2.04.14	Evaluation of Biomarkers for Alzheimer Disease		
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Section:	2.0 Medicine	**Page:**	Page 1 of 24

Policy Statement

I. Cerebrospinal fluid biomarker testing, including but not limited to amyloid beta peptides, tau protein, or neural thread proteins, as an adjunct to clinical diagnosis in individuals with mild cognitive impairment is considered **investigational**.

II. Cerebrospinal fluid biomarker testing, including but not limited to amyloid beta peptides, tau protein, or neural thread proteins, as an adjunct to clinical diagnosis in individuals with mild dementia due to Alzheimer disease is considered **investigational**.

III. Cerebrospinal fluid biomarker testing, including but not limited to amyloid beta peptides, tau protein, or neural thread proteins, as part of an evaluation for the initiation of amyloid beta targeting therapy in individuals with mild cognitive impairment or mild dementia due to Alzheimer disease is considered **investigational**.

IV. Cerebrospinal fluid biomarker testing, including but not limited to amyloid beta peptides, tau protein, or neural thread proteins, as part of an evaluation for the continuation of amyloid beta targeting therapy in individuals with mild cognitive impairment or mild dementia due to Alzheimer disease is considered **investigational**.

V. 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 considered **investigational.**

NOTE: Refer to Appendix A to see the policy statement changes (if any) from the previous version.

Policy Guidelines

Coding
See the Codes table for details.

Description

Biochemical changes associated with the pathophysiology of Alzheimer 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.

Related Policies

- Genetic Testing for Alzheimer Disease
- Selected Positron Emission Tomography Technologies for Evaluation of Alzheimer Disease

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

Regulatory Status

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 must be certified by CLIA for high-complexity testing. To date, the FDA has chosen not to require any regulatory review of these tests. AlzheimAlert™ and AdMark® CSF analysis are examples of tests that may be available in CLIA certified labs.

In November 2020, C2N Diagnostics gained CLIA certification for its Precivity mass-spec amyloid beta assay. This plasma test has received breakthrough device designation from the U.S. Food and Drug Administration (FDA) for review as an in-vitro diagnostic. The test uses a proprietary mass spectrometry platform that combines quantitative measurement of amyloid beta 42 and 40 peptides in plasma along with apolipoprotein E proteotype (equivalent to ApoE genotype) to calculate an individual's likelihood of amyloid plaques in the brain. The test is currently not intended to be used as a stand-alone diagnostic.

In May 2022, the FDA permitted marketing for the first in vitro diagnostic test for early detection of amyloid plaques with AD. The cerebrospinal fluid immunoassay was granted breakthrough device designation and was reviewed through the De Novo premarket review pathway. The Lumipulse G ß-Amyloid Ratio (1-42/1-40) immunoassay (Fujirebio Diagnostics, Inc.) is intended to be used in adult patients, ≥ 55 years, presenting with cognitive impairment who are being evaluated for AD and other causes of cognitive decline. A positive test result is consistent with the presence of amyloid plaques, similar to what would be seen in a PET scan.

In July 2022, the FDA granted breakthrough device designation to the Elecsys Amyloid Plasma Panel (Roche). The Elecsys Amyloid Plasma Panel measures phosphorylated Tau (pTau) 181 protein assay and apolipoprotein (APOE) E4 assay in human blood plasma. Positive results indicate the need for further confirmatory testing for AD. The panel test is intended to be used in conjunction with other clinical information in symptomatic patients who are being evaluated for AD and other causes of cognitive decline.

Roche has also received a Breakthrough Device Designation for the Elecsys® ß-Amyloid (1-42) CSF and Elecsys® Phospho-Tau (181P) CSF in vitro diagnostic immunoassays measuring ß-Amyloid (1-42) and Phospho-Tau concentrations in cerebrospinal fluid (CSF) in adult patients with cognitive impairment who are being evaluated for Alzheimer's disease (AD) or other causes of dementia.

Additional diagnostic blood tests that have received FDA breakthrough device designation include AlzoSure® Predict (Diadem) in January, 2022 and SOBA-AD (AltPep Corporation) in March 2022.

Rationale

Background

Alzheimer Disease

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. 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.

Table 1. National Institute on Aging-Alzheimer's Association Numerical Clinical Staging for Individuals in the Alzheimer Continuum[a]

Stage	Stage 1	Stage 2	Stage 3	Stage 4	Stage 5	Stage 6
Severity	**Pre-clinical**	**Pre-clinical**	**MCI due to Alzheimer disease**	**Mild Dementia**	**Moderate Dementia**	**Severe Dementia**
Clinical Features	• Performance within	• Normal performance	• Performance in the	• Substantial progressive	• Progressive cognitive	• Progressive cognitive

Stage	Stage 1	Stage 2	Stage 3	Stage 4	Stage 5	Stage 6
	expected range on objective cognitive tests. • No evidence of recent cognitive decline or new neuro-behavioral symptoms.	within expected range on objective cognitive tests. • Transitional cognitive decline (change from individual baseline within past 1 to 3 years, and persistent for at least 6 months). • Mild neuro-behavioral changes may coexist or may be the primary complaint rather than cognitive. • No functional impact on daily life activities.	impaired/ abnormal range on objective cognitive tests. • Evidence of decline from baseline. • Performs daily life activities independently, but cognitive difficulty may result in detectable but mild functional impact on the more complex activities of daily life.	cognitive impairment affecting several domains, and/or neurobehavioral disturbance. • Clearly evident functional impact on daily life, affecting mainly instrumental activities. • No longer fully independent/ requires occasional assistance with daily life activities.	impairment or neuro-behavioral changes. • Extensive functional impact on daily life with impairment in basic activities. • No longer independent and requires frequent assistance with daily life activities.	impairment or neuro-behavioral changes. • Clinical interview may not be possible. • Complete dependency due to severe functional impact on daily life with impairment in basic activities, including basic self-care.

Adapted from Table 6, Jack et al (2018)[8,]
[a]Applicable only to individuals in the Alzheimer continuum that fall into 1 of the 4 biomarker groups: 1) A+T+N+ 2) A+T-N- 3) A+T+N- 4) A+T-N+ where A: Aggregated Aβ or associated pathologic state (CSF $A\beta_{42}$, or $A\beta_{42}/A\beta_{40}$ ratio or Amyloid PET), T: Aggregated tau (neurofibrillary tangles) or associated pathologic state (CSF phosphorylated tau or Tau PET) and N: Neurodegeneration or neuronal injury (anatomic MRI, FDG PET or CSF total tau)
For stages 1 to 6: Cognitive test performance may be compared to normative data of the investigator's choice, with or without adjustment (choice of the investigators) for age, sex, education, etc.
For stages 2 to 6: Although cognition is the core feature, neurobehavioral changes—for example, changes in mood, anxiety, or motivation—may coexist.
For stages 3 to 6: Cognitive impairment may be characterized by presentations that are not primarily amnestic.
CSF: cerebrospinal fluid; FDG: fluorodeoxyglucose; MCI: mild cognitive impairment; MRI: magnetic resonance imaging; PET: positron emission tomography.

Biomarkers

Several potential biomarkers of AD are associated with AD pathophysiology (e.g., 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.[9,] Other potential CSF[10,11,], urinary, and blood[12,] 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.[13,] Neurogranin is a dendritic protein and CSF measurement may serve as a biomarker for

dendritic instability and synaptic degeneration.[9,] 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.[14,15,] 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.[9,] 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.[16,] 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.[17,]

Literature Review

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

Cerebrospinal Fluid, Urinary, or Blood Biomarker Testing for Alzheimer Disease

Clinical Context and Test Purpose

The purpose of cerebrospinal fluid (CSF), urinary, or blood biomarker testing for Alzheimer disease (AD) is to provide an alternative or superior method for diagnosis to inform a decision to proceed with appropriate treatment in patients with AD or mild cognitive impairment (MCI).

The question addressed in this evidence review is: Does testing CSF, urinary, or blood biomarkers improve the net health outcome in individuals with suspected MCI or dementia due to AD?

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with MCI or AD.

Interventions

The tests being considered are CSF, urinary, or blood biomarker testing for MCI or AD.

Comparators

Comparators of interest include a clinical diagnosis of MCI or AD.

Outcomes

The general outcomes of interest are test validity, correct treatment, avoiding unnecessary subsequent testing, harms of invasive testing, and quality of life (QOL) for testing to diagnose AD. For testing to predict progression of MCI, the outcomes of interest are correct treatment, avoiding unnecessary subsequent testing, harms of invasive testing, and QOL.

Follow-up is at months to years for CSF, urinary, or blood biomarker testing for the outcomes of interest.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- 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, c-statistic, likelihood ratios) may be included but are less informative;
- Studies should also report reclassification of the diagnostic or risk category.

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Review of Evidence

Cerebrospinal Fluid Biomarker Testing

Diagnosis of Alzheimer Disease

Systematic Reviews

Most studies have relied on clinically diagnosed AD as the criterion standard. Results from the majority of systematic reviews are summarized in Table 2. Studies included in these systematic reviews are not individually reviewed.

Table 2. Systematic Reviews Assessing CSF Biomarkers Performance for Distinguishing Alzheimer Disease From Controls With Clinical Diagnosis as the Reference Standard

Biomarker Studies	Controls Without Dementia, %		Controls With Dementia, %[a]	
	Sensitivity	*Specificity*	*Sensitivity*	*Specificity*
Aβ42				
Rosa et al (2014)[18,]	84 (81 to 85)	79 (77 to 81)	NR	NR
Bloudek et al (2011)[19,]	80 (73 to 85)	82 (74 to 88)	73 (67 to 78)	67 (62 to 72)
Formichi et al (2006)[20,]	NR	NR	55 to 100	80 to 100
tTau				
Bloudek et al (2011)[19,]	82 (76 to 87)	90 (86 to 93)	78 (72 to 83)	75 (68 to 81)
Formichi et al (2006)[20,]	NR	NR	52 to 100	50 to 100
pTau				
Ferreira et al (2014)[21,]	78 to 80	83 to 88	72 to 88	78 to 83
Bloudek et al (2011)[19,]	80 (70 to 87)	83 (75 to 88)	79 (72 to 84)	80 (71 to 86)
Formichi et al (2006)[20,]	NR	NR	37 to 100	80 to 100

Values in parentheses are 95% confidence intervals.
Aβ42: amyloid-β peptide 1-42; CSF: cerebrospinal fluid; NR: not reported; pTau: phosphorylated tau protein; tTau: total tau protein.
[a] Or unspecified.

Fink et al (2020) conducted a systematic review of biomarker accuracy for diagnosing neuropathologically defined AD in older patients with dementia.[22,] The analysis included literature published between January 2012 and November 2019, with 9 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 amyloid beta-42/pTau ratio, tTau/amyloid beta-42 ratio, and pTau compared with tTau alone.

Cure et al (2014) conducted a systematic review with meta-analysis of CSF and imaging studies for the diagnosis of definite AD (autopsy-confirmed).[23,] Literature was searched in January 2012, and 3 studies of CSF markers (pTau, tTau, amyloid beta-42, amyloid beta-40) were identified (N=337 patients). Pooled sensitivity of all CSF tests was 82% (95% confidence interval [CI], 72% to 92%), and pooled specificity was 75% (95% CI, 60% to 90%). Statistical heterogeneity was not reported, but studies varied by AD definitions, controls (patients without dementia or patients with dementia due to other causes), and test thresholds. The summary area under receiver operating characteristic curve, constructed using multiple test thresholds, was 0.84.

Subsection Summary: Clinical Validity of Cerebrospinal Fluid Biomarker Testing for Diagnosis of Alzheimer Disease

Several studies have examined the diagnostic performance of CSF biomarkers for distinguishing patients with probable AD from patients without dementia and from patients with other types of dementia. The range of reported sensitivities and specificities is broad compared with a clinical diagnosis reference standard. In systematic reviews with meta-analyses, sensitivity and specificity rates ranged from 80% to 82% and 82% to 90%, respectively, for differentiating AD from healthy controls, and were 73% and 67%, respectively, for differentiating AD from other dementias. Positive and negative likelihood ratios were 2 to 8 and 0.2 to 0.4, respectively, in either setting. There is limited evidence examining the incremental diagnostic accuracy of CSF biomarkers for AD diagnosis employing autopsy as a criterion standard. Cutoffs for a positive diagnosis are not standardized.

Prognosis for Progression of Mild Cognitive Impairment

Systematic Reviews

There are a variety of systematic reviews that have evaluated the prognostic value of CSF biomarkers for the progression of MCI and conversion to clinically manifest AD. These studies primarily include clinical diagnosis as a reference standard and varying cutoffs for predicting conversion. Tables 3 and 4 present the characteristics and results of key meta-analyses.

Table 3. Characteristics of Key Meta-Analyses That Evaluate the Prognostic Value of CSF Biomarkers for the Progression of MCI and Conversion to Clinically Manifest AD

Study	Dates	Studies	Participants	N (Range)	Design	Duration
Olsson (2016)[24,]	1995-2014	231	Patients with AD or MCI due to AD	AD=15,699 Controls=13,018 Total=27,717 (Range=20 to 1087)	Not specified	Not specified
Ritchie (2017)[25,]	2006-2013	15	Patients with MCI at baseline	N=1,282	Longitudinal cohort	2 mo to 11.8 y
Ritchie (2014)[26,]	2003-2013	17	Participants with cognitive decline but no dementia condition at baseline	Total=2,228 (Range=37 to 588)	Longitudinal cohort	2 mo to 12 y

AD: Alzheimer disease; CSF: cerebrospinal fluid; MCI: mild cognitive impairment; mo: month(s); y: year(s).

Table 4. Results of Key Meta-Analyses

Study	Aß42	tTau	pTau
Olsson (2016))[24,]			
Average ratio (95% CI)	0.56 (0.55 to 0.58)	2.54 (2.44 to 2.64)	1.88 (1.79 to 1.97)
p value	<.001	<.001	<.001
Ritchie (2017)[25,]			
Sensitivity range, %	-	51 to 90	40 to 100
Specificity range, %	-	48 to 88	22 to 86
Median specificity, %	-	72	47.5
Sensitivity at median specificity, % (95% CI)	-	75 (67 to 85)	81 (64 to 91)
Ritchie (2014)[26,]			
Sensitivity range, %	36 to 100	-	-
Specificity range, %	29 to 91	-	-
Median specificity, %	64	-	-
Sensitivity at median specificity, % (95% CI)	81 (72 to 87)	-	-

Average ratio: Alzheimer disease to control ratio for cerebral spinal fluid biomarker concentration.
Aβ42: amyloid-β peptide 1-42; CI: confidence interval; NR: not reported; pTau: phosphorylated tau protein; tTau: total tau protein.

Subsection Summary: Clinical Validity of Cerebrospinal Fluid Biomarker Testing for Prognosis for Progression of Mild Cognitive Impairment

The evidence suggests that biomarker testing may identify an increased risk of conversion from MCI to AD. Studies primarily include clinical diagnosis as a reference standard and varying cutoffs for predicting conversion.

Clinically Useful

Possible clinical uses of CSF biomarker testing could include confirming the diagnosis of AD to begin medications at an earlier stage or ruling out AD, which could lead to further diagnostic testing to determine the etiology of dementia and/or avoidance of unnecessary medication.

No trials were identified that have reported health outcomes after CSF biomarker testing; thus, there is no direct evidence for clinical utility. Decision models can provide indirect evidence of utility if the likelihood of benefits and consequences are estimable. To evaluate the benefits and consequences of CSF biomarker interventions, models would need to describe disease progression, resources used, and QOL. Such estimates are scarce and highly variable.

Although not without controversy because of modest efficacy, cholinesterase inhibitors are used to treat mild-to-moderate AD.[27,28,] Memantine, an *N*-methyl-d-aspartate receptor antagonist, appears to provide a small benefit in treating symptoms in those with the moderate-to-advanced disease.[27,29,] Neither cholinesterase inhibitors nor memantine is disease-modifying.

Given available therapies, in principle, a more accurate diagnosis might allow targeting treatment to those most likely to benefit. However, clinical trial entry criteria and benefits have been based on clinical diagnosis. There is less evidence to support the use of cholinesterase inhibitors in other dementias, but they are still frequently used to treat cognitive symptoms. While the possibility that a more accurate differential diagnosis may 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 AD.[30,31,32,33,] The chain of evidence of clinical utility is incomplete.

Section Summary: Cerebrospinal Fluid Biomarker Testing

Most clinical validity studies of both diagnosis of AD and prognosis for progression of MCI to AD use select patient samples and define optimal test cutoffs without validation. There is no evidence that improved diagnosis or prognosis leads to improved health outcomes or QOL.

Urinary Biomarker Testing

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Zhang et al (2014) conducted a systematic review and meta-analysis of urinary AD-associated neural thread protein (NTP) for diagnosing AD in patients with suspected AD.[34,] Nine studies were included (n=841 patients with probable or possible AD; 37 patients with MCI, 992 with non-AD dementia or controls without dementia). The reference standard was a clinical diagnosis in 8 studies and not described in another. Varying cutoffs for positive diagnosis were used across included studies. Controls were both healthy volunteers and patients with other dementias. 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, 7.1 to 11.1) and 0.12 (95% CI, 0.09 to 0.16), respectively.

Clinically Useful

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

Section Summary: Urinary Marker Testing

A systematic review and meta-analysis that evaluated urinary AD-associated NTP with regard to diagnosing AD in patients with suspected AD concluded that, 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, 7.1 to 11.1) and 0.12 (95% CI, 0.09 to 0.16), respectively.

Blood Biomarker Testing

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Screening and Diagnosis of Alzheimer Disease

Systematic Reviews

Olsson et al (2016) conducted a systematic review of the 15 most promising biomarkers in both CSF and blood to evaluate which may be useful to distinguish patients with AD from controls and patients with MCI due to AD from those with stable MCI.[24,] In total, 231 articles comprising 15,699 patients with AD and 13,018 controls were included in the analysis. Among blood biomarkers, plasma T-tau was the only biomarker found to discriminate patients with AD from controls (p=.02). No differences in plasma concentrations of amyloid beta-42 and amyloid beta-40 biomarkers in individuals with AD as compared to controls were seen in this systematic review; however, these results were reported before the development of more highly sensitive assays and technologies.[16,]

Cohort Studies

Thijssen et al (2020) evaluated whether plasma phosphorylated tau at residue 181 (pTau181) could differentiate between clinically diagnosed or autopsy-confirmed AD and frontotemporal lobar degeneration (N=362).[35,] Results revealed that plasma pTau181 concentrations were increased by 3.5-fold in patients with AD compared to controls and differentiated AD from both clinically diagnosed and autopsy-confirmed frontotemporal lobar degeneration. Plasma pTau181 also identified individuals who were amyloid beta-PET-positive regardless of clinical diagnosis and was reported to be a potentially useful screening test for AD.

Janelidze et al (2020) evaluated the diagnostic and prognostic usefulness of plasma pTau181 in 3 cohorts totaling 589 individuals (patients with MCI, AD dementia, non-AD neurodegenerative diseases, and cognitively unimpaired individuals).[36,] Results revealed plasma pTau181 to be increased

in patients with preclinical AD and further elevated in the MCI and dementia disease stages. Plasma pTau181 also differentiated AD dementia from non-AD neurodegenerative diseases with an accuracy similar to PET Tau and CSF pTau181 and detected AD neuropathology in an autopsy-confirmed cohort.

Palmqvist et al (2020) examined the feasibility of plasma phosphorylated tau at residue 217 (pTau217) as a diagnostic biomarker for AD among 1402 participants from 3 selected cohorts.[37,] Results revealed that plasma pTau217 discriminated AD from other neurodegenerative diseases, with significantly higher accuracy than established plasma- and MRI-based biomarkers, and its performance was not significantly different from key CSF- or PET-based measures.

Clinically Useful

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

Section Summary: Blood Biomarker Testing

Results from a systematic review and various cohort studies have shown that plasma pTau may be beneficial for the early screening and differential diagnosis of AD; however, currently, there is no evidence that improved diagnosis with blood biomarker testing leads to improved health outcomes or QOL.

Cerebrospinal Fluid Biomarkers and Targeted Therapy for Mild Cognitive Impairment or Mild Dementia due to Alzheimer Disease

Clinical Context and Test Purpose

The purpose of CSF biomarkers or PET amyloid scans for individuals with MCI or mild dementia due to AD is to select appropriate patients for initiation or discontinuation of treatment with an amyloid beta plaque targeting therapy (e.g., aducanumab).

The question addressed in this evidence review is: Does testing with CSF biomarkers as an adjunct, or alternative to, amyloid beta PET imaging in individuals with MCI or mild dementia due to AD who are being evaluated for initiation or continuation with an amyloid beta plaque targeting therapy improve the net health outcome?

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with a clinical diagnosis of MCI or mild dementia due to AD, who are being evaluated for an FDA approved amyloid beta plaque targeting therapy or are being evaluated for continuing or discontinuing such therapy.

In the pivotal trials for the amyloid beta plaque targeting therapy aducanumab, enrolled patients had an early stage of AD; MCI due to AD; or mild AD dementia based on an entry criteria of baseline Mini-Mental State Examination (MMSE) score of 24 to 30, baseline Clinical Dementia Rating (CDR) global score of 0.5 and Repeatable Battery for the Assessment of Neurological Status (RBANS) delayed memory index score ≤85. Patients were also clinically staged based on the National Institute on Aging-Alzheimer's criteria (Table 1). The National Institute on Aging-Alzheimer's Association has provided guidance on the clinical diagnosis of MCI and dementia due to AD.[38,39,40,] This includes utilizing a battery of cognitive tests versus a single test to identify individuals with MCI due to AD (stage 3) or mild dementia due to AD (stage 4). The tests should evaluate multiple domains such as cognition and function and specific tests may vary.

Interventions

The test being considered is the CSF biomarker amyloid beta-42/40 ratio. The amyloid beta-42/40 ratio test quantifies the amount of amyloid beta-42 and 40 proteins in a CSF sample (collected via

lumbar puncture) and computes the ratio of those proteins, intended to be an indication of AD pathology. Ratios <0.058 indicate a higher likelihood of a patient having a clinical diagnosis of AD. The ratio, as compared with CSF amyloid beta-42 alone, corrects for interindividual variability in the overall amyloid beta production and CSF turnover, changes in global levels of all amyloid beta isoforms owing to non-AD-related abnormal findings, and variability owing to preanalytical factors.[41,] This concentration ratio has also been suggested to be superior to the concentration of amyloid beta-42 alone when identifying patients with AD.[42,] The test is indicated for patients being evaluated for MCI or mild dementia clinical stages of AD who are under consideration for targeted therapy.

Comparators

Comparators of interest include the amyloid beta PET scan. Amyloid beta PET imaging is a neuroimaging technique with standardized tracer-specific visual reading procedures and documented high reproducibility across PET centers.[43,] It allows non-invasive, in-vivo detection of amyloid plaques with very high sensitivity (96%; 95% CI, 80 to 100) and specificity (100%, 95% CI, 78 to 100) as determined by correlation in patients with confirmed AD who had an autopsy within 1 year of PET imaging. Trials of amyloid beta targeting therapy have traditionally used clinical criteria along with amyloid beta PET imaging to select appropriate patients for participation.

Outcomes

The general outcomes of interest are test validity, symptoms, change in disease status, functional outcomes, health status measures, and QOL. Specific measures of cognitive and functional health outcomes that may be relevant to early AD include the Clinical Dementia Rating-Sum of Boxes (CDR-SOB), MMSE, Alzheimer's Disease Assessment Scale - Cognitive 13-Item Scale (ADAS-Cog 13), Alzheimer's Disease Cooperative Study - Activities of Daily Living - Mild Cognitive Impairment (ADCS-ADL-MCI), and the Neuropsychiatric Inventory-10 (NPI-10).

Follow-up is at months to years for CSF biomarkers or PET amyloid scans for the outcomes of interest.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- 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, c-statistic, likelihood ratios) may be included but are less informative;
- Studies should also report reclassification of the diagnostic or risk category.

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Review of Evidence

Overall, both PET imaging and CSF biomarkers provide overlapping, and in part complementary, diagnostic information with agreement between CSF and PET amyloid results usually good.[43,] There are various studies that evaluate concordance between CSF biomarkers and PET imaging; however, studies that specifically evaluate the CSF biomarker amyloid beta-42/40 in comparison to amyloid PET imaging are limited.

The diagnostic accuracy of CSF biomarkers and amyloid beta 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.[44,] This was the first study to compare the accuracy of regional amyloid beta PET (using the [^{18}F]-flutemetamol) and different CSF assays or ratios of CSF biomarkers, including amyloid beta-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/total tau (t-tau) and amyloid beta-42/hyperphosphorylated tau (p-tau), with an area under the curve (AUC) of 0.93 to 0.94. The best PET measures (i.e., anterior cingulate, posterior cingulate/percuneus, and global neocortical uptake) performed similarly (AUC 0.92 to 0.93). The AUC for CSF amyloid beta-42/40 was numerically poorer as compared to the majority of PET variables; however, the differences were nonsiginficant (p=.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 (amyloid beta-42, t-tau and p-tau) and PET (^{18}F-florbetapir) tracer. In the ADNI cohort, amyloid-beta 42/t-tau and amyloid beta-42/p-tau ratios similarly had higher AUCs than amyloid beta-42 alone.

Lewczuk et al (2017) evaluated whether amyloid beta-42 alone or the amyloid beta-42/40 ratio corresponded better with amyloid beta PET status.[45,] The investigators collected CSF from a mixed cohort (N=200) of cognitively normal and abnormal subjects who had undergone amyloid beta 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 amyloid beta-42 alone and the amyloid beta-42/40 ratio. Results revealed that the amyloid beta-42/40 ratio corresponded better than amyloid beta-42 alone with PET results, with a higher proportion of concordant cases (89.4% vs. 74.9%; p<.0001) and a larger AUC (0.936 vs. 0.814; p<.0001) associated with the ratio.

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, more effective therapy, or avoid unnecessary therapy or testing. Possible clinical uses of CSF biomarker and amyloid PET imaging could include confirming the diagnosis of AD to begin medications at an earlier stage or ruling out AD, which could lead to further diagnostic testing to determine the etiology of dementia and/or avoidance of unnecessary amyloid beta targeted therapy.

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without specific tests. Because these are intervention studies, the preferred evidence would be from randomized controlled trials (RCTs). No direct evidence to support the clinical utility of the CSF biomarker testing (amyloid beta-42/40 ratio) alone or in conjunction with amyloid beta PET scans to initially select appropriate patients for treatment with an amyloid beta 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 amyloid beta imaging to inform continuation of amyloid beta plaque targeting therapy. Prior to the approval of aducanumab, the only approved treatments for AD were for symptoms. Rabinovici et al (2019) published results from a large scale (N=16,008 patients) 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). Disease-specific morbidity or mortality were not evaluable.[46,]

Section Summary: Cerebrospinal Fluid Biomarkers and Positron Emission Tomography Amyloid Scans for Mild Cognitive Impairment or Mild Dementia due to Alzheimer Disease

The evidence supporting a correlation between CSF biomarkers, including amyloid beta-42/40, and PET amyloid scans is limited and includes an evaluation of data from a prospective, longitudinal study and a study of a mixed cohort of cognitively normal and abnormal subjects. Results from the prospective, longitudinal study, that were subsequently replicated in another study utilizing another CSF assay and PET tracer, found that the diagnostic accuracy of CSF and amyloid PET biomarkers to identify MCI-AD was similar. In the evaluation of the mixed cohort, results revealed that the amyloid beta-42/40 ratio corresponded better than amyloid beta-42 alone with PET results. Evidence of the clinical utility of CSF biomarkers alone or in conjunction with amyloid beta PET scans are currently lacking. Further research is required to determine whether use of CSF biomarkers or amyloid PET scans is associated with improved clinical outcomes.

Summary of Evidence

For individuals who have MCI or AD who receive CSF biomarker testing for 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 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 AD 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 AD 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 considered for initial treatment with an approved amyloid beta plaque targeting therapy, 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. Overall, the diagnostic accuracy of CSF biomarkers versus amyloid PET scans to identify MCI-AD was found to be similar but there are no data to support the clinical utility of CSF biomarker use as a component of determining appropriate initiation of amyloid beta targeting therapy. Prior to the availability of amyloid beta targeting therapy, additional data exist suggesting that amyloid beta PET scan results impacted diagnosis of dementias and patient management including use of symptomatic treatment. Further research is required to determine

whether use of CSF biomarkers alone or in conjunction with amyloid PET scans is associated with improved clinical outcomes. 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. Prior to the availability of amyloid beta targeting therapy, additional data exist suggesting that amyloid beta PET scan results impacted diagnosis of dementias and patient management including use of symptomatic treatment. Further research is required to determine whether use of CSF biomarkers alone in conjunction with amyloid beta PET scans are 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.

Supplemental Information

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

National Institute of Aging

2011 Revised Diagnostic Criteria

In 2011, probable Alzheimer disease (AD) was defined by the National Institute on Aging and the Alzheimer's Association workgroup using the following diagnostic criteria:[40,]

"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 1 of the following categories.
    a. Amnestic 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 1 other cognitive domain, as defined earlier in the text.
    b. Nonamnestic 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.
D. 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."

The diagnosis for possible AD dementia should meet the following criteria:

A. Core criteria for the nature of cognitive deficits for AD dementia but is marked by sudden onset of cognitive impairment or insufficient history or documentation describing progressive decline; or
B. All core clinical criteria for AD dementia but presents with concomitant cerebrovascular disease, features of dementia with Lewy bodies, or evidence of another neurological disease or any condition that could affect cognition.

Additionally, a category "Probable AD dementia with evidence of the AD pathophysiological process" has been added. Evidence of the AD pathophysiologic process is supported by detection of low cerebrospinal fluid (CSF) amyloid beta peptide 1-42 (Aβ42), positive positron emission tomography amyloid imaging, or elevated CSF tau, and decreased fluorine 18 fluorodeoxyglucose uptake on positron emission tomography in the temporoparietal cortex with accompanying atrophy by magnetic resonance imaging in relevant structures. Detection of the "pathophysiological process" is further divided by when in the disease natural history markers are expected to be detectable. Biomarker evidence in cases of probable AD may increase the certainty that the dementia is due to AD pathophysiological process.

Note on the 2011 Revised Criteria and Biomarkers

Some of the biomarkers considered in this evidence review are in a category among the 2011 revisions to AD diagnostic criteria, "probable AD dementia with evidence of the AD pathophysiological process."[40,] However, the diagnostic criteria workgroup noted the following:

"[We] do not advocate the use of AD biomarker tests for routine diagnostic purposes at the present time. There are several reasons for this limitation: 1) the core clinical criteria provide very good diagnostic accuracy and utility in most patients; 2) more research needs to be done to ensure that criteria that include the use of biomarkers have been appropriately designed, 3) there is limited standardization of biomarkers from 1 locale to another, and 4) access to biomarkers is limited to varying degrees in community settings. Presently, the use of biomarkers to enhance certainty of AD pathophysiological process may be useful in 3 circumstances: investigational studies, clinical trials, and as optional clinical tools for use where available and when deemed appropriate by the clinician."[40,]

Alzheimer's Association

In 2009, the Alzheimer's Association initiated a quality control program for CSF markers, noting that "Measurements of CSF AD biomarkers show large between laboratory variability, likely caused by factors related to analytical procedures and the analytical kits. Standardization of laboratory procedures and efforts by kit vendors to increase kit performance might lower variability, and will likely increase the usefulness of CSF AD biomarkers."[19,] In 2012, the Alzheimer's Biomarkers Standardization Initiative published consensus recommendations for standardization of preanalytical aspects (e.g., fasting, tube types, centrifugation, storage time, temperature) of CSF biomarker testing.[47,]

In 2013, the Alzheimer's Association published recommendations for operationalizing the detection of cognitive impairment during the Medicare annual wellness visit in primary care settings.[48,] The recommended algorithm for cognitive assessment was based on "current validated tools and commonly used rule-out assessments." Guidelines noted that the 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."

In 2018, the Alzheimer's Association published appropriate use criteria for lumbar puncture and CSF testing for AD.[49,] Table 5 summarizes the indications for these practices. In 2021, the Alzheimer's Association also published international guidelines for the appropriate handling of CSF for routine clinical measurements of amyloid beta and tau.[50,]

Table 5. Indications for Appropriate Use of Lumbar Puncture and CSF Testing in Diagnosing AD

Appropriate Indications
Patients with SCD who are considered at increased risk for AD
MCI that is persistent, progressing, and unexplained
Patients with symptoms that suggest possible AD
MCI or dementia with an onset at an early age (<65 y)
Meeting core clinical criteria for probable AD with typical age of onset
Patients whose dominant symptom is a change in behavior and where AD diagnosis is being considered
Inappropriate Indications
Cognitively unimpaired and within normal range functioning for age as established by objective testing; no conditions suggesting high risk and no SCD or expressed concern about developing AD
Cognitively unimpaired patient based on objective testing, but considered by patient, family informant, and/or clinician to be at risk for AD based on family history
Patients with SCD who are not considered to be at increased risk for AD
Use to determine disease severity in patients having already received a diagnosis of AD
Individuals who are apolipoprotein E (APOE) ε4 carriers with no cognitive impairment
Use of lumbar puncture in lieu of genotyping for suspected ADAD mutation carriers
ADAD mutation carriers, with or without symptoms

AD: Alzheimer disease; ADAD: autosomal-dominant Alzheimer disease; CSF: cerebrospinal fluid; MCI: mild cognitive impairment; SCD: subjective cognitive decline.

In 2022, the Alzheimer's Association Global Workgroup released appropriate use recommendations for blood biomarkers in AD.[51,] The Workgroup recommended "use of blood-based markers as (pre-) screeners to identify individuals likely to have AD pathological changes for inclusion in trials evaluating disease-modifying therapies, provided the AD status is confirmed with PET or CSF testing." The Workgroup also encouraged "studying longitudinal blood-based marker changes in ongoing as well as future interventional trials" but cautioned that these markers "should not yet be used as primary endpoints in pivotal trials." Further, the Workgroup also recommended cautiously starting to use blood-based biomarkers "in specialized memory clinics as part of the diagnostic work-up of patients with cognitive symptoms" with the results confirmed with CSF or PET whenever possible. Additional data are needed before use of blood-based biomarkers as stand-alone diagnostic AD markers, or before considering use in primary care.

National Institute for Health and Care Excellence

In 2018, the National Institute for Health and Care Excellence (NICE) released a guideline on assessment, management, and support for people living with dementia and their caregivers.[52,] The guideline states that in cases of uncertain diagnosis, but highly suspicious for AD, providers can consider examining CSF for total tau or total tau and phosphorylated-tau 181 and either beta amyloid 42 or beta amyloid 42 and beta amyloid 40. People who are older are more likely to receive a false positive with a CSF analysis.

U.S. Preventive Services Task Force Recommendations

In 2020, the U.S. Preventive Services Task Force released recommendations for screening cognitive impairment in older adults, concluding that the current evidence is insufficient to determine benefits versus harms of screening for cognitive impairment in older adults.[53,] The statement discusses that

screening tests are not intended to diagnose MCI or dementia, but a positive screening test result should prompt additional testing consisting of blood tests, radiology examinations, and/or medical and neuropsychologic evaluation.

Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this review are listed in Table 6.

Table 6. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT05020106	Study on the Diagnostic Cut-off Value for Core Biomarkers in Cerebrospinal Fluid and Blood of Alzheimer's Disease	3200	Sep 2022 (recruiting)
NCT03136679	Discovery of Novel Biomarkers That Will Lead to the Early Detection of Alzheimer's Disease	220	Dec 2022 (recruiting)
NCT02612376	Rocky Mountain Alzheimer's Disease Center at the University of Colorado School of Medicine (RMADC at UCSOM) Longitudinal Biomarker and Clinical Phenotyping Study	800	Jan 2024 (recruiting)
NCT03860857	MRI and PET Biomarkers for Cognitive Decline in Older Adults	200	Dec 2024 (recruiting)
NCT04575337	Study on Body Fluid, Gene and Neuroimaging Biomarkers for Early Diagnosis of Alzheimer's Disease	6000	Jun 2025 (recruiting)
Unpublished			
NCT01642420	Quantitative Electroencephalography, Cerebrospinal Fluid Biomarkers, Linear CT Analyses, and Timed Up and GO Dual Task as Diagnostic Tools in Dementia and Their Ability to Predict Disease Progression	115	Feb 2017 (status unknown; updated 09/2012)

NCT: national clinical trial.

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Documentation for Clinical Review

- No records required

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy.

The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.

Type	Code	Description
CPT®	0206U	Neurology (Alzheimer disease); cell aggregation using morphometric imaging and protein kinase C-epsilon (PKCe) concentration in response

Type	Code	Description
		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)
	0346U	Beta amyloid, AB40 and AB42 by liquid chromatography with tandem mass spectrometry (LC-MS/MS), ratio, plasma ***(Code revision effective 7/1/2023)***
	0361U	Neurofilament light chain, digital immunoassay, plasma, quantitative
	0393U	Neurology (e.g., Parkinson disease, dementia with Lewy bodies), cerebrospinal fluid (CSF), detection of misfolded α-synuclein protein by seed amplification assay, qualitative ***(Code effective 7/1/2023)***
	0412U	Beta amyloid, AB42/40 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 ***(Code effective 10/1/2023)***
	0443U	Neurofilament light chain (NfL), ultra-sensitive immunoassay, serum or cerebrospinal fluid ***(Code effective 4/1/2024)***
	0445U	B-amyloid (Abeta42) and phospho tau (181P) (pTau181), electrochemiluminescent immunoassay (ECLIA), cerebral spinal fluid, ratio reported as positive or negative for amyloid pathology ***(Code effective 4/1/2024)***
	81099	Unlisted urinalysis procedure
	83520	Immunoassay for analyte other than infectious agent antibody or infectious agent antigen; quantitative, not otherwise specified
	86849	Unlisted immunology procedure
HCPCS	None	

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action
04/02/2010	New policy Policies combined: • Apolipoprotein E Epsilon (apoE) 4 Allele and Alzheimers Disease: Role for Genetic Testing for Diagnosis and Risk Management • Cerebrospinal Fluid and Urinary Assays of Neuronal (Neural) Thread Protein in the Diagnosis of Alzheimers Dementia
04/19/2012	Added documentation required for clinical review
02/22/2013	Coding update.
02/27/2015	Policy title change from Alzheimer's Disease - Genetic and Biochemical Testing Policy revision without position change
02/01/2017	Policy title change from Biochemical Markers of Alzheimer Disease Policy revision without position change
02/01/2018	Policy revision without position change
02/01/2019	Policy revision without position change

Effective Date	Action
02/01/2020	Annual review. No change to policy statement. Literature review updated.
12/01/2020	Coding update.
02/01/2021	Annual review. No change to policy statement. Literature review updated. Policy title changed from Cerebrospinal Fluid and Urinary Biomarkers of Alzheimer Disease to current one.
12/01/2021	Annual review. Policy statement, guidelines and literature review updated.
11/01/2022	Coding update.
12/01/2022	Annual review. Policy statement, guidelines and literature review updated.
03/01/2023	Coding update.
08/01/2023	Coding update.
11/01/2023	Coding update.
12/01/2023	Annual review. No change to policy statement.
05/01/2024	Coding update.

Definitions of Decision Determinations

Medically Necessary: Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the Member's illness, injury, or disease.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.
Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements and Feedback (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

We are interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California or Blue Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration.

For utilization and medical policy feedback, please send comments to: MedPolicy@blueshieldca.com

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.

Appendix A

POLICY STATEMENT (No changes)	
BEFORE	**AFTER**
Evaluation of Biomarkers for Alzheimer Disease 2.04.14 **Policy Statement:** I. Cerebrospinal fluid biomarker testing, including but not limited to amyloid beta peptides, tau protein, or neural thread proteins, as an adjunct to clinical diagnosis in individuals with mild cognitive impairment is considered **investigational**. II. Cerebrospinal fluid biomarker testing, including but not limited to amyloid beta peptides, tau protein, or neural thread proteins, as an adjunct to clinical diagnosis in individuals with mild dementia due to Alzheimer disease is considered **investigational**. III. Cerebrospinal fluid biomarker testing, including but not limited to amyloid beta peptides, tau protein, or neural thread proteins, as part of an evaluation for the initiation of amyloid beta targeting therapy in individuals with mild cognitive impairment or mild dementia due to Alzheimer disease is considered **investigational**. IV. Cerebrospinal fluid biomarker testing, including but not limited to amyloid beta peptides, tau protein, or neural thread proteins, as part of an evaluation for the continuation of amyloid beta targeting therapy in individuals with mild cognitive impairment or mild dementia due to Alzheimer disease is considered **investigational**. V. 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 considered **investigational.**	**Evaluation of Biomarkers for Alzheimer Disease 2.04.14** **Policy Statement:** I. Cerebrospinal fluid biomarker testing, including but not limited to amyloid beta peptides, tau protein, or neural thread proteins, as an adjunct to clinical diagnosis in individuals with mild cognitive impairment is considered **investigational**. II. Cerebrospinal fluid biomarker testing, including but not limited to amyloid beta peptides, tau protein, or neural thread proteins, as an adjunct to clinical diagnosis in individuals with mild dementia due to Alzheimer disease is considered **investigational**. III. Cerebrospinal fluid biomarker testing, including but not limited to amyloid beta peptides, tau protein, or neural thread proteins, as part of an evaluation for the initiation of amyloid beta targeting therapy in individuals with mild cognitive impairment or mild dementia due to Alzheimer disease is considered **investigational**. IV. Cerebrospinal fluid biomarker testing, including but not limited to amyloid beta peptides, tau protein, or neural thread proteins, as part of an evaluation for the continuation of amyloid beta targeting therapy in individuals with mild cognitive impairment or mild dementia due to Alzheimer disease is considered **investigational**. V. 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 considered **investigational.**