



Biochemical and Cellular Markers of Alzheimer's Disease

Effective: October 1, 2026

Next Review: June 2027

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IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Biochemical and cellular biomarkers may predict risk of Alzheimer's disease (AD); however, the clinical value of this testing is uncertain.

MEDICAL POLICY CRITERIA

- I. Measurement of cerebrospinal fluid or blood biomarkers of Alzheimer's disease, including but not limited to tau protein, amyloid beta peptides, or neural thread proteins, is considered **investigational**.
- II. Measurement of urinary biomarkers of Alzheimer's disease, including but not limited to neural thread proteins, is considered **investigational**.
- III. Skin cell (fibroblast) testing for biomarkers of Alzheimer's disease, including but not limited to the DISCERN™ test, is considered **investigational**.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

CROSS REFERENCES

1. [Genetic Testing for Familial Alzheimer's Disease](#), Genetic Testing, Policy No. 01

BACKGROUND

Alzheimer 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. According to 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.^[1] The cumulative dementia incidence was 14.9% in individuals with MCI over 65 years of age followed for two 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.^[2] 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 two 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. Non-Hispanic White Americans reported a discrimination rate of 9%.^[3]

The diagnosis of Alzheimer's disease (AD) is typically a clinical diagnosis, focusing on the exclusion of other causes of dementia. In 1984 the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's and Related Disorders Association (ADRDA) published clinical criteria for the diagnosis of AD. These organizations defined three categories: possible, probable, and definite AD. The only difference between probable and definite AD is that the definite category requires a brain biopsy confirming the presence of characteristic neurofibrillary tangles. Therefore, definite AD is typically identified only at autopsy. The categories are defined as follows:

I. Possible Alzheimer's Disease

- A. May be made on the basis of the dementia syndrome in the absence of other neurological, psychiatric, or systemic disorders sufficient to cause dementia, and in the presence of variations in the onset, in the presentation, or in the clinical course
- B. May be made in the presence of a second systemic or brain disorder sufficient to produce dementia, which is not considered to be the cause of the dementia
- C. Should be used in research studies when a single gradually progressive severe cognitive deficit is identified in the absence of other identifiable cause

II. Probable Alzheimer's Disease

- A. The criteria for the clinical diagnosis of probable AD include:
 - 1. Dementia, established by clinical examination and documented by the Mini-Mental State Examination, the Blessed Dementia Scale, or some similar examination and confirmed by neuropsychological tests

2. Deficits in two or more areas of cognition
 3. Progressive worsening of memory and other cognitive functions
 4. No disturbance of consciousness
 5. Onset between ages 40 and 90, most often after the age of 65
 6. Absence of systemic disorders or other brain diseases that in and of themselves could account for the progressive deficits in memory and cognition
- B. The diagnosis of probable AD is supported by:
1. Progressive deterioration of specific cognitive functions such as language (aphasia), motor skills (apraxia), and perception (agnosia)
 2. Impaired activities of daily living and altered patterns of behavior
 3. Family history of similar disorders, particularly if confirmed neuropathologically
 4. Laboratory results: normal lumbar puncture as evaluated by standard techniques, normal pattern or non-specific changes in the EEG, and evidence of cerebral atrophy on CT scanning with progression documented by serial observation
- C. Other clinical features consistent with the diagnosis of probable AD, after exclusion of causes of dementia other than AD, include:
1. Plateaus in the course of progression of the illness;
 2. Associated symptoms of depression, insomnia, incontinence, delusions, illusions, hallucinations, sexual disorders, weight loss, and catastrophic verbal, emotional, or physical outbursts
 3. Other neurologic abnormalities in some patients, especially with more advanced disease and including motor signs such as increased muscle tone, myoclonus, or gait disorder
 4. Seizures in advanced disease CT normal for age
- D. Features that make the diagnosis of probable AD uncertain or unlikely include:
1. Sudden apoplectic onset
 2. Focal neurological findings such as hemiparesis, sensory loss, visual field deficits, and incoordination early in the course of the illness
 3. Seizures or gait disturbances at the onset or very early in the course of the illness
- III. Definite Alzheimer's Disease
- A. Clinical criteria for probable Alzheimer's disease AND
 - B. Histopathologic evidence obtained from a biopsy or autopsy

In 2011, the National Institute on Aging and the Alzheimer's Association workgroup revised diagnostic criteria for diagnosis of dementia due to Alzheimer's disease. All probable AD by NINCDS-ADRDA criteria are subsumed in the revised probable AD criteria, which is now defined by the following:

"Meets criteria for dementia [...] and in addition, has the following characteristics:

- A. Insidious onset. Symptoms have a gradual onset over months to years, not sudden over hours or days;
- B. Clear-cut history of worsening of cognition by report or observation; and
- C. The initial and most prominent cognitive deficits are evident on history and examination in one of the following categories.
 - 1. Amnesic presentation: It is the most common syndromic presentation of AD dementia. The deficits should include impairment in learning and recall of recently learned information. There should also be evidence of cognitive dysfunction in at least one other cognitive domain, as defined earlier in the text.
 - 2. Nonamnesic presentations: Language presentation: The most prominent deficits are in word-finding, but deficits in other cognitive domains should be present. Visuospatial presentation: The most prominent deficits are in spatial cognition, including object agnosia, impaired face recognition, simultanagnosia, and alexia. Deficits in other cognitive domains should be present. Executive dysfunction: The most prominent deficits are impaired reasoning, judgment, and problem solving. Deficits in other cognitive domains should be present.

The diagnosis of probable AD dementia should not be applied when there is evidence of (a) substantial concomitant cerebrovascular disease, defined by a history of a stroke temporally related to the onset or worsening of cognitive impairment; or the presence of multiple or extensive infarcts or severe white matter hyperintensity burden; or (b) core features of Dementia with Lewy bodies other than dementia itself; or (c) prominent features of behavioral variant frontotemporal dementia; or (d) prominent features of semantic variant primary progressive aphasia or nonfluent/agrammatic variant primary progressive aphasia; or (e) evidence for another concurrent, active neurological disease, or a non-neurological medical comorbidity or use of medication that could have a substantial effect on cognition."

Diagnosis by exclusion is frustrating for physicians, patients and families, and there has been considerable research interest in identifying an inclusive laboratory test for AD, particularly for use early in the disease process. Abnormal levels in cerebrospinal fluid (CSF) of the tau protein (total tau [tTau] or phosphorylated [pTau]) or an amyloid beta (A β) peptide such as A β 42, have been found in patients with AD, and thus these proteins have been investigated for their diagnostic utility. The tau protein is a microtubule-associated molecule that is found in the neurofibrillary tangles that are typical of Alzheimer's disease. This protein is thought to be related to degenerating and dying neurons, and high levels of tau proteins in the CSF have been associated with AD. A β 42 is a subtype of A β peptide that is produced following the metabolism of an amyloid precursor protein. A β 42 is the key peptide deposited in the amyloid plaques that are characteristic of AD. Low levels of A β 42 in the CSF have been associated with AD, perhaps because the A β 42 is deposited in the amyloid plaques instead of remaining in solution.

Neural thread protein (NTP) is another protein that is associated with neurofibrillary tangles of Alzheimer's disease. Both CSF and urine levels of this protein have been investigated as a biochemical marker of Alzheimer's disease. Urine and CSF tests for neural thread protein may be referred to as the AD7C™ test.

In 2024, the Alzheimer's Association workgroup published revised diagnostic criteria for diagnosis of dementia due to Alzheimer's disease and proposed that amyloid positron emission tomography (PET) and certain CSF or blood-based biomarkers could be used for diagnosis.^[4] These guidelines have been controversial, as they may lead to AD diagnosis in individuals with no cognitive changes. For example, the American Geriatrics Society published a response letter to the draft guidelines, which stated that they were "concerned that the proposed expansion of the NIA-AA guidelines to include usage in clinical care will place many older and multimorbid people at risk of overdiagnosis, which in turn could lead to initiation of treatments with limited benefit and high potential for harm in this population"^[5] Among their concerns, they noted substantial conflicts of interest among the authors and questioned the reduced level of involvement of the National Institute on Aging (NIA), noting that earlier versions of the guidelines were intended to provide a research framework, "a usage that is consistent with the mission of the NIA," and not clinical guidelines.^[5] The NIA removed their name from the title of the final publication.

REGULATORY STATUS

The Lumipulse® G β -Amyloid Ratio (1-42/1-40) Test (Fujirebio Diagnostics) and the Elecsys® CSF assays for pTau181/A β 42 and tTau/A β 42 (Roche) have received 510(k) marketing clearance from the U.S. Food and Drug Administration (FDA).

Many biomarker tests for AD do not have FDA approval or clearance, including:

- AlzheimerAlert™ (Nymox Pharmaceutical Corp.)
- Innatest® assays for tTau, pTau, and A β 42 (Fujirebio Diagnostics)
- AdMark® CSF analysis
- DISCERN™ (Neurodiagnostics) skin sample fibroblast testing
- AD-Detect (Quest Diagnostics)

These are laboratory-developed tests (LDTs). Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; LDTs must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA). Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing.

EVIDENCE SUMMARY

Validation of the clinical use of any prognostic test focuses on three main principles:

1. The analytic validity of the test, which refers to the technical accuracy of the test in detecting a disease marker of interest that is present or in excluding a disease marker that is absent;
2. The clinical validity of the test, which refers to the diagnostic performance of the test (sensitivity, specificity, positive and negative predictive values) in detecting clinical disease; and
3. The clinical utility of the test, i.e., how the results of the diagnostic test will be used to change management of the patient and whether these changes in management lead to

clinically important improvements in health outcomes. The clinical utility of both positive and negative tests must be established.

This evidence review focuses on clinical validity and utility.

Evaluation of evidence of clinical utility requires consideration of the following:

- Reference/criterion standard: The gold standard for definitive diagnosis of AD is autopsy. The accuracy of testing for AD is best established by comparison with this gold standard; therefore, the gold standard must be employed to accurately assess incremental diagnostic improvement.
- Predicting conversion from MCI to AD: Predicting conversion from MCI to AD may rely on a clinical diagnosis, albeit with some attendant error and misclassification, because the prediction of interest is conversion and not the gold standard diagnosis.
- Incremental diagnostic improvement: Incremental diagnostic or prognostic improvement is best demonstrated through evidence that the proposed predictor can correctly reclassify individuals with and without AD, or those with MCI who will and will not progress to AD.^[6] Alternative approaches such as classical receiver operating characteristic (ROC) analyses, while providing some insight, do not allow directly translating improvements in diagnostic or prognostic accuracy to changes in health outcomes.^[7]
- Improved health outcomes (clinical utility): In order to establish clinical utility, AD biomarkers would need to provide information which improves treatment decisions and health outcomes beyond that of clinical diagnosis.
- Test cutoffs: Almost all studies employ optimal (data-driven) test cutoffs to define test accuracy (sensitivity and specificity). This approach is typically accompanied by a degree of optimism and potentially overstates test accuracy.
- Sample definition: Clear description of whether samples included consecutive patients or were selective is required to evaluate potential bias—including verification bias^[8] — and generalizability but almost absent in this literature.
- Validation: Validation in independent samples is required to establish generalizability of markers but has been scant.

Studies were selected for inclusion in the evidence review based on the following criteria:

- The study population represents the population of interest. Eligibility and selection are described.
- The test is compared with a credible reference standard.
- If the test is intended to replace or be an adjunct to an existing test; it should also be compared with that test.
- Studies should report sensitivity, specificity, and predictive values. Studies that completely report true- and false-positive results are ideal. Studies reporting other measures (e.g., receiver operating characteristic, area under receiver operating characteristic [AUC], c-statistic, likelihood ratios) may be included but are less informative.
- Studies should also report reclassification of the diagnostic or risk category.

CEREBRAL SPINAL FLUID BIOMARKER TESTING

Clinical Validity

Diagnosis of AD

Systematic Reviews

Most studies have relied on clinically diagnosed AD as the criterion standard. Results from several systematic reviews are summarized in Table 1. Studies included in these systematic reviews are not individually reviewed.

A Cochrane review by Kokkinou (2021) evaluated the accuracy of plasma and CSF Aβ42 measurement to distinguish Alzheimer’s disease from other forms of dementia.^[9] A literature search was performed through February 2020, and 39 studies with a total of 7,246 patients were included in the analysis. No suitable studies of plasma were identified; thus, the review was focused on CSF measures. None of the studies was rated as having a low risk of bias based on the QUADAS-2 instrument. The pooled sensitivity and specificity estimates for CSF Aβ42 to differentiate Alzheimer’s disease from other dementia subtypes were 79% (95% CI 0.73 to 0.85) and 60% (95% CI 0.52 to 0.67), respectively, based on data from 13 studies (1,704 patients, 880 with Alzheimer’s disease). The authors concluded that while CSF Aβ42 may help to distinguish Alzheimer’s disease from other dementia subtypes, the test tends to misdiagnose those with non-Alzheimer’s dementia as having Alzheimer’s and should not be used alone for dementia classification.

Fink (2020) conducted a systematic review of biomarker accuracy for diagnosing neuropathologically defined AD in older patients with dementia.^[10] The analysis included literature published between January 2012 and November 2019, with nine cohort studies focusing on CSF biomarkers. Overall, CSF biomarkers and ratios had moderate sensitivity (range, 62% to 83%) and specificity (range, 53% to 69%). Biomarker accuracy was higher with Aβ42/pTau ratio, tTau/Aβ42 ratio, and pTau compared with tTau alone.

Olsson (2016) published a systematic review and meta-analysis on the diagnostic performance of the three core CSF biomarkers for the diagnosis of Alzheimer’s disease (Aβ42, tTau, and pTau).^[11] The investigators included 231 cross-sectional cohort and longitudinal studies that contained a cohort with Alzheimer’s disease and a control cohort, or a cohort with MCI due to Alzheimer’s disease and a stable MCI cohort (n=15,699 Alzheimer’s patients and 13,018 controls). Biomarker performance was reported as the ratio between biomarker concentration in patients with Alzheimer’s disease and controls (fold change) or the ratio between biomarker concentration in those with MCI due to Alzheimer’s disease and those with stable MCI who had no further cognitive decline in minimum of two years. In the CSF, tTau was able to differentiate clinically diagnosed Alzheimer’s disease from controls with good performance (average ratio 2.54, 95% confidence interval [CI] 2.44 to 2.64, p<0.0001), with similar effect sizes reported for the emerging biomarker neurofilament light chain protein (NfL) (2.35, 95% CI 1.90 to 2.91, p<0.0001). CSF pTau (1.88, 95% CI 1.79 to 1.97, p<0.0001) and plasma tTau (1.95, 95% CI 1.12 to 3.38, p=0.02) also had large effect sizes when differentiating between controls and patients with Alzheimer’s disease. All other markers, including CSF Aβ42, had only marginal effect sizes. Limitations of this review include the fact that only five of the included studies were considered to be of good quality; and substantial publication bias for all three core biomarkers.

Table 1. CSF Biomarkers Performance for Distinguishing AD from Controls

	Controls without Dementia		Controls with Dementia ^a	
	Sensitivity, %	Specificity, %	Sensitivity, %	Specificity, %
Aβ42				
Ferreira (2014) ^[12]	80 (73 to 85)	82 (74 to 88)	73 (67 to 78)	67 (62 to 72)
Rosa (2014) ^[13]	84 (81 to 85)	79 (77 to 81)	NR	NR
Bloudek (2011) ^[14]	80 (73 to 85)	82 (74 to 88)	73 (67 to 78)	67 (62 to 72)
Formichi (2006) ^[15]	NR	NR	55%-100%	80%-100%
Vogelsgang (2018) ^[16]	NR	NR	NR	NR
tTau				
Ferreira (2014) ^[12]	82 (76 to 87)	90 (86 to 93)	73 to 91	75 to 98
Bloudek (2011) ^[14]	82 (76 to 87)	90 (86 to 93)	78 (72 to 83)	75 (68 to 81)
Formichi (2006) ^[15]	NR	NR	52 to 100	50 to 100
pTau				
Ferreira (2014) ^[12]	78 to 80	83 to 88	72 to 88	78 to 83
Bloudek (2011) ^[14]	80 (70 to 87)	83 (75 to 88)	79 (72 to 84)	80 (71 to 86)
Formichi (2006) ^[15]	NR	NR	37 to 100	80 to 100%
BACE1				
Alexopoulos (2018) ^[17]	NR	NR	NR	NR
α-synuclein				
Wang (2018) ^[18]	NR	NR	NR	NR

Values in parentheses are 95% confidence intervals unless otherwise noted.

CSF: cerebrospinal fluid; NR: not reported; pTau: phosphorylated tau protein; tTau: total tau protein.

Ferreira (2014) published a meta-review of systematic reviews with meta-analyses to assess the use of CSF biomarker tests for AD after publication of revised AD diagnostic criteria^[19] in 2011.^[12] Literature was searched in September 2013, and seven systematic reviews were included. None was published after introduction of the revised AD diagnostic criteria, so primary studies were searched. Twenty-six prospective or retrospective case-control, cross-sectional, or longitudinal studies were included. Most included studies used clinical criteria for AD diagnosis or did not specify. For differentiating AD from controls without dementia, positive and negative likelihood ratios for all three biomarkers ranged from 4 to 8 and from 0.1 to 0.3, respectively.

Rosa (2014) conducted a systematic review with meta-analysis of studies of CSF A β 42 in patients with clinically diagnosed AD.^[13] Literature was searched to May 2013, and 41 prospective or retrospective, cohort, case-control, and cross-sectional studies were included (total n=5,086: 2,932 AD, and 2,154 controls without dementia). Patients with MCI were excluded. Seventy-six percent of studies satisfied all quality domains of the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool. Publication bias was detected. A summary ROC curve was generated from all reported thresholds. Pooled sensitivity and specificity were 84% (95% CI 81 to 85) and 79% (95% CI 77 to 81), respectively. Positive and negative likelihood ratios were 4.5 (95% CI 3.7 to 5.4) and 0.18 (95% CI 0.14 to 0.22), respectively, and their ratio, the diagnostic odds ratio, was 29 (95% CI 21 to 40). Statistical heterogeneity was substantial ($I^2=68\%$); studies varied in test cutoffs used and severity of AD across patient samples. Eleven studies (total n=1,459: 830 AD, 629 controls) reported AB42 CSF levels. Mean (standard deviation [SD]) CSF AB42 was 467 (189) pg/mL in patients with AD and 925 (414) pg/mL in controls (weighted mean difference, 450 pg/mL, 95% CI -600 to -289, $p<0.001$). However, statistical heterogeneity was considerable ($I^2=99\%$).

Cure (2014) published a systematic review with meta-analysis of CSF and imaging studies for the diagnosis of definite AD (autopsy-confirmed).^[20] Literature was searched in January 2012, and three studies of CSF markers (pTau, tTau, A β 42, A β 40) were identified (total n=337). Pooled sensitivity of all CSF tests was 82% (95% CI 72 to 92), and pooled specificity was 75% (95% CI 60 to 90). Statistical heterogeneity was not reported, but studies varied in AD definitions, controls (patients without dementia or patients with dementia due to other causes), and test thresholds. Area under the summary ROC curve constructed using multiple test thresholds was 0.84.

In a systematic review by Noel-Storr (2013), authors assessed the weight and quality of the evidence available from primary diagnostic test accuracy studies for Alzheimer's disease.^[21] Authors identified 142 longitudinal studies relating to the biomarkers of interest, which included subjects who had objective cognitive impairment but no dementia at baseline. Authors concluded the body of evidence for biomarkers was not large and was variable across the different types of biomarkers. Authors suggest that important information is missing from many study reports, highlighting the need for standardization of methodology and reporting to improve the rigor of biomarker validation.

A meta-analysis by Bloudek (2011) included 119 studies on biomarkers and diagnostic imaging in AD.^[14] Sensitivity and specificity were calculated for distinguishing AD from controls without dementia, and for distinguishing AD from non-AD dementias with and without MCI, if available. Selected studies of CSF biomarkers used a variety of thresholds, with clinical diagnosis or autopsy as the reference standard. Twenty studies of the A β 42 CSF marker were included with controls with and without dementia; pooled analysis resulted in a sensitivity of 76% (95% CI 72% to 80%) and a specificity of 77% (95% CI 72% to 82%). CSF total tau was evaluated in 30 studies with a resulting sensitivity of 79% (95% CI 75% to 83%) and specificity of 85% (95% CI 81% to 89%). CSF pTau was evaluated in 24 studies, resulting in a pooled sensitivity of 78% (95% CI 73% to 83%) and specificity of 81% (95% CI 76% to 85%). Six studies evaluated CSF pTau as a biomarker to distinguish patients with AD from patients with MCI, with a pooled sensitivity of 73% (95% CI 54% to 86%) and specificity of 69% (95% CI 53% to 82%). The combination of total tau and A β 42 was evaluated in 12 studies, with a pooled sensitivity of 80% (95% CI 72% to 85%) and specificity of 76% (95% CI 57% to 88%). Comparison of CSF biomarkers, area under the receiver operating characteristic curve was highest for PTau alone (0.85, 95% CI 82 to 88). Study heterogeneity was due to the use of different test thresholds and different assay kits. Sensitivity analysis including studies that used autopsy as the reference standard for pTau resulted in slightly higher sensitivity (82%, 95% CI 75% to 87%) and lower specificity (57%, 95% CI 37% to 75%).

A systematic review by van Harten (2011) of seven studies using CSF biomarkers to differentiate AD from other dementias, reporting positive and negative likelihood ratios of 46 and 0.09, respectively, for differentiating AD (n=175) from Creutzfeldt-Jakob disease (n=110).^[22] With this systematic review excluded, positive and negative likelihood ratios ranged from 2 to 7 and from 0.15 to 0.4, respectively.

Prognosis for Progression of Mild Cognitive Impairment

Systematic Reviews

Ritchie (2014, 2017) published Cochrane reviews assessing the evidence to determine the accuracy of CSF biomarkers for detecting which patients with MCI would progress to AD or other dementias. The two systematic reviews analyzed many of the same studies and reached

the same conclusion.^[23, 24] In the 2017 review, literature was searched in January 2013 and 15 prospective and retrospective studies (1,172 participants with MCI had analyzable data) were included. Only studies that applied a reference standard for Alzheimer's disease dementia diagnosis were included. There were 430 patients that converted to Alzheimer's disease dementia and 130 that converted to other forms of dementia. The sensitivity of tTau values ranged from 51% to 90% and the specificity from 48% to 88%. Sensitivities for pTau ranged from 40% to 100% and specificities ranged from 22% to 86%. In the five studies that evaluated the CSF pTau/A β ratio, the sensitivities were between 80% and 96% and the specificities were between 33% and 95%. Eight of 15 studies were of poor methodological quality, and in the majority of studies there was an unclear risk of bias. The authors conclude that the biomarkers analyzed lack the accuracy to identify patients who will progress from MCI to AD.

The 2014 meta-review of systematic reviews by Ferreira summarized above included studies of CSF biomarkers for differentiating patients with MCI who progress to AD from those who do not.^[12] In systematic reviews with meta-analyses, sensitivity and specificity of A β 42 were 67% (95% CI 59 to 75) and 71% (95% CI 65 to 78), respectively; for tTau, 82% (95% CI 76 to 86) and 70% (95% CI 65 to 85), respectively; and for pTau, 81% (95% CI 69% to 91%) and 65% to 76%, respectively. Positive and negative likelihood ratios for all three tests ranged from 2 to 3 and from 0.3 to 0.5, respectively.

Prognosis for Progression of Mild Cognitive Impairment

The diagnostic accuracy of CSF biomarkers and A β PET for diagnosing early-stage AD were compared using data from the prospective, longitudinal Swedish BioFINDER study that consecutively enrolled patients without dementia with mild cognitive symptoms.^[25] This was the first study to compare the accuracy of regional A β PET (using the [¹⁸F]-flutemetamol) and different CSF assays or ratios of CSF biomarkers, including A β 42/40, for this diagnostic purpose. The study included 34 patients with MCI who developed AD dementia within 3 years and 122 healthy elderly controls. Overall, the best CSF measures for the identification of MCI-AD were amyloid-beta 42/tTau and A β 42/pTau, with an AUC of 0.93 to 0.94. The best PET measures (i.e., anterior cingulate, posterior cingulate/precuneus, and global neocortical uptake) performed similarly (AUC 0.92 to 0.93). The AUC for CSF A β 42/40 was numerically poorer as compared to the majority of PET variables; however, the differences were nonsignificant ($p=0.09$ to $.40$). The combination of CSF and PET was not better than using either biomarker separately. The results were replicated in 146 controls and 64 patients with MCI-AD from the Alzheimer's Disease Neuroimaging Initiative (ADNI) study that utilized another CSF assay (A β 42, tTau and pTau) and PET (¹⁸F-florbetapir) tracer. In the ADNI cohort, amyloid-beta 42/tTau and A β 42/pTau ratios similarly had higher AUCs than A β 42 alone.

Lewczuk (2017) evaluated whether A β 42 alone or the A β 42/40 ratio corresponded better with A β PET status.^[26] The investigators collected CSF from a mixed cohort ($n=200$) of cognitively normal and abnormal subjects who had undergone A β PET within 12 months. Of these, 150 were PET-negative and 50 were PET-positive according to a previously published cutoff. The collected CSF was assayed for A β 42 alone and the A β 42/40 ratio. The A β 42/40 ratio corresponded better than A β 42 alone with PET results, with a higher proportion of concordant cases (89.4% vs. 74.9%, $p<0.0001$) and a larger AUC (0.936 vs. 0.814, $p<0.0001$) associated with the ratio.

Nisenbaum (2022) compared CSF biomarkers to amyloid PET in the EMERGE and ENGAGE phase 3 RCTs of anti-amyloid therapy, aducanumab.^[27] EMERGE and ENGAGE participants had MCI due to AD or mild AD with pathology confirmed amyloid-beta pathology by amyloid PET scan. A population of 350 participants who were screened for the RCTs (EMERGE, n=208; ENGAGE, n=142) were included in a CSF substudy. Amyloid PET imaging was performed using any of the FDA-approved amyloid PET tracers. Expert central readers classified the amyloid PET scans as positive or negative. CSF samples were tested for pTau, tTau, A β 42 and A β 40 via the Lumipulse® system. The mean age for participants in the substudy was 70 years (SD=7). Nearly half (46%) of the participants were female, 93% of participants were White, 1% were Black and 1% were Asian, 37% of participants were ApoE ϵ 4 noncarriers, 47% were heterozygous and 17% were homozygous. The AUC (95% CI) for the A β 42/40 ratio was 0.90 (0.83 to 0.97, p<0.001) with a positive percent agreement of 94% (91 to 97) and a negative percent agreement of 88% (74 to 96). The AUC of tTau/A β 42 ratio was 0.92 (0.86 to 0.97, p<0.001) with positive percent agreement of 92% (89 to 95) and negative percent agreement of 82% (66 to 92).

Clinical Utility

Although not without controversy because of modest efficacy, cholinesterase inhibitors are used to treat mild-to-moderate Alzheimer's disease.^[6] Memantine, an NMDA receptor antagonist, appears to provide a small benefit in those with moderate-to-advanced disease.^[28] Given available therapies, in principle more accurate diagnosis might allow targeting treatment to those most likely to benefit. However, clinical trial entry criteria and benefit have been based on clinical diagnosis. While the possibility that more accurate diagnosis might lead to improved outcomes is plausible, it is not based on current evidence. Pharmacologic interventions for MCI have not demonstrated benefit in reducing progression to Alzheimer's disease.^[29-33]

No direct evidence to support the clinical utility of the CSF biomarker testing (A β 42/40 ratio) alone or in conjunction with A β PET scans to initially select appropriate patients for treatment with an A β plaque targeting therapy (e.g., aducanumab) is available. Additionally, there are no data on the serial use of these tests to determine if there are changes in biomarker results that correlate with clinical cognitive and functional status and/or A β imaging to inform continuation of A β plaque targeting therapy. Prior to the approval of aducanumab, the only approved treatments for AD were for symptoms. Rabinovici (2019) published results from a large scale (n=16,008) multicenter study in the United States, revealing that knowledge of amyloid PET scans was associated with significant changes in diagnosis and patient management, including the administration of medications approved for the symptomatic treatment of AD, other relevant medications addressing dementia risk factors, counseling, and future planning (e.g., medical and financial decision making).^[34] Disease-specific morbidity or mortality were not evaluable.

BLOOD BIOMARKER TESTING

Due to the limited published evidence regarding the impact of blood biomarker testing on patient health outcomes, this evidence review is focused on CSF testing.

Clinical Validity

Systematic Reviews

A systematic review and meta-analysis by Kim (2025) that included 16 studies assessed the performance of pTau for dementia compared to tau PET, the gold standard for in vivo tau assessment.^[35] When comparing individuals with AD to controls, the pooled standardized mean difference (SMD) for pTau181 (1.55, 95% CI 1.20 to 1.90, $p < 0.00001$), pTau217 (1.95, 95% CI 1.55 to 2.34, $p < 0.00001$), and pTau231 (1.12, 95% CI 0.63 to 1.61, $p < 0.00001$) indicated that individuals with AD have a statistically significant increase in levels of pTau proteins. The comparison between MCI and controls also demonstrated elevated levels of tau protein that were statistically significant for pTau181 (SMD 0.59, 95% CI 0.30 to 0.89, $p < 0.0001$), pTau217 (SMD 0.97, 95% CI 0.70 to 1.24, $p < 0.00001$), and pTau231 (SMD 0.33, 95% CI 0.10 to 0.55, $p = 0.004$) for individuals with MCI. Furthermore, when evaluating pTau proteins in plasma between individuals with AD or MCI, individuals with AD had increased serum levels of pTau181 (SMD 0.75, 95% CI 0.49 to 1.02, $p < 0.00001$) and pTau217 (SMD 0.93, 95% CI 0.51 to 1.36, $p < 0.0001$). Plasma pTau isoforms (pTau181, pTau217, and pTau231) were significantly elevated in individuals with AD and MCI compared with controls, and these changes broadly paralleled the tau-PET findings. However, these studies had substantial heterogeneity, possible cohort overlap, variability in analytic approaches, and limited longitudinal evidence, thus plasma pTau levels remain a preliminary biomarker. Standardized methods and further prospective validation and longitudinal studies are needed to establish the clinical validity and utility of pTau proteins as a meaningful biomarker to aid in the clinical diagnosis of AD and MCI.

Three additional systematic reviews examined the performance characteristics of plasma biomarkers compared to amyloid-PET, tau-PET, CSF, and neuropathological reference standards for AD. Therriault (2025) published a meta-analysis of 113 studies comprising of 29,625 individuals to evaluate pTau proteins to identify biologically defined AD. Pooled sensitivity, specificity, area under the receiver operating characteristic curve (AUROC), and diagnostic odds ratios for plasma pTau proteins are presented in Table 2.^[36] Of note, 90% of the studies included in this meta-analysis were rated to have a high risk of bias for not having used predefined or externally derived thresholds. Pahlke (2025) performed a meta-analysis on 49 observational studies to assess the diagnostic test accuracy of plasma pTau and A β tests (pTau217, %pTau217, pTau181, pTau231, and A β 42/A β 40) compared to reference standard tests (CSF AD biomarkers, amyloid PET, or neuropathology) in individuals with cognitive impairment (mild cognitive impairment or dementia).^[37] The pooled sensitivity ranged from 49.3% (95% CI 41.2 to 57.4) to 91.4% (95% CI 86.6 to 94.6), and the pooled specificity ranged from 61.5% (95% CI 45.6 to 75.3) to 96.7% (95% CI 87.8 to 99.2). Most of the included studies were judged to be at high risk of bias, particularly in domains related to individual selection, index test conduct, and reference standard. A diagnostic test accuracy meta-analysis of 30 studies ($n = 9,787$) by Khalafi (2025) evaluated plasma and CSF pTau217 against amyloid and tau PET as the reference standard.^[38] For detecting amyloid PET positivity, plasma pTau217 demonstrated pooled sensitivity of 82% (95% CI 79% to 84%) and pooled specificity of 86% (95% CI 84% to 88%), with a summary receiver operating characteristic (SROC) AUC of 0.91. Performance was higher among cognitively impaired individuals (sensitivity 85%, specificity 86%) than cognitively unimpaired individuals (sensitivity 76%, specificity 83%). Plasma pTau217 showed comparable accuracy to CSF pTau217 in detecting amyloid deposition (SROC AUC 0.91 vs. 0.88), though CSF pTau217 demonstrated higher sensitivity for tau PET positivity (91% vs. 83%). Substantial heterogeneity was observed across studies ($I^2 > 50\%$), which the authors attributed to differences in assay platforms, study populations, and PET radiotracers. The included studies predominantly used clinic-based cohorts with bio-banked specimens. The World Health Organization and the Global CEO initiative have proposed that

plasma biomarkers require 90% sensitivity and specificity to have clinical utility as a diagnostic test for AD.^[39] Furthermore, the Alzheimer's Association Workgroup corroborated this requirement with the recommendation that a minimum accuracy of 90% is needed for the intended-use population since FDA-approved CSF biomarker tests have achieved this feat with amyloid-PET.

Table 2. Performance Characteristics for Plasma Biomarkers from Therriault (2025)^[36]

Biomarker	Pooled Sensitivity (95% CI)	Pooled Specificity (95% CI)	AUROC (95% CI)
pTau217	88.1% (86.7 to 89.5)	88.7% (87.4 to 89.8)	91.1% (88.9 to 92.4)
pTau181	80.5% (78.4 to 82.4)	76.4% (74.1 to 78.6)	81.5% (80.2 to 82.9)
pTau205	76.6% (70.7 to 81.6)	86.0% (78.6 to 91.2)	85.1% (80.7 to 89.6)
pTau212	84.5% (75.5 to 90.6)	87.3% (79.5 to 92.5)	90.3% (86.6 to 94.1)
pTau231	75.2% (71.3 to 78.8)	75.3% (71.2 to 78.9)	80.2% (77.6 to 82.7)

Cohort Studies

Benina (2026) evaluated the diagnostic performance of the Lumipulse® G pTau217/Aβ 1-42 plasma ratio and pTau217 alone for detecting amyloid pathology in 208 participants from three research cohorts (BioFINDER2, BIOCARD, MissionAD) comprising individuals with subjective cognitive decline, MCI, AD dementia, and other cognitive conditions (average age 72.3 years, 54.8% amyloid positive by PET and/or CSF).^[40] Using the Fujirebio Lumipulse® G1200 automated platform with FDA-cleared PET (standardized uptake value ratio ≥1.13) and/or CSF biomarker ratios as reference standards, the pTau217/Aβ 1-42 ratio achieved an AUC of 0.932 (95% CI 0.896 to 0.967) compared to 0.918 (95% CI 0.880 to 0.956) for pTau217 alone. At the optimal Youden threshold, the ratio achieved 84% sensitivity and 95% specificity compared to 81% sensitivity and 93% specificity for pTau217 alone. Under a two-threshold approach using positive and negative likelihood ratio targets of 14/20, the ratio achieved a positive predictive value (PPV) of 94.62% (95% CI 88.0 to 97.7), a positive likelihood ratio of 14.51 (95% CI 6.93 to 39.80), and reduced indeterminate results to 20.2%, compared to 35.1% for pTau 217 alone after nonparametric reclassification. When evaluated against CSF alone, the ratio's PPV reached 97.8%; against PET alone, PPV was 88.9%. Age, sex, and APOE ε4 status did not significantly affect classification accuracy. These results meet the Global CEO Initiative consensus recommendations for confirmatory-level blood biomarker performance (PPV ≥90%, NPV ≥90%, indeterminate ≤20%) for the ratio but not for pTau217 alone.^[39] Limitations include, but not limited to, moderate sample size, racially unbalanced cohort (94.7% White), use of bio-banked research specimens rather than prospective clinical samples, absence of an independent external validation cohort, manufacturer-led study design, and no assessment of health outcomes or clinical utility.

Martínez-Dubarbie (2025) evaluated the diagnostic performance of plasma pTau217, the pTau217/Aβ42 ratio, and NfL in a memory clinic cohort of 493 individuals (340 patients and 153 cognitively unimpaired volunteers; mean age 67.6 years; 50.1% female; 100% Caucasian) using the Fujirebio Lumipulse® G600II platform with CSF biomarkers as the reference standard (amyloid positivity defined as CSF Aβ42/Aβ40 <0.067).^[41] Clinical diagnoses included AD (n=203), frontotemporal dementia (FTD; n=46), non-degenerative pathology (n=68), and other degenerative dementias (n=11). Plasma pTau217 achieved an AUC of 0.95 (95% CI

0.93 to 0.97) to discriminate between amyloid-positive and amyloid-negative individuals, with an optimal Youden cutoff of 0.18 pg/mL (sensitivity 92%, specificity 91%). The plasma pTau217/A β 42 ratio achieved a significantly higher AUC of 0.97 (95% CI 0.95 to 0.98, $p < 0.001$) vs. pTau217 alone with an optimal cutoff of 0.008 (sensitivity 91%, specificity 94%). Using a two-cutoff approach at 95% sensitivity and specificity, plasma pTau217 achieved 95% overall accuracy with 15.2% of individuals falling within the indeterminate zone (3.4% false positive, 1.4% false negative) and the pTau217/A β 42 ratio achieved 91% accuracy with only 4.7% falling within the indeterminate zone. At 97.5% sensitivity and specificity thresholds, both biomarkers achieved 97% accuracy, though the indeterminate zone expanded to 42.6% for pTau217 and 27.1% for the ratio. Plasma pTau217 was significantly higher in AD patients than in healthy controls, FTD, and non-degenerative dementias (all $p < 0.001$), and increased progressively along the disease continuum. The pTau217/A β 42 ratio was less influenced by glomerular filtration rate than pTau217 alone. Limitations include a cross-sectional, single-center design; an entirely Caucasian population; use of CSF as the sole reference standard (no amyloid PET); small subgroups for non-AD dementias; and thresholds derived within the study cohort without independent external validation.

Dyer (2025) assessed the clinical performance of the fully automated Lumipulse® G plasma pTau217 assay of bio-banked samples from 148 consecutive participants (mean age 69.4 years; 54.1% female; 101 MCI, 47 mild dementia) undergoing diagnostic lumbar puncture at a regional specialist memory clinic in Ireland.^[42] CSF-defined amyloid positivity (A β 42/A β 40 ≤ 0.067) was present in 60.8% of participants. Median plasma pTau217 was more than four-fold higher in amyloid-positive versus amyloid-negative individuals (0.64 vs. 0.15 pg/mL, $p < 0.001$), with an AUC of 0.92 (95% CI 0.87 to 0.97) for detection of amyloid status. Using a two-threshold approach at 90% sensitivity and specificity, 16.9% of participants fell in the indeterminate zone (PPV 91.3%, NPV 83.3%), which is below the 20% threshold recommended by the Global CEO Initiative.^[39] At 95% thresholds, the indeterminate zone was 30.4% (PPV 94.5%, NPV 87.5%), and at 97.5% thresholds, 42.6% (PPV 94.3%, NPV 93.8%). The authors estimated that 57.4% to 83.1% of diagnostic lumbar punctures could hypothetically have been avoided if plasma pTau217 had been used as an initial triage test. Limitations include, but are not limited to, the small sample size ($n=148$), single-center design, bio-banked samples, use of CSF as the sole reference standard without amyloid PET, lack of demographic diversity data, and thresholds derived within the study cohort without external validation.

Cousins (2025) evaluated the performance of plasma pTau217/A β 42 ratio, pTau217 alone, and A β 42/A β 40 ratio across self-reported racial groups using the Fujirebio Lumipulse® G1200 platform with amyloid PET as the reference standard.^[43] Cut points were derived in a racially diverse training set from the University of Pennsylvania (UPenn, $n=289$, 28% Black/African American, 62% cognitively normal, 28% MCI, 11% dementia) using a two-threshold approach at 95% sensitivity and specificity, then validated in an independent test set from the Alzheimer's Disease Neuroimaging Initiative (ADNI, $n=846$, 12% Black/African American, 55% cognitively normal, 45% MCI). In the training set, plasma pTau217/A β 42 had the highest AUC (0.95, 95% CI 0.91 to 0.97), with consistent performance in Black participants (AUC 0.96) and White participants (AUC 0.94). In the independent ADNI test set, pTau217/A β 42 achieved accuracy of 0.88 in Black participants and 0.91 in White participants, with the lowest proportion of intermediate classifications among the three biomarkers ($\leq 16\%$). Classification accuracy did not differ significantly by race (odds ratio [OR]=1.45, 95% CI 0.66 to 2.95, $p=0.33$). Race-by-amyloid PET severity interactions were not significant for any biomarker in either propensity-matched or unmatched analyses, indicating that the relationship between plasma biomarker

levels and amyloid burden was consistent across racial groups. Plasma A β 42/A β 40 was significantly higher in Black versus White participants in the UPenn matched sample, though this finding was not replicated in ADNI. False-negative results by pTau217/A β 42 were associated with cognitively normal status (OR 7.79, $p < 0.001$), female sex, and higher BMI. Higher creatinine was associated with elevated pTau217, A β 42, and A β 40 levels but not with the pTau217/A β 42 ratio, suggesting that ratio-based biomarkers may mitigate the influence of renal function on individual analyte levels. Limitations include the relatively small proportion of Black participants in the ADNI test set (12%), preponderance of cognitively normal participants in the Black subgroups, collection from specialized academic centers rather than community settings, and the absence of Hispanic/Latino participants in the analysis.

Wang (2025) evaluated the diagnostic performance of the Lumipulse® G plasma pTau217/A β 42 ratio test using A β and tau positron emission tomography (PET) as reference standards in a clinic cohort ($n=391$) and a community cohort ($n=121$).^[44] For the classification of A β PET status the pTau217/A β 42 ratio test achieved high diagnostic performance with an AUC of 0.966 (95% CI 0.945 to 0.983, $p < 0.05$) in the clinical cohort and an AUC of 0.963 (95% CI 0.924 to 0.992, $p < 0.05$) on the community cohort, which was deemed statistically significant with comparable results seen for the classification of tau PET status (clinical cohort 0.974, 95% CI 0.952 to 0.992, $p > 0.05$; community cohort: 0.947, 95% CI: 0.900 to 0.979, $p > 0.05$). The researchers also performed a head-to-head comparison of plasma (pTau217/A β 42: AUC of 0.978, 95% CI 0.952 to 0.996; $p > 0.05$) and CSF (CSF A β 42/40 AUC of 0.964, 95% CI 0.931 to 0.989) biomarkers based on the Lumipulse® platform, which demonstrated that the biomarkers were clinically equivalent. Furthermore, using a two-cutoff approach the pTau217/A β 42 ratio biomarker was assessed on its performance in the differential diagnosis of AD and the pTau217/A β 42 ratio had a 92.3% accuracy for distinguishing AD from non-AD individuals, with a PPV of 88.8% and negative predictive value (NPV) of 95.5%. Additionally, when applying a two-cutoff approach the pTau217/A β 42 ratio biomarker had improved specificity without impeding sensitivity and reduced the number of intermediate results. Limitations include, but are not limited to, an entirely Chinese population across both cohorts limiting generalizability to diverse populations, reliance on bio-banked samples rather than prospective clinical testing, a relatively young cohort (mean age ~66 years) with underrepresentation of individuals over 80, selection bias in the community cohort toward higher AD risk, differing biomarker levels between cohorts precluding a common cutoff, and absence of independent prospective validation or health outcome assessment.

In October of 2025, the FDA published results from a clinical cohort study that enrolled 312 individuals who presented with cognitive complaints or impairment, subjective or objective, of unknown cause, at eight geographically diverse intended use enrollment sites across U.S. ($n=6$) and Europe ($n=2$) with the goal of comparing the Elecsys® Phospho-Tau (181P) Plasma to amyloid PET scans.^[45] Cognitive assessments (Quick Dementia Rating System, Mini-Mental State Examination, Clinical Dementia Rating [CDR] Global, CDR–Sum of Boxes), Imaging (amyloid PET, magnetic resonance imaging [MRI]) and questionnaires (Medical History, Medication, Quality of Life, Physical Activity, Socio-demographics) were collected from the enrolled individuals. These participants were categorized into three diagnostic groups based on cognitive test results and clinical assessments: 41.0% (128/312) subjective cognitive decline (SCD), 56.1% (175/312) MCI, and 0.96% (3/312) mild dementia. Forty-one individuals had amyloid PET scan positive results with 38 of those individuals also eliciting a positive result via the Elecsys® Phospho-Tau (181P) Plasma test. Additionally, 271 individuals had negative results when using amyloid PET, but only 139 had negative results via the Elecsys® Phospho-Tau (181P) Plasma test. The positive percent agreement (PPA), negative percent

agreement (NPA), PPV, and NPV were 92.7% (95% CI 80.6% to 97.5%), 51.3% (95% CI 45.4% to 57.2%), 22.4% (95% CI 19.5% to 25.0%), and 97.9% (95% CI 94.0% to 99.3%), respectively. The results demonstrate that the Elecsys® Phospho-Tau (181P) Plasma assay is characterized by high PPA and high NPV and is clinically validated for aiding to rule out amyloid pathology.

In May of 2025 the FDA published the results of a clinical cohort study that evaluated the performance of the Lumipulse® G p-tau217/ β -Amyloid 1-42 Plasma Ratio as an aid in the assessment of individuals presenting with cognitive impairment, AD, and other causes of cognitive decline would test positive or negative for amyloid plaques.^[46] The study utilized 499 plasma samples from individuals that participated in different cohort studies (Polaris-AD, AR1001-ADP3-US01; BioFINDER 2; Wisconsin Registry for Alzheimer's Prevention; and BioHermes-001). To estimate clinical performance the results were compared to two adjudicated reference standards, amyloid PET using an FDA-approved tracer or with an FDA authorized amyloid CSF Ratio test and were described by PET-positive predictive value and frequency of positive test results of the tested samples for positive, indeterminate, and negative test results. The results for the Lumipulse® G tests were as follows, 91.8% had a positive result, 50.0% had an indeterminate result, and 2.7% had a negative result, which were consistent with both amyloid PET scans and CSF ratio tests, deeming the test clinically equivalent to the reference standards.

Schindler (2024) reported results from a head-to-head comparison of six leading commercial plasma biomarker assay panels conducted by the Foundation for the National Institutes of Health (FNIH) Biomarkers Consortium using samples from 392 Alzheimer's Disease Neuroimaging Initiative (ADNI) participants (median age 78.1 years; 49.2% female; 93.4% White; 48.7% amyloid PET positive; 49.0% cognitively impaired).^[47] The assays evaluated included 4 pTau217 assays (C2N PrecivityAD2, Fujirebio Lumipulse®, ALZpath Quanterix, Janssen LucentAD Quanterix), two pTau181 assays (Roche NeuroToolKit, Quanterix Neurology 4-Plex), 4 A β 42/A β 40 assays, and assays for glial fibrillary acidic protein (GFAP) and NfL (see Table 3). Using amyloid PET (>20 Centiloids) as the reference standard, plasma pTau217 measures had the highest classification accuracies for amyloid status across all platforms. In the full cohort, the unadjusted AUCs ranged from 0.882 to 0.929 for individual pTau217 assays, compared to 0.734 to 0.815 for pTau181 assays and 0.734 to 0.787 for A β 42/A β 40 assays. In the cognitively impaired sub-cohort (n=192), classification accuracies were higher: C2N %pTau217 combined with A β 42/A β 40 achieved an AUC of 0.958 (95% CI 0.932 to 0.985) and Fujirebio Lumipulse® pTau217 with A β 42/A β 40 had an AUC of 0.952 (95% CI 0.925 to 0.980). Plasma pTau217 also had the highest classification accuracies and correlations with tau PET status, cortical thickness, and dementia severity. Plasma A β 42/A β 40 had much lower classification accuracy due to the small magnitude of change (~10 to 13%) associated with amyloid pathology. In a sub-cohort with CSF data (n=122), plasma biomarker classification accuracies were not significantly different from CSF Elecsys pTau181/A β 42 (AUC 0.915, 95% CI 0.864 to 0.967), though the comparison was underpowered. Limitations include, but are not limited to, very low racial diversity (3.6% Black), use of a single research cohort (ADNI), absence of health outcome data, thresholds derived via Youden Index within the study cohort rather than pre-specified externally, and limited power for sub-cohort analyses.

Palmqvist (2024) reported results from a primary (n=515) and secondary (n=698) care cohort in Sweden evaluating the performance characteristics of biomarker plasma tests compared to standard clinical diagnosis without biomarker testing.^[48] The blood tests assessed included the

ratio of pTau217 to non-pTau217 (%pTau217) and the amyloid probability score 2 (APS2), based on the %pTau217 and A β 42/40 ratio. Thresholds were prespecified based on independent cohorts, including the PARIS and MissionAD cohorts, used to validate the PrecivityAD2™ blood test algorithm. Reference pathological diagnosis was based on CSF analysis of A β 42 and A β 40 via the Lumipulse assay. In patients who could not undergo lumbar puncture, pathological diagnosis was based on flutemetamol 18F PET imaging. In the primary care cohort, the accuracy, PPV, and NPV were 58.0%, 56.8%, and 58.8% for clinical diagnosis, 91.8%, 92.8% and 91.1% for %pTau217, and 93.5%, 94.4%, and 92.8% for APS2, respectively. In the secondary care cohort, outcomes were 71.4%, 65.6%, and 80.7% for clinical diagnosis by a dementia specialist, 94.3%, 95.4%, and 93.3% for %pTau217, and 94.6%, 97.8, and 92.2% for APS2, respectively. The investigator concluded that future studies should evaluate how these biomarker blood tests influence clinical care.

In a subsequent report, Palmqvist (2025) evaluated the performance of the Lumipulse® plasma pTau217 immunoassay in 1,219 patients in secondary care and 548 in primary care across several sites in Sweden, Spain, and Italy.^[49] The overall accuracy, PPV, and NPV of the assay as applied to the primary care cohort was 92% (95% CI 89% to 94%), 90 (95% CI 86% to 94%), and 92 (95% CI 89% to 96%), respectively. Accuracies did not significantly differ across groups with SCD, MCI, and dementia. As expected, the NPV was higher in the SCD group whereas the PPV was higher in the dementia group. Notably, the performance of the assay was significantly decreased with age, as higher pTau217 concentration have been observed in older participants without AD pathology.

Clinical Utility

As with CSF biomarker testing, there is currently no direct or indirect evidence to support the clinical utility of blood markers for diagnosing AD.

URINARY BIOMARKER TESTING

Clinical Validity

Systematic Reviews

Zhang (2014) conducted a systematic review and meta-analysis of urinary AD-associated neural thread protein for diagnosing AD in patients with suspected AD.^[50] Nine studies were included (total n=841 patients with probable or possible AD, 37 patients with MCI, 992 non-AD controls with or without dementia). For probable AD, pooled sensitivity and specificity were 89% (95% CI 86 to 92) and 90% (95% CI 88 to 92), respectively. Pooled positive and negative likelihood ratios were 8.9 (95% CI 7.11 to 11.1) and 0.12 (95% CI 0.09 to 0.16), respectively.

Clinical Utility

As above, there is no direct evidence or indirect chain of evidence to support the clinical utility of urinary markers for diagnosing AD.

Section Summary

At present, the diagnostic accuracy of neural thread protein for diagnosis of AD has not been established. Neither have studies of clinical utility been identified. Additional research on both diagnostic and clinical validity of this biomarker is needed before conclusions can be made about the effectiveness of its use.

SKIN CELL (FIBROBLAST) TESTING

Two small case-control studies have linked various characteristics of fibroblast cell cultures to AD. Chirila (2013) compared skin fibroblast samples between individuals diagnosed with AD (n=10), individuals diagnosed with Parkinson's disease and/or Huntington disease (n=7) and age-matched controls without dementia (n=11), and reported significant differences in various markers of cell culture network formation, aggregation, and migration.^[51] Chirila (2014) reported on differences in cellular aggregation measures between fibroblast samples from AD patients and controls without dementia in samples that overlapped substantially with the previous study (29/38).^[52] It is not clear how the measures in these studies compare to the DISCERN™ test that is commercially available. No studies evaluating the performance of this test were identified.

PRACTICE GUIDELINE SUMMARY

Several clinical practice guidelines address the use of biomarkers in the diagnosis of Alzheimer's disease (AD). Among those which are proponents of their use, support is conditioned on further study, or use within research settings alone.

AMERICAN ACADEMY OF NEUROLOGY

The American Academy of Neurology (AAN) does not address laboratory testing for the clinical evaluation of dementia in their Practice Parameter for the diagnosis of dementia, including AD.^[1] In their practice guideline "Update: Mild Cognitive Impairment," they state that "there are no biomarkers clearly shown to predict progression in patients with MCI."

THE ALZHEIMER'S ASSOCIATION

The 2024 updated consensus recommendations from the Alzheimer's Association Workgroup on diagnostic guidelines for Alzheimer's disease propose that "the following can be diagnostic of AD: amyloid PET; CSF A β 42/40, CSF pTau 181/A β 42, CSF tTau/A β 42; or 'accurate' plasma assays where 'accurate' can be defined as accuracy that is equivalent to approved CSF assays in detecting abnormal amyloid PET in the intended-use population."^[4] However, they also note that not all assays of these biomarkers have sufficient accuracy for diagnostic purposes. Additional biomarkers, including other phosphorylated tau forms, tau PET, and NfL, were recommended as potentially useful for confirming AD pathology and/or staging, but were not recommended as primary diagnostic tests, as they not be used to rule out AD.

AMERICAN PSYCHIATRIC ASSOCIATION

A 2007 guideline on the treatment of patients with AD and other dementias by the American Psychiatric Association (APA) workgroup on AD stated, "Except in rare circumstances (notably the use of CSF-14-3-3 protein when Creutzfeldt-Jakob disease is suspected and recent stroke or viral encephalitis can be excluded), these techniques remain investigational, and there is insufficient evidence for their utility in routine clinical practice."^[53]

ALZHEIMER'S ASSOCIATION

In 2013, recommendations from the Alzheimer's Association (AA) for operationalizing the detection of cognitive impairment during the Medicare annual wellness visit in primary care settings. The recommended algorithm for cognitive assessment was based on "current validated tools and commonly used rule-out assessments." Guideline authors noted that use of

biomarkers (e.g., CSF tau and β -amyloid proteins) “was not considered as these measures are not currently approved or widely available for clinical use.”^[54]

SUMMARY

There is not enough research to show that testing for Alzheimer disease (AD)-related biomarkers improves health outcomes for people who have AD, dementia, or mild cognitive impairment (MCI). No clinical guidelines based on research recommend the use of AD biomarkers. Therefore, the use of cerebral spinal fluid, blood, urinary, and skin cell biomarkers for diagnosis of AD, or for prediction of conversion from MCI to AD, is considered investigational.

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CODES

NOTE: Some of the following CPT codes may be used to identify the steps in testing for tau protein and amyloid beta peptides. There are no specific codes used for testing for neural thread protein.

Codes	Number	Description
CPT	0206U	Neurology (Alzheimer disease); cell aggregation using morphometric imaging and protein kinase C-epsilon (PKCe) concentration in response to amylospheroid treatment by ELISA, cultured skin fibroblasts, each reported as positive or negative for Alzheimer disease
	0207U	Neurology (Alzheimer disease); quantitative imaging of phosphorylated ERK1 and ERK2 in response to bradykinin treatment by in situ immunofluorescence, using cultured skin fibroblasts, reported as a probability index for Alzheimer disease (List separately in addition to code for primary procedure)
	0358U	Neurology (mild cognitive impairment), analysis of β -amyloid 1-42 and 1-40, chemiluminescence enzyme immunoassay, cerebral spinal fluid, reported as positive, likely positive, or negative
	0412U	Beta amyloid, A β 42/40 ratio, immunoprecipitation with quantitation by liquid chromatography with tandem mass spectrometry (LC-MS/MS) and qualitative ApoE isoform specific proteotyping, plasma combined with age, algorithm reported as presence or absence of brain amyloid pathology
	0445U	β -a Amyloid Beta (Abeta42) and phospho tau (181P) (pTau181), electrochemiluminescent immunoassay (ECLIA), cerebral spinal fluid, ratio reported as positive or negative for amyloid pathology
	0459U	B-amyloid (Abeta42) and total tau (tTau), electrochemiluminescent immunoassay (ECLIA), cerebral spinal fluid, ratio reported as positive or negative for amyloid pathology
	0479U	Tau, phosphorylated, pTau217
	0503U	Neurology (Alzheimer disease), beta amyloid (A β 40, A β 42, A β 42/40 ratio) and tau-protein (ptau217, np-tau217, ptau217/nptau217 ratio), blood, immunoprecipitation with quantitation by liquid chromatography with tandem mass spectrometry (LC-MS/MS), algorithm score reported as likelihood of positive or negative for amyloid plaques
	0551U	Tau, phosphorylated, pTau217, by single-molecule array (ultrasensitive digital protein detection), using plasma (Deleted 01/01/2026)
	0568U	Neurology (dementia), beta amyloid (AB40, AB42, AB42/40 ratio), tau-protein phosphorylated at residue (eg, pTau217), neurofilament light chain (NfL), and glial fibrillary acidic protein (GFAP), by ultra-high sensitivity molecule array detection, plasma, algorithm reported as positive, intermediate, or negative for Alzheimer pathology
	0596U	Neurology (Alzheimer disease), plasma, 3 distinct isoform-specific peptides (APOE2, APOE3, and APOE4) by liquid chromatography with tandem mass spectrometry (LCMS/MS), reported as an APOE prototype
	0649U	Neurology (Alzheimer disease), DNA, targeted next-generation sequencing (NGS) of AD-1 and AD-2 target regions, whole blood, prognostic algorithmic analysis, reported as categorization of cognitive status
	81099	Unlisted urinalysis procedure
	82233	Beta-amyloid; 1-40
	82234	Beta-amyloid; 1-42
	83520	Immunoassay for analyte other than infectious agent antibody or infectious agent antigen; quantitative; not otherwise specified
	84393	Tau, phosphorylated
	84394	Tau, total
	86849	Unlisted immunology procedure

Codes	Number	Description
HCPCS	None	

Date of Origin: October 1999