2.04.14	Cerebrospinal Fluid and Urinary Biomarkers of Alzheimer Disease		
Original Policy Date:	April 2, 2010	**Effective Date:**	February 1, 2020
Section:	2.0 Medicine	**Page:**	Page 1 of 20

Policy Statement

Measurement of cerebrospinal fluid biomarkers of Alzheimer disease is considered **investigational** including but not limited to:

- Tau protein
- Amyloid beta peptides
- Neural thread proteins

Measurement of urinary biomarkers of Alzheimer disease is considered **investigational**, including but not limited to neural thread proteins.

Policy Guidelines

Coding

There are no specific CPT codes for this testing.

The following CPT code may be used to report testing for tau protein and amyloid-β peptides:

- **83520**: Immunoassay for analyte other than infectious agent antibody or infectious agent antigen; quantitative, not otherwise specified

An example of this testing is the ADmark® CSF Analysis, which tests for phosphorylated tau protein, total tau protein, and amyloid-ß peptide 1-42 peptide in cerebrospinal fluid (CSF). A laboratory website lists this test as being reported with 3 units of code 83520.

There are no specific codes used for testing for neural thread protein.

An example of this testing is the AlzheimAlert™ test by Nymox Pharmaceutical Corp.

Nymox lists on its website that the test is reported with the following code when performed in urine:

- **81099**: Unlisted urinalysis procedure

Nymox lists on its website that the test is reported with the following code when performed in CSF:

- **86849**: Unlisted immunology procedure

Description

Biochemical changes associated with the pathophysiology of Alzheimer disease (AD) are being evaluated to aid in the diagnosis of AD. Some common biomarkers studied are amyloid-peptide 1-42 and total or phosphorylated tau protein in cerebrospinal fluid.

Related Policies

- Beta-Amyloid Imaging with Positron Emission Tomography for Alzheimer Disease
- Genetic Testing for 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. AlzheimAlert™ and AdMark® CSF analysis are available under the auspices of the Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments for high-complexity testing. To date, the U.S. Food and Drug Administration (FDA) has chosen not to require any regulatory review of this test.

Rationale

Background

Alzheimer Disease

The diagnosis of Alzheimer disease (AD) is divided into 3 categories: possible, probable, and definite AD. A diagnosis of possible AD dementia is made when the patient meets core clinical criteria for AD dementia but has an atypical course or an etiologically mixed presentation. Probable AD dementia is diagnosed clinically when the patient meets core clinical criteria for dementia and has a typical clinical course for AD. A typical clinical course is defined as an insidious onset, with the initial and most prominent cognitive deficits being either amnestic or nonamnestic (e.g., language, visuospatial, or executive function deficits), and a progressively worsening cognition over time. A diagnosis of definite AD requires postmortem confirmation of AD pathology, including the presence of extracellular ß-amyloid plaques and intraneuronal neurofibrillary tangles in the cerebral cortex.[1]

Mild Cognitive Impairment

Mild cognitive impairment (MCI) may be diagnosed when a dementia diagnosis cannot be made yet there is a significant change in cognition.[2] MCI is characterized by impairment in one or more cognitive domains yet there remains preserved functional independence. In some patients, MCI may be a predementia phase of AD. Patients with MCI or suspected AD may undergo ancillary testing (e.g., neuroimaging, laboratory tests, neuropsychological assessment) to rule out vascular, traumatic, and medical causes of cognitive decline and to evaluate genetic factors. Because clinical diagnosis can be difficult, particularly early in the course of disease, there has been considerable interest in developing an accurate laboratory test for AD.

Biomarkers

Several potential biomarkers of AD are associated with AD pathophysiology (e.g., ß-amyloid plaques, neurofibrillary tangles).

Elevated cerebrospinal fluid (CSF) levels of specific proteins have been found in patients with AD. They include tau protein, phosphorylated at AD-specific epitopes such as phosphorylated threonine 181 or total tau protein, or an amyloid-ß peptide such as 1-42 (Aß42). Other potential

CSF[3,4] and serum[5] 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. Aß42 is a subtype of amyloid-ß peptide produced from metabolism of amyloid precursor protein. Aß42 is the key peptide deposited in amyloid plaques characteristic of AD. Low levels of Aß42 in the CSF have been associated with AD, perhaps because Aß42 is deposited in amyloid plaques instead of remaining in fluid. Investigators have suggested that the tau/Aß42 ratio may be a more accurate diagnostic marker than either alone.[6] A variety of kits are commercially available to measure Aß42 and tau proteins. Between-laboratory variability in CSF biomarker measurement is large.[7,8]

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.

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.

Alzheimer Disease

The diagnosis of AD is divided into three categories: possible, probable, and definite AD. A diagnosis of possible AD is made when the patient meets core clinical criteria for AD but has an atypical course or an etiologically mixed presentation. Probable AD is diagnosed clinically when the patient meets core clinical criteria for dementia and has a typical clinical course for AD. A typical clinical course is defined as an insidious onset, with the initial and most prominent cognitive deficits being either amnestic or non-amnestic (e.g., language, visuospatial, or executive function deficits), and a progressively worsening cognition over time. A diagnosis of definite AD requires postmortem confirmation of AD pathology, including the presence of extracellular β-amyloid plaques and intraneuronal neurofibrillary tangles in the cerebral cortex.[7,]

Mild Cognitive Impairment

MCI may be diagnosed when a dementia diagnosis cannot be made yet there is a significant change in cognition.[8,] MCI is characterized by impairment in one or more cognitive domains yet there remains preserved functional independence. In some patients, MCI may be a predementia phase of AD. Patients with MCI or suspected AD may undergo ancillary testing (e.g., neuroimaging, laboratory tests, neuropsychological assessment) to rule out vascular, traumatic, and medical causes of cognitive decline and to evaluate genetic factors. Because clinical diagnosis can be difficult, particularly early in the course of the disease, there has been considerable interest in developing an accurate laboratory test for AD.

Cerebrospinal Fluid Biomarker Testing

Clinical Context and Test Purpose

The purpose of CSF biomarker testing for AD is to provide an alternative or superior method for diagnosis to inform appropriate treatment in patients with AD or MCI.

The question addressed in this evidence review is: Does testing CSF biomarkers improve the net health outcome in individuals with MCI or AD?

The following PICOs were used to select literature to inform this review.

Patients
The relevant population of interest are individuals with AD or MCI.

Interventions
The therapy being considered is CSF biomarker testing for AD, which is managed by neurologists and primary care providers in an outpatient clinical setting.

Comparators
Comparators of interest include clinical diagnosis of AD or MCI, which is managed by neurologists and primary care providers in an outpatient clinical setting.

Outcomes
The general outcomes of interest are symptoms, change in disease status, morbid events, functional outcomes, quality of life (QOL), medication use, and resource utilization.

Follow-up at two years is of interest for CSF biomarker testing for AD for symptoms, change in disease status, morbid events, functional outcomes, QOL, medication use, and resource utilization.

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.

Technically Reliable
Assessment of technical reliability focuses on specific tests and operators and requires a review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

Clinically Valid
Diagnosis of AD

Systematic Reviews
Most studies have relied on clinically diagnosed AD as the criterion standard. Systematic reviews of these studies are described next; the results are summarized in Table 1. Studies included in systematic reviews are not individually reviewed.

Rosa et al (2014) conducted a systematic review with meta-analysis of studies of CSF Aβ42 in patients with clinically diagnosed AD.[9] Literature was searched to May 2013, and 41 prospective or retrospective, cohort, case-control, and cross-sectional studies were included (total n=5086 patients; 2932 AD, 2154 nondemented controls). Patients with MCI were excluded, and 66% of studies satisfied all quality domains of the Quality Assessment of Diagnostic Accuracy Studies tool. Publication bias was detected. A summary receiver operating characteristic curve was generated from all reported thresholds. Pooled sensitivity and specificity were high (see Table 1). Positive and negative likelihood ratios were 4.5 (95% confidence interval [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 (n=1459 patients; 830 AD, 629 controls) reported Aβ42 CSF levels. Mean (standard deviation) CSF Aβ42 levels were 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 pg/mL; p<0.001). However, statistical heterogeneity was considerable (I^2=99%).

Ferreira et al (2014)[10], published a meta-review of systematic reviews with meta-analyses to assess the use of CSF biomarker tests for AD after the publication of revised AD diagnostic criteria[11], in 2011. Literature was searched in September 2013, and 7 systematic reviews were included. None of the reviews were published after the introduction of the revised AD diagnostic criteria, and as a result, primary studies were searched. Twenty-six prospective or retrospective case-control, cross-sectional, or longitudinal studies were included. Most selected studies used clinical criteria for AD diagnosis or did not specify. Data on sensitivity and specificity for Aβ42 and total tau protein (tTau) both for demented controls and controls without dementia were available only from Bloudek et al (2011)[12], and are found in Table 1. For differentiating AD from nondemented controls, positive and negative likelihood ratios for all three biomarkers ranged from 4 to 8 and from 0.1 to 0.3, respectively. For differentiating AD from other dementias, a systematic review of 7 studies by van Harten et al (2011) reported positive and negative likelihood ratios of 46 and 0.09, respectively, for differentiating AD (n=175) from Creutzfeldt-Jakob disease (n=110).[13], With this systematic review excluded, positive and negative likelihood ratios ranged from 2 to 7 and from 0.15 to 0.4, respectively.

Ameta-analysis by Bloudek et al (2011) included 119 studies on biomarkers and diagnostic imaging in AD.[12], Sensitivity and specificity were calculated for distinguishing AD from nondemented controls, 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 Aβ42 CSF marker were included with nondemented and demented controls; pooled analysis resulted in a sensitivity of 76% (95% CI, 72% to 80%) and a specificity of 77% (95% CI, 72% to 82%). CSF tTau 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 phosphorylated tau protein (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 tTau and Aβ42 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 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%). Table 1 separates sensitivity and specificity for patients with and without dementia.

In a review of studies using clinical diagnosis as the criterion standard, Formichi et al (2006) identified studies examining diagnostic accuracy of the following CSF markers for AD: tTau (41 studies; 2287 AD patients, 1384 controls), pTau (12 studies; 760 AD patients, 396 controls), and Aβ42 (14 studies; 688 AD patients, 477 controls).[14],Sensitivity and specificity for the biomarkers can be found in Table 1. Although primarily a descriptive review, test accuracies varied widely, and only one study included a majority of autopsy-confirmed AD diagnoses.

Table 1. Systematic Reviews Assessing CSF Biomarkers Performance for Distinguishing Alzheimer Disease From Controls With Clinical Diagnosis as the Reference Standard

Biomarkers Studies	Controls Without Dementia, %		Controls With Dementia, %[a]	
	Sensitivity	*Specificity*	*Sensitivity*	*Specificity*
Aβ42				
Rosa et al (2014)[9],	84 (81 to 85)	79 (77 to 81)	NR	NR

Bloudek et al (2011)[12,]	80 (73 to 85)	82 (74 to 88)	73 (67 to 78)	67 (62 to 72)
Formichi et al (2006)[14,]	NR	NR	55-100	80-100
tTau				
Bloudek et al (2011)[12,]	82 (76 to 87)	90 (86 to 93)	78 (72 to 83)	75 (68 to 81)
Formichi et al (2006)[14,]	NR	NR	52-100	50-100
pTau				
Ferreira et al (2014)[10,]	78-80	83-88	72-88	78-83
Bloudek et al (2011)[12,]	80 (70 to 87)	83 (75 to 88)	79 (72 to 84)	80 (71 to 86)
Formichi et al (2006)[14,]	NR	NR	37-100	80-100

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.

Cure et al (2014) conducted a systematic review with meta-analysis of CSF and imaging studies for the diagnosis of definite AD (autopsy-confirmed).[15,] Literature was searched in January 2012, and 3 studies of CSF markers (pTau, tTau, Aβ42, Aβ40) were identified (total n=337 patients). 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 by AD definitions, controls (nondemented patients 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.

Observational Studies
In a report, Howell et al (2017) evaluated the clinical validity of CSF biomarkers in diverse populations by prospectively recruiting 135 older Americans to undergo detailed clinical, neuropsychological, genetic, magnetic resonance imaging, and CSF analysis.[16,] Despite finding comparable levels of CSF Aβ42 and Aβ42/Aβ40, cognitive impairment in African Americans was noted to be associated with smaller changes in CSF tau markers but greater impact from similar magnetic resonance imaging white matter hyperintensity burden than Caucasians leading to the conclusion that race-associated differences in CSF tau markers and ratios may lead to underdiagnosis of AD in African Americans.

As noted in the Background section, for patients with clinically diagnosed AD, some have suggested the tau/Aβ42 ratio is a more accurate predictor than either marker alone. For example, using optimal cutoffs, de Jong et al (2006) reported sensitivity and a specificity of 95% and 90%, respectively, in a sample with clinically diagnosed AD (n=61) and vascular dementia (n=61).[17,] In contrast, Le Bastard et al (2007) found the pTau/Aβ42 ratio lacked specificity to distinguish AD from vascular dementia in a sample of 85 patients (vascular dementia [n=64], AD [n=21]; 76/85 autopsy-confirmed diagnoses); specificity was 52% and sensitivity ranged from 91% to 95%.[18,]

A multicenter study by Park et al (2017) drew 194 patients from 6 memory clinics in South Korea. Of the 194 patients, 76 showed Alzheimer disease dementia (ADD); 47 had other neurologic disorders (OND) involving cognitive impairment, and 71 had no sign of cognitive impairment, and thus served as a control group.[19,] The primary aim was to find accurate cutoff values for CSF biomarkers to distinguish between AD and either control or OND. When the ADD group was compared with the control group, cutoff values were as follows: 481 pg/mL (Aß42), 326 pg/mL (tTau), 57 pg/mL (pTau), with improved tTau/Aß42 ratios (0.55; sensitivity, 99%; specificity, 95%) and pTau/Aß42 (0.10; sensitivity, 96%; specificity, 96%). When the ADD group was compared with the OND group, the same pattern held for ratio cutoff values (especially tTau/Aß42) being more accurate than those of individual proteins (i.e., Aß42=478 pg/mL, tTau=327 pg/mL, pTau=48 pg/mL, [sensitivity range, 83%-93%; specificity range, 70%-85%] vs tTau/Aß42=0.76 [sensitivity, 93%; specificity, 92%]; and pTau/Aß42=0.12 [sensitivity, 95%; specificity, 89%]). Additionally, area under the curve measurements showed greater accuracy in ratios (tTau/Aß42 and pTau/ Aß42) than in

individual biomarkers: for ADD vs control, the area under the curve for both ratio biomarkers were 0.99 (95% CI, 0.98 to 1.0), and for ADD vs OND, area under the curve measurements were similar (0.94 for both). While study limitations included a younger-than-average group of AD patients and a small comparison group with several neurologic disorders, the authors concluded that the combined biomarker ratio was superior to individual markers at accurately predicting AD. They based this conclusion on the comparability of cutoff values between this study and previous studies.

The Aβ42/Aβ40 ratio is also being investigated as a marker for patients with uncertain clinical diagnosis. Because Aβ40 is not incorporated into amyloid plaques, CSF Aβ40 levels are considered more stable than those of Aβ42. Sauvee et al (2014) examined the Aβ42/Aβ40 ratio in 122 patients with atypical dementia who had discordant CSF biomarker results (i.e. , tTau, pTau, Aβ42).[20] Using 0.05 as the ratio threshold, biologic profiles were determined in 72 (59%) of 122 patients with the addition of the Aβ42/Aβ40 ratio. However, of 35 patients diagnosed with AD by biologic profile, 9 (26%) did not meet clinical criteria for AD or mixed dementia. Janelidze et al (2016) also found that the Aβ42/Aβ40 ratio was significantly better than Aβ42 alone in detecting brain amyloid deposition in prodromal AD and in differentiating AD dementia from non-AD dementias across 3 different immunoassays and 3 patient cohorts.[21]

Vogelgsang et al (2018) conducted an analysis of CSF from 114 patients to determine the reproducibility of using amyloid-β40 and amyloid-β42 in AD screenings. CSF samples for each patient were collected under routine clinical conditions at two different sites, and the samples for each patient were compared for discrepancies. Statistical analysis showed that the inclusion of Aβ42/40, compared with Aβ42 alone, leads to 16.8% fewer discordant results. Limitations included the sample size and the observational design.[22]

Kahle et al (2000) reported on the diagnostic potential of CSF levels of tTau and neural thread protein (NTP) in a group of 35 patients with dementia (30 with probable or definite AD), 5 patients with dementia with Lewy bodies, 29 patients with Parkinson disease, and 16 elderly healthy control patients.[23] Levels of both tau proteins and NTP were elevated in patients with AD compared with controls; sensitivity and specificity were 63% and 93%, respectively, for tau, and 70% and 80%, respectively, for NTP.

Alexopoulos et al (2018) conducted a retrospective study of data from the Alzheimer Disease Neuroimaging Initiative databank to evaluate the utility of measuring β-site amyloid-β precursor protein BACE1 activity and soluble AβPP β levels in CSF as predictors for AD.[24] In the study, data from 56 patients with AD dementia, 76 patients with MCI from AD, 39 patients with MCI with normal CSF markers, and 48 control patients without preclinical AD were analyzed using several statistical tests. There were no differences in soluble AβPP β levels among any of the groups, and the AD-dementia group did not show a difference in BACE1 activity compared with the other groups. However, BACE1 activity was significantly higher in MCI-AD patients compared with both MCI-nonAD (p=0.02) and control groups (p<0.001). Limitations included a relatively small sample size, the retrospective design, and patients recruited at specialized centers.

Wang et al (2018) conducted a longitudinal study of whether the addition of total and phosphorylated a-synuclein to the AD biomarker panel improves the panel's performance.[25] The researchers analyzed 792 baseline and longitudinal CSF samples from 87 AD patients, 177 MCI patients, and 104 age-matched healthy controls across up to 7 years as part of the AD Neuroimaging Initiative. Statistical analysis showed that a-synuclein predicted AD Assessment Scale-Cognitive (p=0.0015), memory (p=0.00025) and executive-function (p<0.0001) composite scores and progression from MCI to AD (p=0.0011). Limitations include cohort heterogeneity and longitudinal design.

Trombetta et al (2018) conducted an observational study to identify biomarkers with good to excellent reliability at predicting AD.[26] The researchers analyzed baseline CSF samples from 20 patients with MCI or mild dementia due to AD who were enrolled in a clinical drug trial. The

researchers identified 32 biomarker candidates that consistently and reliably were associated with the incidence of AD. Limitations included the observational design and small sample size.

Subsection Summary: Clinical Validity of CSF Biomarker Testing for Diagnosis of AD
Several studies have examined the diagnostic performance of CSF biomarkers for distinguishing probable AD from nondemented controls and from patients with other types of dementia. The range of reported sensitivities and specificities is broad compared with 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 nondemented controls, and were 73% and 67%, respectively, for differentiating AD from other dementias. Positive and negative likelihood ratios were two to eight and 0.2 to 0.4, respectively, in either setting. A multicenter study found higher sensitivity and specificity for ratios (tTau/Aß42 and pTau/Aß42) than for individual biomarkers, with sensitivity and specificity for the ratios ranging from 89% to 99% in distinguishing between AD and controls or other cognitive disorders. There is limited evidence examining the incremental diagnostic accuracy of CSF biomarkers for AD diagnosis employing autopsy as a criterion standard. Cutoffs for positive diagnosis are not standardized. Current evidence does not demonstrate improvement over a clinical diagnosis.

Prognosis for Progression of MCI
Studies have evaluated the prognostic value of CSF biomarkers for the progression of MCI and conversion to clinically manifest AD.

Systematic Reviews
Ritchie et al (2014) published a Cochrane review of CSF amyloid-β protein (primarily Aβ42) for detecting which patients with MCI would progress to AD or other dementias.[27] Literature was searched in December 2012, and 14 prospective or retrospective cohort studies of AD were included (1349 patients with MCI). Studies that enrolled patients younger than 50 years of age or with less than 2 years of follow-up were excluded. Risk of bias was moderate-to-high in most studies. Diagnosed by clinical criteria, AD developed in 436 (32%) of 1349 patients. Due to the heterogeneity of thresholds used, summary sensitivity and specificity were not calculated; however, sensitivity and specificity ranges and sensitivity based on a median specificity of 64% are included in Table 3.Positive and negative likelihood ratios were 2.2 (95% CI, 2.0 to 2.5) and 0.31 (95% CI, 0.21 to 0.48), respectively, also based on a median specificity of 64%. Analysis of the pre- and post-test probabilities of conversion to AD among patients with MCI in primary and secondary care settings showed little incremental value of Aβ42 testing in either setting.

The meta-review of systematic reviews by Ferriera et al (2014; previously discussed) included studies of CSF biomarkers for differentiating patients with MCI who progressed to AD from those who did not.[10] In systematic reviews with meta-analyses, sensitivity and specificity rates for Aβ42 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.

Olsson et al (2016) performed a comprehensive systematic review and meta-analysis of 231 articles including 15699 patients with AD and 13,018 controls, published between 1984 and 2014, which described both diagnostic and prognostic performance of CSF biomarkers.[28] Five articles were classified as high-quality and 226 as medium-quality; only studies with autopsy confirmation were eligible to be scored as high-quality. Diagnostic and prognostic accuracy was not reported due to the large variation in cutoffs for positivity. Instead, biomarker performance was summarized using the ratio of biomarker concentration in patients with AD and controls (i.e., fold change), or the ratio of biomarker concentration in those with MCI due to AD, and those with stable MCI who had no further cognitive decline during two years of follow-up. A fold change ratio above one indicates that the concentration of the biomarker is higher in the AD population than in the control population, and a ratio below one indicates the concentration is higher in the control population than in the AD population. Summary fold change was calculated with

random-effects meta-analysis. CSF tTau, pTau, and Aβ42 levels were consistently and strongly associated with AD diagnosis, as summarized in Table 3. All 3 biomarkers differentiated between cohorts with MCI due to AD and those with stable MCI: Aβ42 average ratio was 0.67 (95% CI, 0.63 to 0.73); pTau average ratio was 1.72 (95% CI, 1.46 to 2.02); and tTau average ratio was 1.76 (95% CI, 1.64 to 1.89).

Ritchie et al (2017) evaluated the use of CSF biomarker tests in predicting conversion from MCI to AD in a systematic review that included 15 studies and a total of 1172 patients whose data could be evaluated.[29] Estimated sensitivity was reported for CSF tTau and CSF pTau based on a median 72% and 47.5% specificity, respectively, as shown in Table 3.Table 3 also includes CSF tTau and pTau sensitivity and specificity ranges for seven studies. For CSF tTau, the positive and negative likelihood ratios were 2.72 (95% CI, 2.43 to 3.04) and 0.32 (95% CI, 0.22 to 0.47). Sensitivities for CSF pTau (drawn from 6 studies) ranged from 40% to 100%, with specificity ranging from 22% to 86%; for this test, positive and negative likelihood ratios were 1.55 (95% CI, 1.31 to 1.84) and 0.39 (95% CI, 0.19 to 0.82). For the CSF p-tau/ABeta ratio, 5 studies produced a sensitivity range between 80% and 95% and a specificity range from 33% to 95%, while a single study was identified for CSF t-tau/ABeta ratio. Of the 1172 patients whose progression to dementia was tracked, 560 presented either ADD (n=430) or other dementia (n=130) within 1 to 4 years. Reviewers included studies with considerable heterogeneity, and in some cases, poor methodologic quality.

Tables 2 and 3 do not include Ferreria (2014)[10] due to the study overlap.

Table 2. 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)[28]	1995-2014	231	Patients with AD or MCI due to AD.	AD=15,699 Controls=13,018 Total=27,717 (Range=20-1087)	Not specified	Not specified
Ritchie (2017)[29]	2006-2013	15	Patients with MCI at baseline.	N=1282	Longitudinal cohort	2 mo-11.8 y
Ritchie (2014)[27]	2003-2013	17	Participants with cognitive decline but no dementia condition at baseline.	Total=2228 (Range=37-588)	Longitudinal cohort	2 mo-12 y

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

Table 3. Results of Key Meta-Analyses

Study	Aß42	tTau	pTau
Olsson (2016))[28]			
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)[29]			
Sensitivity range, %	-	51-90	40-100
Specificity range, %	-	48-88	22-86
Median specificity, %	-	72	47.5
Sensitivity at median specificity, % (95% CI)	-	75 (67 to 85)	81 (64 to 91)
Ritchie (2014)[27]			
Sensitivity range, %	36-100	-	-
Specificity range, %	29-91	-	-
Median specificity, %	64	-	-
Sensitivity at median specificity, % (95% CI)	81 (72 to 87)	-	-

Average ratio: Alzheimer's 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.

Observational Studies

The main goal of the 3-part cohort study by Hansson et al (2018) was to assess whether the Elecsys CSF immunoassays for biomarkers Aβ(1-42), pTau/Aβ(1-42), and tTau/Aβ(1-42) could be used to develop global cutoffs that are transferable across populations, even when CSF samples were analyzed in different laboratories.[30] However, the study also aimed to determine whether these biomarkers can predict clinical progression of cognitive impairment. The investigators determined that CSF biomarker cutoffs could be transferred from one independent cohort to another, but the data more relevant to this evidence review describes the predictive value of these particular CSF biomarkers. A cohort of 619 patients with MC was examined, and investigators found a significant difference in progression (defined by the Clinical Dementia Rating—Sum of Boxes measurement, from baseline to 2 years) between biomarker-positive and biomarker-negative patients for all 3 biomarkers evaluated. Biomarker-positive patients progressed 1.4-1.6 points from baseline, and biomarker-negative patients progressed less than 0.5 points. Results also indicated that pTau/Aβ(1-42) and tTau/Aβ(1-42) ratios showed a greater difference in progression between biomarker-positive and biomarker-negative groups than Aβ(1-42) alone. Study limitations were mainly associated with the main goals of the study, but one limitation is the preanalytical protocol for the cohort used in the assessment of clinical progression included many sample handling steps, which may not have been exactly replicated in this study.

Liu et al (2017) conducted an observational study of 94 patients (17 potential AD patients, 35 patients with MCI, and 41 control patients with subjective memory complaints) who received extensive dementia screenings.[31] Samples from the patients were tested for levels of let-7b miRNA. The results were analyzed using numerous statistical tests. Analysis found that when let-7b is added to predicted parameters in CSF screening, the predicted probability of the occurrence of AD increases from 75.9% to 89.7% (CI: 0.844-1.000, $p<0.001$). Limitations include the small sample size and the lack of further validation.

Subsection Summary: Clinical Validity of CSF Biomarker Testing for Prognosis for Progression of MCI

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. CSF biomarkers added little to no incremental value over neuropsychological testing or imaging.

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 anti-Alzheimer medications.

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.[32,33] 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.[32,34] 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.[35,36,37,38,] The chain of evidence of clinical utility is incomplete.

Section Summary: CSF Biomarker Testing
The technical reliability of CSF biomarker measurement in AD is limited by variability between laboratories and assay methods. Most clinical validity studies of both diagnosis and prognosis 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
Clinical Context and Test Purpose
The purpose of urinary biomarker testing for AD is to provide an alternative or superior method of diagnosis to inform a decision to proceed with appropriate treatment in patients with AD or MCI.

The question addressed in this evidence review is: Does testing of urinary biomarkers improve the net health outcome in individuals with MCI or AD?

The following PICOs were used to select literature to inform this review.

Patients
The relevant population of interest are individuals with AD or MCI.

Interventions
The therapy being considered is urinary biomarker testing for AD, which is managed by neurologists and primary care providers in an outpatient clinical setting.

Comparators
Comparators of interest include clinical diagnosis of AD or MCI, which is managed by neurologists and primary care providers in an outpatient clinical setting.

Outcomes
The general outcomes of interest are symptoms, change in disease status, morbid events, functional outcomes, QOL, medication use, and resource utilization.

Though not completely standardized, follow-up for AD or MCI symptoms would typically occur in the months to years after starting treatment**.**

Study Selection Criteria
Methodologically credible studies were selected using the principles described in the first indication.

Technically Reliable
Assessment of technical reliability focuses on specific tests and operators and requires a review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

Clinically Valid
Zhang et al (2014) conducted a systematic review and meta-analysis of urinary AD-associated NTP for diagnosing AD in patients with suspected AD.[39,] Nine studies were included (total n=841

patients with probable or possible AD; 37 patients with MCI, 992 non-AD demented or nondemented controls). The reference standard was a clinical diagnosis in eight 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 1 to 11.1) and 0.12 (95% CI, 0.09 to 0.16), respectively.

In a prospective multicenter study conducted at 8 sites, Goodman et al (2007) enrolled 168 patients with recent referrals to memory clinics.[40,] The Urinary Neural Thread Protein Test was 91.4% (32/35) sensitive for a diagnosis of probable AD and 90.1% (39/43) specific among healthy patients.

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
Limited data on the technical reliability of urine NTP markers are available. Studies of clinical validity include both patients with dementia and normal control. Cut points for positive diagnosis varied. There is no direct evidence to support improvements in health outcomes and the chain of evidence is incomplete.

Summary of Evidence
For individuals who have AD or mild cognitive impairment (MCI) who receive cerebrospinal fluid biomarker testing for AD, the evidence includes systematic reviews, meta-analyses, and case series. These studies assess using cerebrospinal fluid biomarkers for diagnosis of AD or for the prognosis of progression of MCI to AD. The relevant outcomes are symptoms, change in disease status, morbid events, functional outcomes, quality of life (QOL), medication use, and resource utilization. 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 the effects of the technology on health outcomes.

For individuals who have AD or MCI who receive urinary biomarker testing for AD, the evidence includes a systematic review and observational studies. The relevant outcomes are symptoms, change in disease status, morbid events, functional outcomes, QOL, medication use, and resource utilization. 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 the effects of the technology on health outcomes.

Supplemental Information
Practice Guidelines and Position Statements

National Institute of Neurological and Communicative Disorders et al 1984 Diagnostic Criteria
The NINCDS and the Alzheimer Disease and Related Disorders Association (ADRDA;1984) developed clinical criteria for the diagnosis of Alzheimer disease (AD).[11,] Although research to date continues to use the NINCDS-ADRDA's AD classification, in 2011, the National Institute on Aging and the Alzheimer's Association revised the diagnostic criteria for dementia due to AD.[41,] In the 1984 guidelines, the diagnostic categories were defined as summarized in Table 4.

Table 4. The 1984 Diagnostic Categories for Alzheimer Disease

Diagnostic Categories for AD
Possible
Clinical diagnosis of possible AD: 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, the presentation, or 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 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.
Probable
Criteria for the clinical diagnosis of probable AD included: A. 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; B. Deficits in 2 or more areas of cognition; C. Progressive worsening of memory and other cognitive functions; D. No disturbance of consciousness; E. Onset between ages 40 and 90 years, most often after the age of 65 years; and F. Absence of systemic disorders or other brain diseases that in and of themselves could account for the progressive deficits in memory and cognition.
Other clinical features consistent with the diagnosis of probable AD, after exclusion of causes of dementia other than AD, including A. Plateaus in the course of progression of the illness; B. Associated symptoms of depression, insomnia, incontinence, delusions, illusions, hallucinations, sexual disorders, weight loss, and catastrophic verbal, emotional, or physical outbursts; C. Other neurological abnormalities in some patients, especially with more advanced disease and including motor signs such as increased muscle tone, myoclonus, or gait disorder; and D. Seizures in advanced disease CT normal for age.
Features that make the diagnosis of probable AD uncertain or unlikely include: A. Sudden apoplectic onset; B. Focal neurological findings such as hemiparesis, sensory loss, visual field deficits, and incoordination early in the course of the illness; and C. Seizures or gait disturbances at the onset or very early in the course of the illness.
Definite
Criteria for diagnosis of definite AD are: A. Clinical criteria for probable Alzheimer disease; AND B. Histopathologic evidence obtained from a biopsy or autopsy.

AD: Alzheimer Disease; CT: computed tomography.

2011 Revised Diagnostic Criteria

In 2011, probable AD was defined by the National Institute on Aging and the Alzheimer's Association workgroup using the following diagnostic criteria[41,]:

"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.
    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 one other cognitive domain, as defined earlier in the text.
    b. Non amnestic 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."

All probable AD by NINCDS-ADRDA criteria is subsumed in the revised probable AD criteria. Revised criteria include a category of "Probable AD dementia with increased level of certainty" due to documented decline or having a causative AD genetic mutation. 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-β 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.

Note on the 2011 Revised Criteria and Biomarkers

The biomarkers considered in this evidence review include in a category among the 2011 revisions to AD diagnostic criteria, "probable AD dementia with evidence of the AD pathophysiological process."[41,] 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 one 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."[41,]

Alzheimer's Association

The Alzheimer's Association (2009) 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."[12,] The Alzheimer's Biomarkers Standardization Initiative (2012) published consensus recommendations for standardization of preanalytical aspects (e.g., fasting, tube types, centrifugation, storage time, temperature) of CSF biomarker testing.[42,]

The Alzheimer's Association (2013) published recommendations for operationalizing the detection of cognitive impairment during the Medicare annual wellness visit in primary care settings.[43,]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."

The Alzheimer's Association (2018) published appropriate use criteria for lumbar puncture and CSF testing for AD.[44] Table 5 summarizes the indications for these practices.

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.

U.S. Preventive Services Task Force Recommendations

Not applicable.

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 Table6.

Table 6. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT03136679	Discovery of Novel Biomarkers That Will Lead to the Early Detection of Alzheimer's Disease	220	Dec 2022 (recruiting)
NCT03287765	Evaluating the Relationship Between Tau PET Imaging and CSF Biomarkers of AD in Humans	80	Nov 2021 (recruiting)
NCT02612376	Rocky Mountain Alzheimer's Disease Centerat the University of Colorado School of Medicine (RMADC at UCSOM)Longitudinal Biomarker and Clinical Phenotyping Study	800	Dec 2030 (recruiting)
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)
Unpublished			
NCT01931566	A Double-Blind, Randomized, Placebo-Controlled, Parallel Group Study to Simultaneously Qualify a	3494	Aug 2018 (terminated)[a]

	Biomarker Algorithm for Prognosis of Risk of Developing Mild Cognitive Impairment Due to Alzheimer's Disease (MCI Due to AD) and to Test the Safety and Efficacy of Pioglitazone (AD-4833 SR 0.8 mg QD) to Delay the Onset of MCI Due to AD in Cognitively Normal Subjects

NCT: national clinical trial.
[a] Terminated due to lack of drug efficacy.

References

1. Albert MS, DeKosky ST, Dickson D, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement. May 2011;7(3):270-279. PMID 21514249
2. Hyman BT, Phelps CH, Beach TG, et al. National Institute on Aging-Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease. Alzheimers Dement. Jan 2012;8(1):1-13. PMID 22265587
3. Galasko D, Clark C, Chang L, et al. Assessment of CSF levels of tau protein in mildly demented patients with Alzheimer's disease. Neurology. Mar 1997;48(3):632-635. PMID 9065538
4. Motter R, Vigo-Pelfrey C, Kholodenko D, et al. Reduction of beta-amyloid peptide42 in the cerebrospinal fluid of patients with Alzheimer's disease. Ann Neurol. Oct 1995;38(4):643-648. PMID 7574461
5. Zhang J, Peng M, Jia J. Plasma amyloid-beta oligomers and soluble tumor necrosis factor receptors as potential biomarkers of AD. Curr Alzheimer Res. May 2014;11(4):325-331. PMID 24635842
6. Maddalena A, Papassotiropoulos A, Muller-Tillmanns B, et al. Biochemical diagnosis of Alzheimer disease by measuring the cerebrospinal fluid ratio of phosphorylated tau protein to beta-amyloid peptide42. Arch Neurol. Sep 2003;60(9):1202-1206. PMID 12975284
7. Dumurgier J, Vercruysse O, Paquet C, et al. Intersite variability of CSF Alzheimer's disease biomarkers in clinical setting. Alzheimers Dement. Jul 2013;9(4):406-413. PMID 23141384
8. Mattsson N, Andreasson U, Persson S, et al. The Alzheimer's Association external quality control program for cerebrospinal fluid biomarkers. Alzheimers Dement. Jul 2011;7(4):386-395 e386. PMID 21784349
9. Shaw LM, Vanderstichele H, Knapik-Czajka M, et al. Qualification of the analytical and clinical performance of CSF biomarker analyses in ADNI. Acta Neuropathol. May 2011;121(5):597-609. PMID 21311900
10. Lewczuk P, Beck G, Ganslandt O, et al. International quality control survey of neurochemical dementia diagnostics. Neurosci Lett. Nov 27 2006;409(1):1-4. PMID 17045397
11. Verwey NA, van der Flier WM, Blennow K, et al. A worldwide multicentre comparison of assays for cerebrospinal fluid biomarkers in Alzheimer's disease. Ann Clin Biochem. May 2009;46(Pt 3):235-240. PMID 19342441
12. Monge-Argilés JA, Munoz-Ruiz C, Sanchez-Paya J, et al. Comparison of two analytical platforms for CSF biomarkers of Alzheimer's disease. Biomed Res Int. 2014;2014:765130. PMID 24971348
13. Rosa MI, Perucchi J, Medeiros LR, et al. Accuracy of cerebrospinal fluid Abeta(1-42) for Alzheimer's disease diagnosis: a systematic review and meta-analysis. J Alzheimers Dis. Jan 2014;40(2):443-454. PMID 24448789
14. Ferreira D, Perestelo-Perez L, Westman E, et al. Meta-review of CSF core biomarkers in Alzheimer's disease: the state-of-the-art after the new revised diagnostic criteria. Front Aging Neurosci. Apr 2014;6:47. PMID 24715863
15. McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement. May 2011;7(3):263-269. PMID 21514250

16. van Harten AC, Kester MI, Visser PJ, et al. Tau and p-tau as CSF biomarkers in dementia: a meta-analysis. Clin Chem Lab Med. Mar 2011;49(3):353-366. PMID 21342021
17. Cure S, Abrams K, Belger M, et al. Systematic literature review and meta-analysis of diagnostic test accuracy in Alzheimer's disease and other dementia using autopsy as standard of truth. J Alzheimers Dis. May 19 2014;42(1):169-182. PMID 24840572
18. Bloudek LM, Spackman DE, Blankenburg M, et al. Review and meta-analysis of biomarkers and diagnostic imaging in Alzheimer's disease. J Alzheimers Dis. 2011;26(4):627-645. PMID 21694448
19. Formichi P, Battisti C, Radi E, et al. Cerebrospinal fluid tau, A beta, and phosphorylated tau protein for the diagnosis of Alzheimer's disease. J Cell Physiol. Jul 2006;208(1):39-46. PMID 16447254
20. Howell JC, Watts KD, Parker MW, et al. Race modifies the relationship between cognition and Alzheimer's disease cerebrospinal fluid biomarkers. Alzheimers Res Ther. Nov 02 2017;9(1):88. PMID 29096697
21. de Jong D, Jansen RW, Kremer BP, et al. Cerebrospinal fluid amyloid beta42/phosphorylated tau ratio discriminates between Alzheimer's disease and vascular dementia. J Gerontol A Biol Sci Med Sci. Jul 2006;61(7):755-758. PMID 16870640
22. Le Bastard N, Van Buggenhout M, De Leenheir E, et al. LOW specificity limits the use of the cerebrospinal fluid AB1-42/P-TAU181P ratio to discriminate Alzheimer's disease from vascular dementia. J Gerontol A Biol Sci Med Sci. Aug 2007;62(8):923-924; author reply 924-925. PMID 17702886
23. Park SA, Chae WS, Kim HJ, et al. Cerebrospinal fluid biomarkers for the diagnosis of Alzheimer disease in South Korea. Alzheimer Dis Assoc Disord. Jan-Mar 2017;31(1):13-18. PMID 28030437
24. Sauvee M, DidierLaurent G, Latarche C, et al. Additional use of Abeta(4)(2)/Abeta(4)(0) ratio with cerebrospinal fluid biomarkers P-tau and Abeta(4)(2) increases the level of evidence of Alzheimer's disease pathophysiological process in routine practice. J Alzheimers Dis. Mar 2014;41(2):377-386. PMID 24614902
25. Janelidze S, Zetterberg H, Mattsson N, et al. CSF Abeta42/Abeta40 and Abeta42/Abeta38 ratios: better diagnostic markers of Alzheimer disease. Ann Clin Transl Neurol. Mar 2016;3(3):154-165. PMID 27042676
26. Vogelgsang J, Wedekind D, Bouter C, et al. Reproducibility of Alzheimer's Disease Cerebrospinal Fluid-Biomarker Measurements under Clinical Routine Conditions. J Alzheimers Dis. 2018;62(1):203-212. PMID 29439341
27. Kahle PJ, Jakowec M, Teipel SJ, et al. Combined assessment of tau and neuronal thread protein in Alzheimer's disease CSF. Neurology. Apr 11 2000;54(7):1498-1504. PMID 10751266
28. Alexopoulos P, Thierjung N, Grimmer T, et al. Cerebrospinal Fluid BACE1 Activity and sAbetaPPbeta as Biomarker Candidates of Alzheimer's Disease. Dement Geriatr Cogn Disord. 2018;45(3-4):152-161. PMID 29788013
29. Wang H, Stewart T, Toledo JB, et al. A Longitudinal Study of Total and Phosphorylated alpha-Synuclein with Other Biomarkers in Cerebrospinal Fluid of Alzheimer's Disease and Mild Cognitive Impairment. J Alzheimers Dis. 2018;61(4):1541-1553. PMID 29376878
30. Trombetta BA, Carlyle BC, Koenig AM, et al. The technical reliability and biotemporal stability of cerebrospinal fluid biomarkers for profiling multiple pathophysiologies in Alzheimer's disease. PLoS One. 2018;13(3):e0193707. PMID 29505610
31. Ritchie C, Smailagic N, Noel-Storr AH, et al. Plasma and cerebrospinal fluid amyloid beta for the diagnosis of Alzheimer's disease dementia and other dementias in people with mild cognitive impairment (MCI). Cochrane Database Syst Rev. Jun 10 2014;6(6):CD008782. PMID 24913723
32. Olsson B, Lautner R, Andreasson U, et al. CSF and blood biomarkers for the diagnosis of Alzheimer's disease: a systematic review and meta-analysis. Lancet Neurol. Jun 2016;15(7):673-684. PMID 27068280
33. Ritchie C, Smailagic N, Noel-Storr AH, et al. CSF tau and the CSF tau/ABeta ratio for the diagnosis of Alzheimer's disease dementia and other dementias in people with mild cognitive impairment (MCI). Cochrane Database Syst Rev. Mar 22 2017;3:Cd010803. PMID 28328043

34. Liu Y, He X, Li Y, et al. Cerebrospinal fluid CD4+ T lymphocyte-derived miRNA-let-7b can enhances the diagnostic performance of Alzheimer's disease biomarkers. Biochem Biophys Res Commun. Jan 1 2018;495(1):1144-1150. PMID 29170128
35. Raina P, Santaguida P, Ismaila A, et al. Effectiveness of cholinesterase inhibitors and memantine for treating dementia: evidence review for a clinical practice guideline. Ann Intern Med. Mar 4 2008;148(5):379-397. PMID 18316756
36. Kaduszkiewicz H, Zimmermann T, Beck-Bornholdt HP, et al. Cholinesterase inhibitors for patients with Alzheimer's disease: systematic review of randomised clinical trials. BMJ. Aug 6 2005;331(7512):321-327. PMID 16081444
37. McShane R, Areosa Sastre A, Minakaran N. Memantine for dementia. Cochrane Database Syst Rev. Apr 19 2006(2):CD003154. PMID 16625572
38. Schneider LS, Mangialasche F, Andreasen N, et al. Clinical trials and late-stage drug development for Alzheimer's disease: an appraisal from 1984 to 2014. J Intern Med. Mar 2014;275(3):251-283. PMID 24605808
39. Feldman HH, Ferris S, Winblad B, et al. Effect of rivastigmine on delay to diagnosis of Alzheimer's disease from mild cognitive impairment: the InDDEx study. Lancet Neurol. Jun 2007;6(6):501-512. PMID 17509485
40. Winblad B, Gauthier S, Scinto L, et al. Safety and efficacy of galantamine in subjects with mild cognitive impairment. Neurology. May 27 2008;70(22):2024-2035. PMID 18322263
41. Petersen RC, Thomas RG, Grundman M, et al. Vitamin E and donepezil for the treatment of mild cognitive impairment. N Engl J Med. Jun 9 2005;352(23):2379-2388. PMID 15829527
42. Levy S, McConville M, Lazaro GA, et al. Competitive ELISA studies of neural thread protein in urine in Alzheimer's disease. J Clin Lab Anal. Jan 2007;21(1):24-33. PMID 17245761
43. Zhang J, Zhang CH, Li RJ, et al. Accuracy of urinary AD7c-NTP for diagnosing Alzheimer's disease: a systematic review and meta-analysis. J Alzheimers Dis. Dec 2014;40(1):153-159. PMID 24346218
44. Goodman I, Golden G, Flitman S, et al. A multi-center blinded prospective study of urine neural thread protein measurements in patients with suspected Alzheimer's disease. J Am Med Dir Assoc. Jan 2007;8(1):21-30. PMID 17210499
45. McKhann G, Drachman D, Folstein M, et al. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology. Jul 1984;34(7):939-944. PMID 6610841
46. Vanderstichele H, Bibl M, Engelborghs S, et al. Standardization of preanalytical aspects of cerebrospinal fluid biomarker testing for Alzheimer's disease diagnosis: a consensus paper from the Alzheimer's Biomarkers Standardization Initiative. Alzheimers Dement. Jan 2012;8(1):65-73. PMID 22047631
47. Cordell CB, Borson S, Boustani M, et al. Alzheimer's Association recommendations for operationalizing the detection of cognitive impairment during the Medicare Annual Wellness Visit in a primary care setting. Alzheimers Dement. Mar 2013;9(2):141-150. PMID 23265826
48. Herukka SK, Simonsen AH, Andreasen N, et al. Recommendations for cerebrospinal fluid Alzheimer's disease biomarkers in the diagnostic evaluation of mild cognitive impairment. Alzheimers Dement. Mar 2017;13(3):285-295. PMID 28341066
49. Blue Cross Blue Shield Association. Medical Policy Reference Manual, No. 2.04.14 (December 2019).

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. Inclusion or exclusion of codes does not constitute or imply member coverage or provider reimbursement.

IE
The following services may be considered investigational.

Type	Code	Description
CPT®	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
02/01/2020	Annual review. No change to policy statement. Literature review updated.

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 (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.

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.