AD) is a fatal neurodegenerative disease that causes progressive loss in memory, language, and thinking, with the eventual loss of ability to perform social and functional activities in daily life. Survival after a diagnosis of dementia due to AD generally ranges between 4 and 8 years; however, life expectancy can be influenced by other factors, such as comorbid medical conditions. It is estimated that 6.2 million Americans aged 65 and older are currently living with AD dementia, and the number is projected to reach over 12 million by 2050.[1] Per the 2018 American Academy of Neurology practice guideline update on mild cognitive impairment (MCI), the prevalence of MCI was 6.7% for ages 60 to 64, 8.4% for ages 65 to 69, 10.1% for ages 70 to 74, 14.8% for ages 75 to 79, and 25.2% for ages 80 to 84.[2] The cumulative dementia incidence was 14.9% in individuals with MCI >65 years of age followed for 2 years.

Data from the National Institute on Aging have shown that Black Americans are approximately 1.5 to 2 times more likely to develop AD and related dementias as compared to Whites.[3] Additionally, Black participants in AD research studies were 35% less likely to be diagnosed with AD and related dementias and were found to have more risk factors for the disease as well as greater cognitive impairment and symptom severity than White participants. Findings from 2 national surveys conducted by the Alzheimer's Association also found that people of color face discrimination when seeking health care for AD and related dementias with the highest level of discrimination in dementia health care reported by Black Americans (50%) followed by Native (42%), Asian (34%), and Hispanic (33%) Americans.[4] Non-Hispanic White Americans reported a discrimination rate of 9%.

Pathophysiology
The pathologic hallmarks of AD are extracellular deposits of amyloid beta, referred to as amyloid plaques, and intracellular aggregates of hyperphosphorylated tau in the form of neurofibrillary tangles. There are different forms of amyloid such as plaques, oligomers, and monomers, and the roles of these different forms and their contributions to the pathophysiology of AD is not well understood. Generally referred to as the "amyloid hypothesis", it is believed that aggregation of amyloid beta oligomers in the brain leads to amyloid plaques. Amyloid aggregation in addition to accumulation of tau pathology and neurodegeneration are thought to be the main drivers of the disease process. These changes in the brain result in widespread neurodegeneration and cell death, and ultimately cause the clinical signs and symptoms of dementia.5,6,

The pathophysiological changes and clinical manifestations of AD are progressive and occur along a continuum, and accumulation of amyloid beta may begin 20 years or more before symptoms arise.7, The National Institute on Aging-Alzheimer's Association (NIA-AA) has created a "numeric clinical staging scheme" (Table 1) that avoids traditional syndromal labels and is applicable for only those in the Alzheimer continuum. This staging scheme is primarily used in the research setting and reflects the sequential evolution of AD from an initial stage characterized by the appearance of abnormal AD biomarkers in asymptomatic individuals. As biomarker abnormalities progress, the earliest subtle symptoms become detectable. Further progression of biomarker abnormalities is accompanied by progressive worsening of cognitive symptoms, culminating in dementia.

Biomarkers

Several potential biomarkers of AD are associated with AD pathophysiology (eg, amyloid beta plaques, neurofibrillary tangles). Altered cerebrospinal fluid (CSF) levels of specific proteins have been found in patients with AD. These include tau protein, phosphorylated at AD-specific epitopes such as phosphorylated threonine 181 or total tau protein, an amyloid beta peptide such as 1-42 (Aβ42), and the synaptic protein, neurogranin.[2] Other potential CSF, urinary, and blood, peptide markers have been explored. Tau protein is a microtubule-associated molecule found in neurofibrillary tangles that are typical of AD. Tau protein is thought to be related to degenerating and dying neurons and high levels of tau protein in the CSF have been associated with AD. Amyloid beta-42 is a subtype of amyloid beta peptide produced from the metabolism of the amyloid precursor protein. Amyloid beta-42 is the key peptide deposited in amyloid plaques characteristic of AD. Low levels of amyloid beta-42 in the CSF have been associated with AD, perhaps because amyloid beta-42 is deposited in amyloid plaques instead of remaining in the fluid. Investigators have suggested the tau/amyloid beta-42 ratio may be a more accurate diagnostic marker than either alone. Neurogranin is a dendritic protein and CSF measurement may serve as a biomarker for dendritic instability and synaptic degeneration. Elevated CSF neurogranin may predict prodromal AD in MCI and has been confirmed in AD dementia and prodromal AD in several studies.

A variety of kits are commercially available to measure amyloid beta-42 and tau proteins. Between-laboratory variability in CSF biomarker measurement is large. Neural thread protein is associated with neurofibrillary tangles of AD. Both CSF and urine levels of this protein have been investigated as a potential marker of AD. Urine and CSF tests for neural thread protein may be referred to as the AD7C test.

More recently, research has focused on blood as a new matrix for AD biomarkers that have already been validated in the CSF. As blood is more accessible than CSF, blood sampling would be preferable to CSF when taking samples to measure AD biomarkers, both for clinical diagnosis or screening. However, developing blood AD biomarkers has proven complex. While the CSF is continuous with the brain extracellular fluid, with a free exchange of molecules from the brain to the CSF, only a fraction of brain proteins enter the bloodstream. Examples of blood biomarkers that are currently under examination for use in AD include amyloid beta, tau protein, and neurofilament light. Results from initial studies show that these blood biomarkers may potentially assist in early and more precise diagnosis, prognosis, or monitoring of disease progression and treatment in AD. In 2019, the Geneva AD Biomarker Roadmap Initiative expert panel concluded that of the currently assessed blood biomarkers plasma pTau has shown analytical validity and initial evidence of clinical validity, whereas the maturity level for amyloid beta remains to be partially achieved.

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). Laboratories that offer laboratory-developed tests (LDTs) must be certified by CLIA for high-complexity testing. To date, the FDA has chosen not to require any regulatory review of these tests. Several AD biomarker tests are available as LDTs.

The FDA has cleared the following AD biomarker tests for marketing via the De Novo and 510(k) pathways:

- Lumipulse *G* Amyloid Ratio (1-42/1-40)
- Elecsys B-Amyloid (1-42) CSF II, Elecsys Phospho-Tau (181P) CSF

- Elecsys ß-Amyloid (1-42) CSF II, Elecsys Total-Tau CSF

For individuals who have mild cognitive impairment (MCI) or dementia who receive cerebrospinal fluid (CSF) biomarker testing for Alzheimer disease (AD), the evidence includes systematic reviews. These studies assess using CSF biomarkers for diagnosis of AD or for the prognosis of progression of MCI to AD. Relevant outcomes include test validity, correct treatment, avoiding unnecessary subsequent testing, harms of invasive testing, and quality of life (QOL). Most clinical validity studies have been derived from select patient samples and defined optimal test cutoffs without validation; thus, the generalizability of results is uncertain. For predicting conversion from MCI to AD, limited evidence has suggested that testing may define increased risk. Whether an earlier diagnosis leads to improved health outcomes through a delay of AD onset due to medical therapy or other interventions or improved QOL is unknown. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have MCI or dementia who receive urinary biomarker testing for AD, the evidence includes a systematic review. Relevant outcomes include test validity, correct treatment, avoiding unnecessary subsequent testing, harms of invasive testing, and QOL. Clinical validity studies have included normal healthy controls and defined optimal test cutoffs without validation; thus, clinical validity is uncertain. Whether an earlier diagnosis leads to improved health outcomes through a delay of AD onset or improved QOL is unknown. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have MCI or dementia who receive blood biomarker testing for AD, the evidence includes a systematic review and cohort studies. Relevant outcomes include test validity, correct treatment, avoiding unnecessary subsequent testing, harms of invasive testing, and QOL. Clinical validity studies have primarily focused on the biomarker, plasma pTau, and have shown that this biomarker may be beneficial in screening for and diagnosing AD. Whether an earlier diagnosis leads to improved health outcomes through a delay of AD onset or improved QOL is unknown. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have MCI or mild dementia due to AD, who are being treated with an amyloid beta plaque targeting therapy and are being evaluated for therapy continuation, the evidence includes multisite longitudinal studies and an analysis of a mixed cohort. Two of these studies assess the correlation between CSF biomarkers and PET amyloid scans and another assesses the clinical utility of amyloid PET in cognitively impaired patients who met appropriate use criteria for clinical amyloid PET. Relevant outcomes include test validity, symptoms, change in disease status, functional outcomes, health status measures, and QOL. The diagnostic accuracy of CSF biomarkers versus amyloid beta PET scans to identify MCI-AD was found to be similar. Further research is required to determine whether the use of CSF biomarkers alone in conjunction with amyloid beta PET scans is useful for determining whether or not amyloid beta targeting therapy should be continued. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have MCI or mild dementia due to AD who are being considered for initial treatment with an approved amyloid beta plaque targeting therapy, the evidence includes randomized controlled trials, multisite longitudinal studies, and an analysis of a mixed cohort. These studies assess both the correlation between CSF biomarkers and positron emission tomography (PET) amyloid scans and the clinical utility of amyloid PET or CSF biomarkers in cognitively impaired patients who are being evaluated for treatment with anti-amyloid therapies. Relevant outcomes include test validity, symptoms, change in disease status, functional outcomes, health status measures, and QOL. Overall, the diagnostic accuracy of CSF biomarkers versus amyloid PET scans to identify MCI-AD was found to be similar. CSF biomarkers have been used as an alternative to PET amyloid scans to establish eligibility regarding the presence of amyloid beta pathology in randomized controlled trials that showed the efficacy of anti-amyloid therapies, which in turn demonstrates that the CSF biomarkers can identify patients who may benefit from therapy. The FDA-approved labels for lecanemab and donanemab state that the presence of amyloid beta pathology should be

confirmed prior to initiating treatment. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

CODING

Medicare Advantage Plans and Commercial Products

The following CPT code(s)/test(s) are considered medically necessary for Medicare Advantage Plans and Commercial Products when the above criteria are met:

82233 Beta-amyloid; 1-40 (Abeta 40)
82234 Beta-amyloid; 1-42 (Abeta 42)
84393 Tau, phosphorylated (eg, pTau 181, pTau 217), each
84394 Tau, total (tTau)

This code can be used for Lumipulse® G ß-Amyloid Ratio (1-42/1-40) test
0358U Neurology (mild cognitive impairment), analysis of B-amyloid 1-42 and 1-40, chemiluminescence enzyme immunoassay, cerebral spinal fluid, reported as positive, likely positive, or negative

This code can be used for Elecsys® Phospho-Tau (181P) CSF (pTau181) and β-Amyloid (1-42) CSF II (Abeta 42) Ratio test
0445U βamyloid (Abeta42) and Phospho Tau (181P) (pTau181), electrochemiluminescence immunoassay (ECLIA), cerebral spinal fluid, ratio reported as positive or negative for amyloid pathology

This code can be used for Elecsys® Total Tau CSF (tTau) and B-Amyloid (1-42) CSF II (Abeta 42) Ratio test
0459U βamyloid (Abeta42) and Phospho Tau (181P) (pTau181), electrochemiluminescence immunoassay (ECLIA), cerebral spinal fluid, ratio reported as positive or negative for amyloid pathology

The following CPT code(s), when filed with one of the ICD-10 Diagnosis Code(s)* listed below, are considered not covered for Medicare Advantage Plans and not medically necessary for Commercial Products:

This code can be used for Neurofilament Light Chain (NfL) test
0361U Neurofilament light chain, digital immunoassay, plasma, quantitative (Code Deleted Effective 12/31/2025)

This code can be used for Neurofilament Light Chain (NfL) test (Washington University in St. Louis School of Medicine-Neuromuscular Laboratory)
0443U Neurofilament light chain (NfL), ultra-sensitive immunoassay, serum or cerebrospinal fluid

Not all testing addressed in this policy has been assigned specific CPT codes. Therefore, the following CPT codes may be used. Testing using these CPT codes is not covered for Medicare Advantage Plans and not medically necessary for Commercial Products when filed with one of the ICD-10 Diagnosis Code(s)* listed below:
The following CPT code may be used to test urine:
81099 Unlisted Urinalysis Procedure

The following CPT code(s) may be used to report testing for tau protein and amyloid-β peptides:
83520 Immunoassay for analyte other than infectious agent antibody or infectious agent antigen; quantitative, not otherwise specified

The following CPT code may be used to test cerebrospinal fluid:
86849 Unlisted Immunology Procedure

***ICD-10 Diagnosis Code(s)**
F03.90-F03.91
G30.0-G30.9
G31.1

G31.84
R41.81

The following CPT code(s) are not covered for Medicare Advantage Plans and not medically necessary for Commercial Products:

This code can be used for PrecivityAD® blood test

0412U Beta amyloid, Aβ42/40 ratio, immunoprecipitation with quantitation by liquid chromatography with tandem mass spectrometry (LC-MS/MS) and qualitative ApoE isoformspecific proteotyping, plasma combined with age, algorithm reported as presence or absence of brain amyloid pathology

RELATED POLICIES

Biomarker Testing Mandate
Genetic Testing Services
Proprietary Laboratory Analysis (PLA) and Multianalyte Assays with Algorithmic Analyses (MAAA)
Unlisted Procedures

PUBLISHED

Provider Update, September 2025
Provider Update, January 2025
Provider Update, February 2024
Provider Update, January/November 2023
Provider Update, April 2021

REFERENCES

1. 2021 Alzheimer's disease facts and figures. Alzheimers Dement. Mar 2021; 17(3): 327-406. PMID 33756057
2. Petersen RC, Lopez O, Armstrong MJ, et al. Practice guideline update summary: Mild cognitive impairment: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. Neurology.Jan 16 2018; 90(3): 126-135. PMID 29282327
3. National Institutes on Aging. Data shows racial disparities in Alzheimer's disease diagnosis between Black and white research study participants. December 16, 2021. https://www.nia.nih.gov/news/data-shows-racial-disparities-alzheimers-disease-diagnosis-between-black-and-white-research. Accessed August 23, 2023.
4. Centers for Disease Control and Prevention. Barriers to equity in Alzheimer's and dementia care. June 2, 2021. https://www.cdc.gov/aging/publications/features/barriers-to-equity-in-alzheimers-dementia-care/index.html. Accessed August 23, 2023.
5. Alzheimer's Association. 2022 Alzheimer's disease facts and figures. https://www.alz.org/media/documents/alzheimers-facts-and-figures.pdf. Accessed April 18, 2025.
6. Roberts RO, Aakre JA, Kremers WK, et al. Prevalence and Outcomes of Amyloid Positivity Among Persons Without Dementia in a Longitudinal, Population-Based Setting. JAMA Neurol. Aug 01 2018; 75(8): 970-979. PMID 29710225
7. Vermunt L, Sikkes SAM, van den Hout A, et al. Duration of preclinical, prodromal, and dementia stages of Alzheimer's disease in relation to age, sex, and APOE genotype. Alzheimers Dement. Jul 2019; 15(7): 888-898. PMID 31164314
8. Jack CR, Bennett DA, Blennow K, et al. NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease. Alzheimers Dement. Apr 2018; 14(4): 535-562. PMID 29653606
9. Blennow K, Zetterberg H. Biomarkers for Alzheimer's disease: current status and prospects for the future. J Intern Med. Dec2018; 284(6): 643-663. PMID 30051512
10. Galasko D, Clark C, Chang L, et al. Assessment of CSF levels of tau protein in mildly demented patients with Alzheimer's disease. Neurology. Mar 1997; 48(3): 632-5. PMID 9065538
11. Motter R, Vigo-Pelfrey C, Kholodenko D, et al. Reduction of beta-amyloid peptide42 in the cerebrospinal fluid of patients with Alzheimer's disease. Ann Neurol. Oct 1995; 38(4): 643-8. PMID 7574461

12. Zhang J, Peng M, Jia J. Plasma amyloid-β oligomers and soluble tumor necrosis factor receptors as potential biomarkers of AD. Curr Alzheimer Res. May 2014; 11(4): 325-31. PMID 24635842
13. Maddalena A, Papassotiropoulos A, Muller-Tillmanns B, et al. Biochemical diagnosis of Alzheimer disease by measuring the cerebrospinal fluid ratio of phosphorylated tau protein to beta-amyloid peptide42. Arch Neurol. Sep 2003; 60(9): 1202-6. PMID12975284
14. Dumurgier J, Vercruysse O, Paquet C, et al. Intersite variability of CSF Alzheimer's disease biomarkers in clinical setting.Alzheimers Dement. Jul 2013; 9(4): 406-13. PMID 23141384
15. Mattsson N, Andreasson U, Persson S, et al. The Alzheimer's Association external quality control program for cerebrospinal fluid biomarkers. Alzheimers Dement. Jul 2011; 7(4): 386-395.e6. PMID 21784349
16. Teunissen CE, Verberk IMW, Thijssen EH, et al. Blood-based biomarkers for Alzheimer's disease: towards clinical implementation. Lancet Neurol. Jan 2022; 21(1): 66-77. PMID 34838239
17. Ashton NJ, Leuzy A, Karikari TK, et al. The validation status of blood biomarkers of amyloid and phospho-tau assessed with the 5-phase development framework for AD biomarkers. Eur J Nucl Med Mol Imaging. Jul 2021; 48(7): 2140-2156. PMID 33677733
18. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), American Psychiatric Association, Arlington, VA 2013.
19. McKhann G, Drachman D, Folstein M, et al. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology. Jul 1984; 34(7): 939-44. PMID 6610841
20. McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement. May 2011; 7(3): 263-9. PMID 21514250
21. Rosa MI, Perucchi J, Medeiros LR, et al. Accuracy of cerebrospinal fluid A(1-42) for Alzheimer's disease diagnosis: a systematic review and meta-analysis. J Alzheimers Dis. 2014; 40(2): 443-54. PMID 24448789
22. Bloudek LM, Spackman DE, Blankenburg M, et al. Review and meta-analysis of biomarkers and diagnostic imaging in Alzheimer's disease. J Alzheimers Dis. 2011; 26(4): 627-45. PMID 21694448
23. Formichi P, Battisti C, Radi E, et al. Cerebrospinal fluid tau, A beta, and phosphorylated tau protein for the diagnosis of Alzheimer's disease. J Cell Physiol. Jul 2006; 208(1): 39-46. PMID 16447254
24. Ferreira D, Perestelo-Perez L, Westman E, et al. Meta-Review of CSF Core Biomarkers in Alzheimer's Disease: The State-of-the-Art after the New Revised Diagnostic Criteria. Front Aging Neurosci. 2014; 6: 47. PMID 24715863
25. Fink HA, Linskens EJ, Silverman PC, et al. Accuracy of Biomarker Testing for Neuropathologically Defined Alzheimer Disease in Older Adults With Dementia. Ann Intern Med. May 19 2020; 172(10): 669-677. PMID 32340038
26. Cure S, Abrams K, Belger M, et al. Systematic literature review and meta-analysis of diagnostic test accuracy in Alzheimer's disease and other dementia using autopsy as standard of truth. J Alzheimers Dis. 2014; 42(1): 169-82. PMID 24840572
27. Olsson B, Lautner R, Andreasson U, et al. CSF and blood biomarkers for the diagnosis of Alzheimer's disease: a systematic review and meta-analysis. Lancet Neurol. Jun 2016; 15(7): 673-684. PMID 27068280
28. Ritchie C, Smailagic N, Noel-Storr AH, et al. CSF tau and the CSF tau/ABeta ratio for the diagnosis of Alzheimer's disease dementia and other dementias in people with mild cognitive impairment (MCI). Cochrane Database Syst Rev. Mar 22 2017; 3:CD010803. PMID 28328043
29. Ritchie C, Smailagic N, Noel-Storr AH, et al. Plasma and cerebrospinal fluid amyloid beta for the diagnosis of Alzheimer's disease dementia and other dementias in people with mild cognitive impairment (MCI). Cochrane Database Syst Rev. Jun 102014; (6): CD008782. PMID 24913723
30. Raina P, Santaguida P, Ismaila A, et al. Effectiveness of cholinesterase inhibitors and memantine for treating dementia: evidence review for a clinical practice guideline. Ann Intern Med. Mar 04 2008; 148(5):
31. Kaduszkiewicz H, Zimmermann T, Beck-Bornholdt HP, et al. Cholinesterase inhibitors for patients with Alzheimer's disease: systematic review of randomised clinical trials. BMJ. Aug 06 2005; 331(7512): 321-7. PMID 16081444
32. McShane R, Areosa Sastre A, Minakaran N. Memantine for dementia. Cochrane Database Syst Rev. Apr 19 2006; (2):CD003154. PMID 16625572

33. Schneider LS, Mangialasche F, Andreasen N, et al. Clinical trials and late-stage drug development for Alzheimer's disease: an appraisal from 1984 to 2014. J Intern Med. Mar 2014; 275(3): 251-83. PMID 24605808
34. Feldman HH, Ferris S, Winblad B, et al. Effect of rivastigmine on delay to diagnosis of Alzheimer's disease from mild cognitive impairment: the In DDEx study. Lancet Neurol. Jun 2007; 6(6): 501-12. PMID 17509485
35. Winblad B, Gauthier S, Scinto L, et al. Safety and efficacy of galantamine in subjects with mild cognitive impairment. Neurology. May 27 2008; 70(22): 2024-35. PMID 18322263
36. Petersen RC, Thomas RG, Grundman M, et al. Vitamin E and donepezil for the treatment of mild cognitive impairment. N EnglJ Med. Jun 09 2005; 352(23): 2379-88. PMID 15829527
37. Zhang J, Zhang CH, Li RJ, et al. Accuracy of urinary AD7c-NTP for diagnosing Alzheimer's disease: a systematic review and meta-analysis. J Alzheimers Dis. 2014; 40(1): 153-9. PMID 24346218
38. Krishna G, Thangaraju Sivakumar P, Dahale AB, et al. Potential Utility of Plasma Biomarker Panels in Differential Diagnosis of Alzheimer's Disease. J Alzheimers Dis Rep. 2024; 8(1): 1-7. PMID 38229828
39. Schraen-Maschke S, Duhamel A, Vidal JS, et al. The free plasma amyloid Aβ 1 - 42 /Aβ 1 - 40 ratio predicts conversion to dementia for subjects with mild cognitive impairment with performance equivalent to that of the total plasma Aβ 1 - 42 /Aβ 1 - 40 ratio. The BALTAZAR study. Neurobiol Dis. Apr 2024; 193: 106459. PMID 38423192
40. Thijssen EH, La Joie R, Wolf A, et al. Diagnostic value of plasma phosphorylated tau181 in Alzheimer's disease and frontotemporal lobar degeneration. Nat Med. Mar 2020; 26(3): 387-397. PMID 32123386
41. Janelidze S, Mattsson N, Palmqvist S, et al. Plasma P-tau181 in Alzheimer's disease: relationship to other biomarkers, differential diagnosis, neuropathology and longitudinal progression to Alzheimer's dementia. Nat Med. Mar 2020; 26(3): 379-386. PMID 32123385
42. Palmqvist S, Janelidze S, Quiroz YT, et al. Discriminative Accuracy of Plasma Phospho-tau217 for Alzheimer Disease vs Other Neurodegenerative Disorders. JAMA. Aug 25 2020; 324(8): 772-781. PMID 32722745
43. Jack CR, Albert MS, Knopman DS, et al. Introduction to the recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement. May 2011; 7(3): 257-62. PMID 21514247
44. Albert MS, DeKosky ST, Dickson D, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for a Alzheimer's disease. Alzheimers Dement. May 2011; 7(3): 270-9. PMID 21514249
45. Budd Haeberlein S, Aisen PS, Barkhof F, et al. Two Randomized Phase 3 Studies of Aducanumab in Early Alzheimer's Disease. J Prev Alzheimers Dis. 2022; 9(2): 197-210. PMID 35542991
46. Salloway S, Chalkias S, Barkhof F, et al. Amyloid-Related Imaging Abnormalities in 2 Phase 3 Studies Evaluating Aducanumab in Patients With Early Alzheimer Disease. JAMA Neurol. Jan 01 2022; 79(1): 13-21. PMID 34807243
47. van Dyck CH, Swanson CJ, Aisen P, et al. Lecanemab in Early Alzheimer's Disease. N Engl J Med. Jan 05 2023; 388(1): 9-21. PMID 36449413
48. Janelidze S, Pannee J, Mikulskis A, et al. Concordance Between Different Amyloid Immunoassays and Visual Amyloid Positron Emission Tomographic Assessment. JAMA Neurol. Dec 01 2017; 74(12): 1492-1501. PMID 29114726
49. Hansson O, Lehmann S, Otto M, et al. Advantages and disadvantages of the use of the CSF Amyloid (A) 42/40 ratio in the diagnosis of Alzheimer's Disease. Alzheimers Res Ther. Apr 22 2019; 11(1): 34. PMID 31010420
50. Chetelat G, Arbizu J, Barthel H, et al. Amyloid-PET and 18 F-FDG-PET in the diagnostic investigation of Alzheimer's disease and other dementias. Lancet Neurol. Nov 2020; 19(11): 951-962. PMID 33098804
51. Palmqvist S, Zetterberg H, Mattsson N, et al. Detailed comparison of amyloid PET and CSF biomarkers for identifying early Alzheimer disease. Neurology. Oct 06 2015; 85(14): 1240-9. PMID 26354982
52. Lewczuk P, Matzen A, Blennow K, et al. Cerebrospinal Fluid A42/40 Corresponds Better than A42 to Amyloid PET inAlzheimer's Disease. J Alzheimers Dis. 2017; 55(2): 813-822. PMID 27792012
53. Nisenbaum L, Martone R, Chen T, et al. CSF biomarker concordance with amyloid PET in Phase 3 studies of aducanumab. Alzheimers Dement. Aug 2023; 19(8): 3379-3388. PMID 36795603

54. Summary Review for Leqembi (lecanemab) Application Number: 761269Orig1s000. Center for Drug Evaluation and Research. Available at https://www.accessdata.fda.gov/drugsatfda_docs/summary_review/2023/761269Orig1s000SumR.pdf. Accessed on August 23, 2023.
55. Prescribing Label for LEQEMBI (lecanemab-irmb) injection, for intravenous use. Available at https://www.leqembi.com/-/media/Files/Leqembi/Prescribing-Information.pdf?hash=3d7bf1a2-5db2-4990-8388-81086f415676. Accessed on August 23, 2023.
56. Vanderstichele H, Bibl M, Engelborghs S, et al. Standardization of preanalytical aspects of cerebrospinal fluid biomarker testing for Alzheimer's disease diagnosis: a consensus paper from the Alzheimer's Biomarkers Standardization Initiative. Alzheimers Dement. Jan 2012; 8(1): 65-73. PMID 22047631
57. Cordell CB, Borson S, Boustani M, et al. Alzheimer's Association recommendations for operationalizing the detection of cognitive impairment during the Medicare Annual Wellness Visit in a primary care setting. Alzheimers Dement. Mar 2013; 9(2):141-50. PMID 23265826
58. Shaw LM, Arias J, Blennow K, et al. Appropriate use criteria for lumbar puncture and cerebrospinal fluid testing in the diagnosisof Alzheimer's disease. Alzheimers Dement. Nov 2018; 14(11): 1505-1521. PMID 30316776
59. Hansson O, Batrla R, Brix B, et al. The Alzheimer's Association international guidelines for handling of cerebrospinal fluid for routine clinical measurements of amyloid and tau. Alzheimers Dement. Sep 2021; 17(9): 1575-1582. PMID 33788410
60. Hansson O, Edelmayer RM, Boxer AL, et al. The Alzheimer's Association appropriate use recommendations for blood biomarkers in Alzheimer's disease. Alzheimers Dement. Jul 31 2022. PMID 35908251
61. Dementia: assessment, management and support for people living with dementia and their carers. National Institute for Health and Care Excellence. Published June 20, 2018. https://www.nice.org.uk/guidance/ng97. Accessed August 23, 2023.
62. Cognitive impairment in older adults: screening. U.S. Preventative Task Force. Published February 25, 2020. https://uspreventiveservicestaskforce.org/uspstf/recommendation/cognitive-impairment-in-older-adults-screening. Accessed August 23, 2023.

CLICK THE ENVELOPE ICON BELOW TO SUBMIT COMMENTS