**Policy Statement**

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

I. Tau protein  
II. Amyloid beta peptides  
III. Neural thread proteins

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

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

**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-β 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

**Effective October 1, 2020**, there is a new CPT code that represents DISCERN™ by NeuroDiagnostics. Per the manufacturer, the Discem skin biopsy test can differentiate Alzheimer Disease from non-AD dementias. This service may have been previously billed with 86849-Unlisted immunology procedure. Fibroblasts are cultured from a skin biopsy and subjected to morphological aggregation examination which is then scored.

- **0206U**: Neurology (Alzheimer disease); cell aggregation using morphometric imaging and protein kinase C-epsilon (PKCe) concentration in response to amylopherooid treatment by ELISA, cultured skin fibroblasts, each reported as positive or negative for Alzheimer disease

**Effective October 1, 2020**, there is a new CPT code that represents a child code to 0206U. Phosphorylation of ERK1 and ERK2 in skin biopsy fibroblasts is measured in response to bradykinin treatment using in situ immunofluorescence and quantitative imaging.
• **0207U**: Neurology (Alzheimer disease); quantitative imaging of phosphorylated ERK1 and ERK2 in response to bradykinin treatment by in situ immunofluorescence, using cultured skin fibroblasts, reported as a probability index for Alzheimer disease (List separately in addition to code for primary procedure)

## 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-β 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 (CLIA). AlzheimAlert™ and AdMark® CSF analysis are available under the auspices of CLIA. Laboratories that offer laboratory-developed tests must be licensed by CLIA 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

**Biomarkers**

Several potential biomarkers of Alzheimer disease (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. These 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 CSF and serum 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 the metabolism of the 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 the fluid. Investigators have suggested the
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.

**Alzheimer Disease**

The diagnosis of Alzheimer disease (AD) is divided into 3 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.

**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. MCI is characterized by impairment in 1 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.

**Clinical Context and Test Purpose**

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

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

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

**Populations**

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

**Interventions**

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

**Comparators**

Comparators of interest include a 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 diagnosis accuracy, correct treatment, avoiding unnecessary subsequent testing, harms of invasive testing, and quality of life (QOL) for testing to diagnose AD. For testing to predict progression of MCI, the outcomes of interest are correct treatment, avoiding unnecessary subsequent testing, harms of invasive testing, and QOL.

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

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

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.

Cerebrospinal Fluid Biomarker Testing
Diagnosis of Alzheimer Disease

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 amyloid-β 1-42 (Aβ42) in patients with clinically diagnosed AD. 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 controls without dementia). 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) 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 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 controls with dementia and controls without dementia were available only from Bloudek et al (2011) and are found in Table 1. For differentiating AD from controls without dementia, 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 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). With this systematic review excluded, positive and negative likelihood ratios ranged from 2 to 7 and from 0.15 to 0.4, respectively.

A meta-analysis by Bloudek et al (2011) included 119 studies on biomarkers and diagnostic imaging in AD. Sensitivity and specificity were calculated for distinguishing AD from controls without dementia, and for distinguishing AD from non-AD dementias with and without MCI, if available. Selected studies of CSF biomarkers used a variety of thresholds, with clinical diagnosis or autopsy as the reference standard. Twenty studies of the Aβ42 CSF marker were included with controls without dementia and patients with dementia; pooled analysis resulted in a sensitivity of 76% (95% CI, 72% to 80%) and a specificity of 77% (95% CI, 72% to 82%). CSF 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; 2,287 AD patients, 1,384 controls), pTau (12 studies; 760 AD patients, 396 controls), and Aβ42 (14 studies; 688 AD patients, 477 controls). Sensitivity and specificity for the biomarkers can be found in Table 1. Although primarily a descriptive review, test accuracies varied widely, and only 1 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      | Controls Without Dementia, % | Controls With Dementia, % |
| Aβ42            | Sensitivity     | Specificity     | Sensitivity     | Specificity     |
| 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            | Bloudek et al (2011) | 82 (76 to 87) | 90 (86 to 93) | 78 (72 to 83) | 75 (68 to 81) |
| Formichi et al (2006) | NR              | NR              | 52-100          | 50-100          |
| pTau            | Ferreira et al (2014) | 78-80            | 83-88          | 72-88          | 78-83          |
### Biomarkers Studies

<table>
<thead>
<tr>
<th></th>
<th>Controls Without Dementia, %</th>
<th>Controls With Dementia, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bloudek et al (2011)</td>
<td>80 (70 to 87)</td>
<td>83 (75 to 88)</td>
</tr>
<tr>
<td>Formichi et al (2006)</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

Values in parentheses are 95% confidence intervals.

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

a Or unspecified.

Fink et al (2020) conducted a systematic review of biomarker accuracy for diagnosing neuropathologically defined AD in older patients with dementia. The analysis included literature published between January 2012 and November 2019, with 9 cohort studies focusing on CSF biomarkers. Overall, CSF biomarkers and ratios had moderate sensitivity (range, 62% to 83%) and specificity (range, 53% to 69%). Biomarker accuracy was higher with Aβ42/pTau ratio, tTau/Aβ42 ratio, and pTau compared with tTau alone.

Cure et al (2014) conducted a systematic review with meta-analysis of CSF and imaging studies for the diagnosis of definite AD (autopsy-confirmed). 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 (patients without dementia or patients with dementia due to other causes), and test thresholds. The summary area under receiver operating characteristic curve, constructed using multiple test thresholds, was 0.84.

### Prospective and Retrospective 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. 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.

Wang et al (2018) conducted a longitudinal study of whether the addition of total and phosphorylated α-synuclein to the AD biomarker panel improves the panel's performance. 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 α-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.

### Subsection Summary: Clinical Validity of CSF Biomarker Testing for Diagnosis of Alzheimer Disease

Several studies have examined the diagnostic performance of CSF biomarkers for distinguishing patients with probable AD from patients without dementia and from patients with other types of dementia. The range of reported sensitivities and specificities is broad compared with a clinical diagnosis reference standard; in systematic reviews with meta-analyses, sensitivity and specificity rates ranged from 80% to 82% and 82% to 90%, respectively, for differentiating AD from healthy controls, and were 73% and 67%, respectively, for differentiating AD from other dementias. Positive and negative likelihood ratios were 2 to 8 and 0.2 to 0.4, respectively, in either setting. Some evidence points that ratios (Aβ42/pTau or tTau/Aβ42) or pTau may have higher accuracy than tTau alone. There is limited evidence examining the incremental diagnostic accuracy of CSF biomarkers for AD diagnosis employing autopsy as a criterion standard. Cutoffs for a positive diagnosis are not standardized.
Prognosis for Progression of Mild Cognitive Impairment

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. Literature was searched in December 2012, and 14 prospective or retrospective cohort studies of AD were included (1,349 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. 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.

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. 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 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 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. 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 7 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 pTau /Aβ 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 tTau /Aβ 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.
Reviewer included studies with considerable heterogeneity, and in some cases, poor methodologic quality.

Tables 2 and 3 do not include Ferreria (2014)\textsuperscript{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

<table>
<thead>
<tr>
<th>Study</th>
<th>Dates</th>
<th>Studies</th>
<th>Participants</th>
<th>Design</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olsson (2016)\textsuperscript{2a}</td>
<td>1995-2014</td>
<td>231</td>
<td>Patients with AD or MCI due to AD.</td>
<td>AD=15,699 Controls=13,018 Total=27,717 (Range=20-1087)</td>
<td>Not specified</td>
</tr>
<tr>
<td>Ritchie (2017)\textsuperscript{12}</td>
<td>2006-2013</td>
<td>15</td>
<td>Patients with MCI at baseline.</td>
<td>N=1,282</td>
<td>Longitudinal cohort 2 mo-11.8 y</td>
</tr>
<tr>
<td>Ritchie (2014)\textsuperscript{13}</td>
<td>2003-2013</td>
<td>17</td>
<td>Participants with cognitive decline but no dementia condition at baseline.</td>
<td>Total=2,228 (Range=37-588)</td>
<td>Longitudinal cohort 2 mo-12 y</td>
</tr>
</tbody>
</table>

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

### Table 3. Results of Key Meta-Analyses

<table>
<thead>
<tr>
<th>Study</th>
<th>Aβ42</th>
<th>t\textsuperscript{2}tau</th>
<th>p\textsuperscript{3}tau</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olsson (2016)\textsuperscript{2a}</td>
<td>Average ratio (95% CI)</td>
<td>0.56 (0.55 to 0.58)</td>
<td>2.54 (2.44 to 2.64)</td>
</tr>
<tr>
<td></td>
<td>P value</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Ritchie (2017)\textsuperscript{12}</td>
<td>Sensitivity range, %</td>
<td>-</td>
<td>51-90</td>
</tr>
<tr>
<td></td>
<td>Specificity range, %</td>
<td>-</td>
<td>48-88</td>
</tr>
<tr>
<td></td>
<td>Median specificity, %</td>
<td>-</td>
<td>72</td>
</tr>
<tr>
<td></td>
<td>Sensitivity at median specificity, % (95% CI)</td>
<td>-</td>
<td>75 (67 to 85)</td>
</tr>
<tr>
<td>Ritchie (2014)\textsuperscript{13}</td>
<td>Sensitivity range, %</td>
<td>36-100</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Specificity range, %</td>
<td>29-91</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Median specificity, %</td>
<td>64</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Sensitivity at median specificity, % (95% CI)</td>
<td>81 (72 to 87)</td>
<td>-</td>
</tr>
</tbody>
</table>

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; p\textsuperscript{3}tau: phosphorylated tau protein; t\textsuperscript{2}tau: total tau protein.

### Prospective and Retrospective 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), p\textsuperscript{3}tau/Aβ(1-42), and t\textsuperscript{2}tau/Aβ(1-42) could be used to develop global cutoffs that are transferable across populations, even when CSF samples were analyzed in different laboratories.\textsuperscript{22} 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 1 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 MCI 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 p\textsuperscript{3}tau/Aβ(1-42) and t\textsuperscript{2}tau/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 1 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.

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

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

**Section Summary: Cerebrospinal Fluid 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**

**Clinically Valid**

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

Zhang et al (2014) conducted a systematic review and meta-analysis of urinary AD-associated neural thread protein (NTP) for diagnosing AD in patients with suspected AD. Nine studies were included (total n=841 patients with probable or possible AD; 37 patients with MCI, 992 with non-AD dementia or controls without dementia). The reference standard was a clinical diagnosis in 8 studies and not described in another. Varying cutoffs for positive diagnosis were used across included studies. Controls were both healthy volunteers and patients with other dementias. For probable AD, pooled sensitivity and specificity were 89% (95% CI, 86% to 92%) and 90% (95% CI,
88% to 92%), respectively. Pooled positive and negative likelihood ratios were 8.9 (95% CI, 7.1 to 11.1) and 0.12 (95% CI, 0.09 to 0.16), respectively.

**Clinically Useful**

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

**Section Summary: Urinary Marker Testing**

Limited data on the technical reliability of urine NTP markers are available. Studies of clinical validity include both patients with dementia and controls without dementia. 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 (CSF) biomarker testing for AD, the evidence includes systematic reviews and prospective and retrospective studies. These studies assess using CSF biomarkers for diagnosis of AD or for the prognosis of progression of MCI to AD. Relevant outcomes include diagnosis accuracy, correct treatment, avoiding unnecessary subsequent testing, harms of invasive testing, and quality of life (QOL). Most clinical validity studies have been derived from select patient samples and defined optimal test cutoffs without validation; thus, the generalizability of results is uncertain. For predicting conversion from MCI to AD, limited evidence has suggested that testing may define increased risk. Whether an earlier diagnosis leads to improved health outcomes through a delay of AD onset due to medical therapy or other interventions or improved QOL is unknown. The evidence is insufficient to determine that the technology results in an improvement in the net health outcomes.

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

**Supplemental Information**

**Practice Guidelines and Position Statements**

**National Institute of Aging**

**2011 Revised Diagnostic Criteria**

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

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.

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

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

Additionally, a category "Probable AD dementia with evidence of the AD pathophysiological process" has been added. Evidence of the AD pathophysiologic process is supported by detection of low cerebrospinal fluid (CSF) amyloid-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. Biomarker evidence in cases of probable AD may increase the certainty that the dementia is due to AD pathophysiological process.

Note on the 2011 Revised Criteria and Biomarkers

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

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

In 2018, the Alzheimer’s Association published appropriate use criteria for lumbar puncture and CSF testing for AD. Table 4 summarizes the indications for these practices.

### Table 4. Indications for Appropriate Use of Lumbar Puncture and CSF Testing in Diagnosing AD

<table>
<thead>
<tr>
<th>Appropriate Indications</th>
<th>Inappropriate Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with SCD who are considered at increased risk for AD</td>
<td>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</td>
</tr>
<tr>
<td>MCI that is persistent, progressing, and unexplained</td>
<td>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</td>
</tr>
<tr>
<td>MCI or dementia with an onset at an early age (&lt;65 y)</td>
<td>Patients with SCD who are not considered to be at increased risk for AD</td>
</tr>
<tr>
<td>Meeting core clinical criteria for probable AD with typical age of onset</td>
<td>Use to determine disease severity in patients having already received a diagnosis of AD</td>
</tr>
<tr>
<td>Patients with symptoms that suggest possible AD</td>
<td>Individuals who are apolipoprotein E (APOE) ε4 carriers with no cognitive impairment</td>
</tr>
<tr>
<td>MCI or dementia with an onset at an early age (&lt;65 y)</td>
<td>Use of lumbar puncture in lieu of genotyping for suspected ADAD mutation carriers</td>
</tr>
<tr>
<td>Meeting core clinical criteria for probable AD with typical age of onset</td>
<td>ADAD mutation carriers, with or without symptoms</td>
</tr>
</tbody>
</table>


### National Institute for Health and Care Excellence

In 2018, the National Institute for Health and Care Excellence (NICE) released a guideline on assessment, management, and support for people living with dementia and their carers. The guideline states that in cases of uncertain diagnosis, but highly suspicious for AD, providers can consider examining CSF for total tau or total tau and phosphorylated-tau 181 and either Aβ42 or Aβ42 and Aβ40. People who are older are more likely to receive a false positive with a CSF analysis.

### U.S. Preventive Services Task Force Recommendations

In 2020, the U.S. Preventive Services Task Force released recommendations for screening cognitive impairment in older adults, concluding that the current evidence is insufficient to determine benefits versus harms of screening for cognitive impairment in older adults. The statement discusses that screening tests are not intended to diagnose mild cognitive impairment or dementia, but a positive screening test result should prompt additional testing consisting of blood tests, radiology examinations, and/or medical and neuropsychologic evaluation.

### Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.
Ongoing and Unpublished Clinical Trials
Some currently ongoing and unpublished trials that might influence this review are listed in Table 5.

Table 5. Summary of Key Trials
<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ongoing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT03136679</td>
<td>Discovery of Novel Biomarkers That Will Lead to the Early Detection of Alzheimer's Disease</td>
<td>220</td>
<td>Dec 2022 (recruiting)</td>
</tr>
<tr>
<td>NCT02612376</td>
<td>Rocky Mountain Alzheimer's Disease Center at the University of Colorado School of Medicine (RMADC at UCSOM) Longitudinal Biomarker and Clinical Phenotyping Study</td>
<td>800</td>
<td>Dec 2030 (recruiting)</td>
</tr>
<tr>
<td>Unpublished</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT01642420</td>
<td>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</td>
<td>115</td>
<td>Feb 2017 (status unknown; updated 09/2012)</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.
* Terminated due to lack of drug efficacy.

References


**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.

<table>
<thead>
<tr>
<th>Type</th>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT®</td>
<td>0206U</td>
<td>Neurology (Alzheimer disease); cell aggregation using morphometric imaging and protein kinase C-epsilon (PKCe) concentration in response to amylospheroid treatment by ELISA, cultured skin fibroblasts, each reported as positive or negative for Alzheimer disease <strong>(Code effective 10/1/2020)</strong></td>
</tr>
<tr>
<td></td>
<td>0207U</td>
<td>Neurology (Alzheimer disease); quantitative imaging of phosphorylated ERK1 and ERK2 in response to bradykinin treatment by in situ immunofluorescence, using cultured skin fibroblasts, reported as a probability index for Alzheimer disease <strong>(List separately in addition to code for primary procedure)</strong> <strong>(Code effective 10/1/2020)</strong></td>
</tr>
<tr>
<td></td>
<td>81099</td>
<td>Unlisted urinalysis procedure</td>
</tr>
<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>
</tr>
</tbody>
</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>
</tr>
</thead>
<tbody>
<tr>
<td>04/02/2010</td>
<td>New policy Policies combined:</td>
</tr>
<tr>
<td></td>
<td>- Apolipoprotein E Epsilon (apoE) 4 Allele and Alzheimer's Disease.</td>
</tr>
<tr>
<td></td>
<td>- Role for Genetic Testing for Diagnosis and Risk Management.</td>
</tr>
<tr>
<td></td>
<td>- Cerebrospinal Fluid and Urinary Assays of Neuronal (Neural) Thread</td>
</tr>
<tr>
<td></td>
<td>- Protein in the Diagnosis of Alzheimer's Dementia.</td>
</tr>
<tr>
<td>04/19/2012</td>
<td>Added documentation required for clinical review</td>
</tr>
<tr>
<td>02/22/2013</td>
<td>Coding Update</td>
</tr>
<tr>
<td>02/27/2015</td>
<td>Policy title change from Alzheimer's Disease - Genetic and Biochemical</td>
</tr>
<tr>
<td></td>
<td>- Testing</td>
</tr>
<tr>
<td></td>
<td>- Policy revision without position change</td>
</tr>
<tr>
<td>02/01/2017</td>
<td>Policy title change from Biochemical Markers of Alzheimer Disease.</td>
</tr>
<tr>
<td></td>
<td>- Policy revision without position change</td>
</tr>
<tr>
<td>02/01/2018</td>
<td>Policy revision without position change</td>
</tr>
<tr>
<td>02/01/2019</td>
<td>Policy revision without position change</td>
</tr>
<tr>
<td>02/01/2020</td>
<td>Annual review. No change to policy statement. Literature review updated.</td>
</tr>
<tr>
<td>12/01/2020</td>
<td>Coding update</td>
</tr>
<tr>
<td>02/01/2021</td>
<td>Annual review. No change to policy statement. Literature review updated.</td>
</tr>
<tr>
<td></td>
<td>- Policy title changed from Cerebrospinal Fluid and Urinary Biomarkers of Alzheimer Disease to current one.</td>
</tr>
</tbody>
</table>

### 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 government 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.
### Appendix A

<table>
<thead>
<tr>
<th>POLICY STATEMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BEFORE</strong></td>
</tr>
<tr>
<td><strong>Red font: Verbiage removed</strong></td>
</tr>
<tr>
<td><strong>Cerebrospinal Fluid and Urinary Biomarkers of Alzheimer Disease 2.04.14</strong></td>
</tr>
<tr>
<td><strong>Policy Statement:</strong> Measurement of cerebrospinal fluid biomarkers of Alzheimer disease is considered investigational including but not limited to:</td>
</tr>
<tr>
<td>I. Tau protein</td>
</tr>
<tr>
<td>II. Amyloid beta peptides</td>
</tr>
<tr>
<td>III. Neural thread proteins</td>
</tr>
<tr>
<td>Measurement of urinary biomarkers of Alzheimer disease is considered investigational, including but not limited to neural thread proteins.</td>
</tr>
</tbody>
</table>