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-beta 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-beta 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-beta 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 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 β-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., β-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-β peptide such as 1-42 (Aβ42). Other potential
CSF³⁴ and serum⁵ 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. Aβ42 is a subtype of amyloid-β peptide produced from metabolism of
amyloid precursor protein. Aβ42 is the key peptide deposited in amyloid plaques characteristic
of AD. Low levels of Aβ42 in the CSF have been associated with AD, perhaps because Aβ42 is deposited in amyloid plaques instead of remaining in fluid. Investigators have suggested that the tau/Aβ42 ratio may be a more accurate diagnostic marker than either alone. A variety of kits are commercially available to measure Aβ42 and tau proteins. Between-laboratory variability in CSF biomarker measurement is large.

Neural thread protein is associated with neurofibrillary tangles of AD. Both CSF and urine levels of this protein have been investigated as a potential marker of AD. Urine and CSF tests for neural thread protein may be referred to as the AD7C test.

**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.

**Biomarker Testing**

**Clinical Context and Test Purpose**

The purpose of testing for Alzheimer disease (AD)-related biomarkers in patients who have AD or mild cognitive impairment (MCI) is to improve diagnostic accuracy or to predict conversion from MCI to AD.

The question addressed in this evidence review is: Does cerebrospinal fluid (CSF) biomarker or urinary biomarker testing improve the net health outcome in individuals with AD or MCI?

The following Patients, Interventions, Comparators, Outcomes, Timing, and Setting (PICOTS) were used to select literature to inform this review.

**Patients**

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

**Interventions**

The relevant interventions are cerebrospinal fluid (CSF) biomarker testing and urinary biomarker testing for AD.

**Comparators**

The diagnosis of AD or MCI is currently made based on expert clinical evaluation.

**Outcomes**

The relevant general outcomes of interest are test accuracy and validity, symptoms, change in disease status, morbid events, functional outcomes, quality of life, medication use, and resource utilization.

The outcome of primary interest is a biomarker test with high sensitivity and specificity for the diagnosis of AD or MCI. An additional outcome of interest is a biomarker test that would predict risk for progression from MCI to AD. False-positive test results can lead to recommendations for unnecessary further diagnostic testing and inappropriate or futile interventions as well as psychosocial harms. False-negative test results can lead to pursuit of further low-yield diagnostic testing and delay of appropriate interventions.

**Timing**

The biomarker testing might be used when the clinical evaluation of AD or MCI is uncertain. A confirmation of a diagnosis of AD or MCI requires 6 to 12 months of clinical surveillance.
Setting
Biomarker testing would be used in the specialty care or setting.

Cerebrospinal Fluid Biomarker Testing
Technically Reliable
The technical reliability of a test is its ability to accurately and reliably measure the marker of interest. Measures of technical reliability include sensitivity (detection rate), specificity (1− false-positive rate), reliability (repeatability of test results), and assay robustness (resistance to small changes in preanalytic or analytic variables). Measurements of the CSF concentrations of the amyloid-β peptide 1-42 (Aβ42), total tau protein (tTau), and phosphorylated (pTau) have high variability across different laboratories and across different analytic platforms. Shaw et al (2011) reported on a 7-center interlaboratory standardization study using Alzheimer Disease Neuroimaging Initiative participants for CSF Aβ42, tTau, and pTau measures with a within-laboratory percent coefficient of variation (CV) ranging from 5.3% to 10.8% and interlaboratory percent CV ranging from 13.1% to 17.9%.9 Lewczuk et al (2006) compared CSF Aβ-42, tTau, and pTau measurements across 14 laboratories in Germany, Austria, and Switzerland, with interlaboratory percent CV of 20% to 30%.10 Venney et al (2009) reported an interlaboratory percent CV of 37%, 16%, and 15% for CSF Aβ42, tTau, and pTau, respectively, and a within-laboratory percent CV of 25%, 18%, and 7%.11 Monge-Argilés et al (2014) found that enzyme-linked immunosorbent assay and a multiplex (xMAP) technology for measurement of CSF Aβ42, tTau, and pTau yielded different absolute values for the various analytes, always higher in enzyme-linked immunosorbent assay, although the values were highly correlated.12 Mattsson et al (2011) reported on results of an external quality control program for CSF biomarkers.8 Forty laboratories using commercially available kits for Aβ, tTau, or pTau were sent CSF samples for analysis several times a year from a central source. Total CVs between the laboratories were ranged from 13% to 36%.

Clinically Valid
Diagnosis of AD
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.13 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 (QUADAS-2) tool. Publication bias was detected. A summary receiver operating characteristic curve was generated from all reported thresholds. Pooled sensitivity and specificity were 84% (95% confidence interval [CI], 81% to 85%) and 79% (95% CI, 77% to 81%), respectively. Positive and negative likelihood ratios were 4.5 (95% CI, 3.7 to 5.4) and 0.18 (95% CI, 0.14 to 0.22), respectively; and their ratio, the diagnostic odds ratio, was 29 (95% CI, 21 to 40). Statistical heterogeneity was substantial (I²=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 (I²=99%).

Ferreira et al (2014)14 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 criteria15 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. Results for both the systematic reviews and the individual studies are summarized in Table 1. For differentiating AD from nondemented controls, positive and negative likelihood ratios for all 3 biomarkers ranged from 4 to 8 and from 0.1 to 0.3, respectively. For differentiating AD from other dementias, a 2011 systematic review of 7 studies reported positive and negative likelihood ratios of 46 and 0.09, respectively, for differentiating AD (n=175) from Creutzfeldt-jakob disease (n=110).16 With this systematic review excluded, positive and negative likelihood ratios ranged from 2 to 7 and from 0.15 to 0.4, respectively.

Cure et al (2014) conducted a systematic review with meta-analysis of CSF and imaging studies for the diagnosis of definite AD (autopsy-confirmed).17 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 the receiver operating characteristic curve, constructed using multiple test thresholds, was 0.84.

A 2011 meta-analysis included 119 studies on biomarkers and diagnostic imaging in AD.18 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 total tau was evaluated in 30 studies with a resulting sensitivity of 79% (95% CI, 75% to 83%) and specificity of 85% (95% CI, 81% to 89%). CSF pTau was evaluated in 24 studies, resulting in a pooled sensitivity of 78% (95% CI, 73% to 83%) and specificity of 81% (95% CI, 76% to 85%). Six studies evaluated CSF pTau as a biomarker to distinguish patients with AD from patients with MCI, with a pooled sensitivity of 73% (95% CI, 54% to 86%) and specificity of 69% (95% CI, 53% to 82%). The combination of total tau and 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 the receiver operating characteristic curve was highest for pTau alone (0.85; 95% CI, 82 to 88). Study heterogeneity was due to the use of different test thresholds and different assay kits. Sensitivity analysis including studies that used autopsy as the reference standard for pTau resulted in slightly higher sensitivity (82%; 95% CI, 75% to 87%) and lower specificity (57%; 95% CI, 37% to 75%).

In a 2006 review of studies using clinical diagnosis as the criterion standard, Formichi et al identified studies examining diagnostic accuracy of the following CSF markers for AD: tTau (41 studies; 2287 AD patients, 1384 controls; sensitivity, 52%-100%; specificity, 50%-100%), p Tau (12 studies; 760 AD patients, 396 controls; sensitivity, 37%-100%; specificity, 80%-100%), and Aβ42 (14 studies; 688 AD patients, 477 controls; sensitivity, 55%-100%; specificity, 80%-100%).19 Although primarily a descriptive review, test accuracies varied widely, and only 1 study included a majority of autopsy-confirmed AD diagnoses.

| Table 1. CSF Biomarkers Performance for Distinguishing Alzheimer Disease From Controls With Clinical Diagnosis as the Reference Standard |
|---|---|---|---|---|---|---|
| Biomarkers Studies | Study Type | Nondemented Controls, % | Controls With Dementia, % |
| | | Sensitivity | Specificity | Sensitivity | Specificity |
| Aβ42 | Ferreira et al (2014) | Systematic review | 80 (73 to 85) | 82 (74 to 88) | 73 (67 to 78) | 67 (62 to 72) |
| | Rosa et al (2014) | 84 (81 to 85) | 79 (77 to 81) | NR | NR |
| | Bloudek et al (2011) | 80 (73 to 85) | 82 (74 to 88) | 73 (67 to 78) | 67 (62 to 72) |
| | Formichi et al (2006) | NR | NR | 55-100 | 80-100 |
| tTau | Ferreira et al (2014) | Systematic review | 82 (76 to 87) | 90 (86 to 93) | 73-91 | 75-98 |
### Biomarkers Studies

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

**Aβ42:** amyloid-β peptide 1-42; **CSF:** cerebrospinal fluid; **NR:** not reported; **pTau:** phosphorylated tau protein; **tTau:** total tau protein.

### In a 2017 report, Howell et al 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. 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 that the tau/Aβ42 ratio is a more accurate predictor than either marker alone. For example, using optimal cutoffs, de Jong et al (2006) reported a sensitivity and a specificity of 95% and 90%, respectively, in a sample with clinically diagnosed AD (n=61) and vascular dementia (n=61). 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%.

### A 2017 multicenter study by Park et al 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. 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 (Aβ42), 326 pg/mL (tTau), 57 pg/mL (pTau), with improved tTau/Aβ42 ratios (0.55; sensitivity, 99%; specificity, 95%) and pTau/Aβ42 (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/Aβ42) being more accurate than those of individual proteins (i.e., Aβ42=478 pg/mL, tTau=327 pg/mL, pTau=48 pg/mL, [sensitivity range, 83%–93% specificity range, 70%–85%] vs tTau/Aβ42=0.76 [sensitivity, 93%; specificity, 92%]; and pTau/Aβ42=0.12 [sensitivity, 95%; specificity, 89%]). Additionally, area under the curve measurements showed greater accuracy in ratios (tTau/Aβ42 and pTau/ Aβ42) 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., tau, pTau, Aβ42). Using 0.05 as the ratio threshold, biologic profiles were determined in 72 (59%) of 122 patients.
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.25

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.26 Levels of both tau protein 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.

Subsection Summary: Clinical Validity of Cerebrospinal Fluid 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 2 to 8 and 0.2 to 0.4, respectively, in either setting. A multicenter study found higher sensitivity and specificity for ratios (tTau/Aβ42 and pTau/Aβ42) 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 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 progression of MCI and conversion to clinically manifest AD.

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. Sensitivity ranged from 36% to 100%, and specificity from 29% to 91%. Due to heterogeneity of thresholds used, summary sensitivity and specificity were not calculated. However, a summary receiver operating characteristic curve was generated using the median specificity of 64%; pooled sensitivity was 81% (95% CI, 72% to 87%). 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. Analysis of the pre- and posttest 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 2014 meta-review of systematic reviews by Ferriera et al (previously discussed) included studies of CSF biomarkers for differentiating patients with MCI who progressed to AD from those who did not.14 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 3 tests ranged from 2 to 3 and from 0.3 to 0.5, respectively.

In 2016, Olsson et al performed a comprehensive systematic review and meta-analysis of 231 articles including 15,699 patients with AD and 13,018 controls, published between 1984 and 2014,
which described both diagnostic and prognostic performance of CSF biomarkers. 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 were not reported due to 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 2 years of follow-up. A fold change ratio above 1 indicates that the concentration of the biomarker is higher in the AD population than in the control population, and a ratio below 1 indicates that the concentration is higher in the control population than in the AD population. Summary fold change was calculated with randomeffects meta-analysis. CSF tTau, pTau, and Aβ42 levels were consistently and strongly associated with AD diagnosis: CSF tTau average ratio was 2.54 (95% CI, 2.44 to 2.64); pTau average ratio was 1.88 (95% CI, 1.79 to 1.97); and Aβ42 average ratio was 0.56 (95% CI, 0.55 to 0.58). 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. Estimated sensitivity was reported for CSF t-tau and CSF p-tau, respectively: 75% (95% CI, 67% to 85%) and 81% (95% CI, 64% to 91%). Seven studies involved CSF t-tau and showed sensitivity and specificity rates ranging from 51% to 90% and from 48% to 88% respectively; 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 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.

Subsection Summary: Clinical Validity of Cerebrospinal Fluid 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 consequence are estimable. To evaluate the benefits and consequences of CSF biomarker interventions, models would need to describe disease progression, resources use, and quality of life. 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. Memantine, an N-methyl-D-aspartate receptor antagonist, appears to provide a small benefit in treating symptoms in those with moderate-to-advanced disease. Neither cholinesterase inhibitors nor memantine is disease-modifying.
Given available therapies, in principle, more accurate diagnosis might allow targeting treatment to those most likely to benefit. However, clinical trial entry criteria and benefit have been based on clinical diagnosis. There is less evidence to support use of cholinesterase inhibitors in other dementias, but they are still frequently used to treat cognitive symptoms. While the possibility that 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. The chain of evidence of clinical utility is incomplete.

Section Summary: Cerebrospinal Fluid Marker 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 quality of life.

Urinary Biomarker Testing
Technically Reliable
Searches have identified a single publication describing components of technical reliability for a competitive enzyme-linked immunosorbent assay format affinity assay to measure NTP in urine samples. Seven hundred twenty replicates were assayed at 4 clinical laboratories by 4 different trained personnel, on 3 different days each, consisting of high, medium, and low-NTP urines in 20 replicates each per day. The CVs were reported to vary from 2.3% to 7.1% in high-NTP urine, from 1.5% to 8.5% in medium-NTP urine, and from 2.5% to 15% in low-NTP urine. Between- and within-laboratory variation were not reported. Three lots of high-, medium-, and low-NTP controls were tested in 4 replicates each for 3 days. The CVs varied from 4.3% to 8.6%. Twenty replicates of low-NTP urine samples were spiked with known concentrations of NTP to 18.9, 23.9, 28.9, 33.9, and 38.9 mg/mL; mean recovery was 105.5%.

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. 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 clinical diagnosis in 8 studies and not described in another. Varying cutoffs for positive diagnosis were used across included studies. Controls were both health 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.

In a prospective multicenter study conducted at 8 sites, Goodman et al (2007) enrolled 168 patients with recent referrals to memory clinics. 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. Cutoff 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 who receive cerebrospinal fluid biomarker testing for AD, the evidence includes systematic reviews, meta-analyses, and case
series. Relevant outcomes are symptoms, change in disease status, morbid events, functional outcomes, quality of life, medication use, and resource utilization. The technical reliability of cerebrospinal fluid biomarker measurement in AD is limited by variability between laboratories and assay methods. 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 mild cognitive impairment to AD, limited evidence has suggested that testing may define increased risk. Whether an earlier diagnosis leads to improved health outcomes through delay of AD onset due to medical therapy or other interventions or improved quality of life is unknown. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have AD or mild cognitive impairment who receive urinary biomarker testing for AD, the evidence includes a systematic review and observational studies. Relevant outcomes are symptoms, change in disease status, morbid events, functional outcomes, quality of life, medication use, and resource utilization. Limited data are available on the technical reliability of urinary biomarker measurement in AD. 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 delay of AD onset or improved quality of life 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

In 1984, National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and Alzheimer Disease and Related Disorders Association (ADRDA) developed clinical criteria for the diagnosis of Alzheimer disease (AD). 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.

In the 1984 guidelines, the diagnostic categories were defined as summarized in Table 2.

<table>
<thead>
<tr>
<th>Table 2. The 1984 Diagnostic Categories for Alzheimer Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Possible</strong></td>
</tr>
<tr>
<td>Clinical diagnosis of possible AD:</td>
</tr>
<tr>
<td>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.</td>
</tr>
<tr>
<td>B. May be made in the presence of a second systemic or brain disorder sufficient to produce dementia, which is not considered to be the cause of the dementia.</td>
</tr>
<tr>
<td>C. Should be used in research studies when a single gradually progressive severe cognitive deficit is identified in the absence of other identifiable cause.</td>
</tr>
<tr>
<td><strong>Probable</strong></td>
</tr>
<tr>
<td>Criteria for the clinical diagnosis of probable AD included:</td>
</tr>
<tr>
<td>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;</td>
</tr>
<tr>
<td>B. Deficits in 2 or more areas of cognition;</td>
</tr>
<tr>
<td>C. Progressive worsening of memory and other cognitive functions;</td>
</tr>
<tr>
<td>D. No disturbance of consciousness;</td>
</tr>
<tr>
<td>E. Onset between ages 40 and 90 years, most often after the age of 65 years; and</td>
</tr>
<tr>
<td>F. Absence of systemic disorders or other brain diseases that in and of themselves could account for the progressive deficits in memory and cognition.</td>
</tr>
<tr>
<td>Other clinical features consistent with the diagnosis of probable AD, after exclusion of causes of dementia other than AD, include</td>
</tr>
</tbody>
</table>

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Diagnostic Categories for AD

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:

“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. 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.”

All probable AD by NINCDS-ADRDA criteria are 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 pathophysiologic 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.” 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.”

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.” 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.

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. The recommended algorithm for cognitive assessment was based on “current validated tools and commonly used rule-out assessments.” Guidelines noted that use of biomarkers (e.g., CSF tau and β-amyloid proteins) “was not considered as these measures are not currently approved or widely available for clinical use.”

EU Joint Program-Neurodegenerative Disease Research
In 2017, the EU Joint Program-Neurodegenerative Disease Research sponsored a meta-review with accompanying recommendations on the performance of CSF biomarkers of AD, compared with clinical measures or other biomarkers. Minimal data from the individual systematic reviews and meta-analyses were discussed; instead, using the GRADE method, the consensus group rated the studies based on their relevance to 6 predetermined clinical questions. Of these questions, two were key, assessing the efficacy of cerebrospinal fluid in (1) determining whether mild cognitive impairment is caused by AD, and (2) predicting the decay of cognitive ability and/or the onset of AD dementia; for all questions, CSF was compared with clinical factors and a number of known biomarkers. The absence of follow-up data made any conclusive answer to the first question impossible. For the second question, the consensus group strongly recommended CSF biomarkers over clinical measures alone; however, insufficient data precluded a strong recommendation of CSF over other biomarkers. The group offered additional recommendations regarding appropriate cutoff points for levels of Aβ42, and pre- and posttesting counseling to address the possible implications of biomarkers.

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 unpublished trials that might influence this review are listed in Table 3.

Table 3. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
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<tbody>
<tr>
<td>Ongoing</td>
<td>Discovery of Novel Biomarkers That Will Lead to the Early Detection of Alzheimer's Disease</td>
<td>220</td>
<td>Apr 2019</td>
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<tr>
<td>NCT03136679</td>
<td>A Double Blind, Randomized, Placebo Controlled, Parallel Group Study to Simultaneously Qualify 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</td>
<td>3494</td>
<td>Jul 2019</td>
</tr>
<tr>
<td>NCT03287765</td>
<td>Evaluating the Relationship Between Tau PET Imaging and CSF Biomarkers of AD in Humans</td>
<td>80</td>
<td>May 2021</td>
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<tr>
<td>NCT02612376</td>
<td>Rocky Mountain Alzheimer's Disease Center Longitudinal Biomarker and Clinical Phenotyping Study</td>
<td>800</td>
<td>Dec 2030</td>
</tr>
<tr>
<td>Unpublished</td>
<td>Effect of Insulin Sensitizer Metformin on AD Biomarkers</td>
<td>20</td>
<td>Sep 2017</td>
</tr>
</tbody>
</table>

References


### 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 a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement.

### IE

The following services may be considered investigational.

<table>
<thead>
<tr>
<th>Type</th>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT®</td>
<td>81099</td>
<td>Unlisted urinalysis procedure</td>
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<tr>
<td></td>
<td>83520</td>
<td>Immunoassay for analyte other than infectious agent antibody or infectious agent antigen; quantitative, not otherwise specified</td>
</tr>
<tr>
<td></td>
<td>86849</td>
<td>Unlisted immunology procedure</td>
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<tr>
<td>HCPCS</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>ICD-10 Procedure</td>
<td>None</td>
<td>All Diagnoses</td>
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</table>

### Policy History

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

<table>
<thead>
<tr>
<th>Effective Date</th>
<th>Action</th>
<th>Reason</th>
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</thead>
<tbody>
<tr>
<td>04/02/2010</td>
<td>New policy Policies combined:</td>
<td>Medical Policy Committee</td>
</tr>
<tr>
<td></td>
<td>• Apolipoprotein E Epsilon (apoE) 4 Allele and Alzheimer's Disease: Role for Genetic Testing for Diagnosis and Risk Management</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Cerebrospinal Fluid and Urinary Assays of Neuronal (Neural) Thread Protein in the Diagnosis of Alzheimer's Dementia</td>
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<tr>
<td>04/19/2012</td>
<td>Added documentation required for clinical review</td>
<td>Administrative Review</td>
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<tr>
<td>02/22/2013</td>
<td>Coding Update</td>
<td>Administrative Review</td>
</tr>
<tr>
<td>02/27/2015</td>
<td>Policy title change from Alzheimer's Disease - Genetic and Biochemical Testing Policy revision without position change</td>
<td>Medical Policy Committee</td>
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<tr>
<td>02/01/2017</td>
<td>Policy title change from Biochemical Markers of Alzheimer Disease Policy revision without position change</td>
<td>Medical Policy Committee</td>
</tr>
<tr>
<td>02/01/2018</td>
<td>Policy revision without position change</td>
<td>Medical Policy Committee</td>
</tr>
</tbody>
</table>
**Definitions of Decision Determinations**

**Medically Necessary:** A treatment, procedure, or drug is medically necessary only when it has been established as safe and effective for the particular symptoms or diagnosis, is not investigational or experimental, is not being provided primarily for the convenience of the patient or the provider, and is provided at the most appropriate level to treat the condition.

**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. Please call (800) 541-6652 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.