Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

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Title: Cerebrospinal Fluid and Urinary Biomarkers of Alzheimer's Disease

Description/Background

Alzheimer Disease

Alzheimer Disease (AD) is a fatal neurodegenerative disease that causes progressive loss in memory, language, and thinking, with the eventual loss of ability to perform social and functional activities in daily life. Survival after a diagnosis of dementia due to AD generally ranges between 4 and 8 years; however, life expectancy can be influenced by other factors, such as comorbid medical conditions. It is estimated that 6.2 million Americans aged 65 and older are currently living with AD dementia, and the number is projected to reach over 12 million by 2050.[1] Per the 2018 American Academy of Neurology practice guideline update on mild cognitive impairment (MCI), the prevalence of MCI was 6.7% for ages 60 to 64, 8.4% for ages 65 to 69, 10.1% for ages 70 to 74, 14.8% for ages 75 to 79, and 25.2% for ages 80 to 84.2, The cumulative dementia incidence was 14.9% in individuals with MCI >65 years of age followed for 2 years.

Pathophysiology

The pathologic hallmarks of AD are extracellular deposits of amyloid beta, referred to as amyloid plaques, and intracellular aggregates of hyperphosphorylated tau in the form of neurofibrillary tangles. There are different forms of amyloid such as plaques, oligomers, and monomers, and the roles of these different forms and their contributions to the pathophysiology of AD is not well understood. Generally referred to as the "amyloid hypothesis", it is believed that aggregation of amyloid beta oligomers in the brain leads to amyloid plaques. Amyloid aggregation in addition to accumulation of tau pathology and neurodegeneration are thought to be the main drivers of the disease process. These changes in the brain result in widespread neurodegeneration and cell death, and ultimately cause the clinical signs and symptoms of dementia.[3,4]

The pathophysiological changes and clinical manifestations of AD are progressive and occur along a continuum, and accumulation of amyloid beta may begin 20 years or more before

symptoms arise.[5] The National Institute on Aging-Alzheimer's Association (NIA-AA) has created a "numeric clinical staging scheme" (Table 1) that avoids traditional syndromal labels and is applicable for only those in the Alzheimer continuum. This staging scheme is primarily used in the research setting and reflects the sequential evolution of AD from an initial stage characterized by the appearance of abnormal AD biomarkers in asymptomatic individuals. As biomarker abnormalities progress, the earliest subtle symptoms become detectable. Further progression of biomarker abnormalities is accompanied by progressive worsening of cognitive symptoms, culminating in dementia.

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

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

Adapted from Table 6, Jack et al (2018)[5].

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

Biomarkers

Several potential biomarkers of AD are associated with AD pathophysiology (e.g., 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 threonine 181 (P-tau) or total tau protein (T-tau), or an amyloid-beta peptide such as Aβ42.[7] Other potential CSF[8,9]and serum[10] peptide markers also have been explored. Tau protein is a microtubule-associated molecule that is found in the neurofibrillary tangles that are typical of AD. Tau protein is thought to be related to degenerating and dying neurons, and high levels of tau proteins in the CSF have been associated with AD. Aβ42 is a subtype of amyloid beta peptide that is produced following the metabolism of amyloid precursor protein. Aβ42 is the key peptide deposited in the 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 a Tau/Aβ42 ratio, a potentially more accurate diagnostic marker than either alone.[11] Neurogranin is a dendritic protein and CSF measurement may serve as a biomarker for dendritic instability and synaptic degeneration.[7] Elevated CSF neurogranin may predict prodromal AD in MCI and has been confirmed in AD dementia and prodromal AD in several studies.

A variety of kits are commercially available to measure Aβ42 and tau proteins. Between laboratory variability in CSF biomarker measurement is large.[12,13] Neural thread protein is associated with the neurofibrillary tangles of AD. Both CSF and urine levels of this protein have been investigated as a potential marker of AD. Urine and CSF tests for neural thread protein may be referred to as the AD7C test.

More recently, research has focused on blood as a new matrix for AD biomarkers that have already been validated in the CSF. As blood is more accessible than CSF, blood sampling would be preferable to CSF when taking samples to measure AD biomarkers, both for clinical diagnosis or screening.[7] However, developing blood AD biomarkers has proven complex. While the CSF is continuous with the brain extracellular fluid, with a free exchange of molecules from

the brain to the CSF, only a fraction of brain proteins enter the bloodstream. Examples of blood biomarkers that are currently under examination for use in AD include amyloid beta, tau protein, and neurofilament light. In a recent retrospective multicohort diagnostic performance study, both plasma tau phosphorylated at threonine 217 (p-tau217) and at threonine 181 (p-tau181) had excellent diagnostic performance for differentiating patients with AD syndromes from other neurodegenerative disorders.[14] At this time, although a growing area of research, blood AD biomarkers are not addressed in this review.

Regulatory Status

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA). AlzheimAlert™ and AdMark® CSF analysis are available under the auspices of CLIA. Laboratories that offer LDTs 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 these tests.

In November 2020, C2N Diagnostics gained CLIA certification for its Precivity mass-spec amyloid beta assay. This plasma test has received breakthrough device designation from the U.S. Food and Drug Administration (FDA) for review as an in-vitro diagnostic. The test is currently not intended to be used as a stand-alone diagnostic.

Medical Policy Statement

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

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

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

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

Measurement of urinary biomarkers of Alzheimer's disease is considered experimental/ investigational, including but not limited to neural thread proteins. There is insufficient evidence in medical literature to determine the effect of this testing on patient clinical outcomes.

Inclusionary and Exclusionary Guidelines (Clinically based guidelines that may support individual consideration and pre-authorization decisions)

N/A

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure)*

Established codes:

N/A

Other codes (investigational, not medically necessary, etc.):

83520 84999 81009 86849

Rationale

The clinical purposes of testing for Alzheimer's disease (AD)-related biomarkers are to improve diagnostic accuracy or to predict conversion from mild cognitive impairment (MCI) to AD.

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

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

CEREBROSPINAL FLUID BIOMARKER TESTING for ALZHEIMER DISEASE

Clinical Context and Test Purpose
The purpose of CSF biomarker testing for AD is to provide an alternative or superior method for diagnosis to inform appropriate treatment in patients with AD or mild cognitive impairment (MCI).

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

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

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

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

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

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

Follow-up at 2- years is of interest for CSF biomarker testing for AD for symptoms, change in disease status, morbid events, functional outcomes, QOL, medication use, and resource utilization.

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., ROC [receiver operating characteristics], AUROC [area under receiver operating characteristic], c-statistic, likelihood ratios) may be included but are less informative.
- Studies should also report reclassification of diagnostic or risk category.

Diagnosis of Alzheimer Disease

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

Table 2. Systematic Reviews Assessing CSF Biomarkers Performance for Distinguishing Alzheimer Disease from Controls with Clinical Diagnosis Reference Standard

Biomarker Studies	Controls Without Dementia, %		Controls with Dementia, %[a]	
	Sensitivity	**Specificity**	**Sensitivity**	**Specificity**
Aβ42				
Rosa (2013)[15]	84% (81 to 85)	79% (77 to 81)	NR	NR
Bloudek (2011)[16]	80% (73 to 85)	82% (74 to 88)	73% (67 to 78)	67% (62 to 72)
Formichi (2006)[17]	NR	NR	55%-100%	80%-100%
tTau				
Bloudek (2011)[16]	82% (76 to 87)	90% (86 to 93)	78% (72 to 83)	75% (68 to 81)
Formichi (2006)[17]	NR	NR	52%-100%	50%-100%
pTau				
Ferreira (2014)[18]	78%-80%	83%-88%	72%-88%	78%-83%
Bloudek et al (2011)[16]	80 (70 to 87)	83 (75 to 88)	79 (72 to 84)	80 (71 to 86)
Formichi et al (2006)[17]	NR	NR	37 to 100	80 to 100

Values in parentheses are 95% confidence intervals unless otherwise noted.
Aβ42: amyloid-β peptide 1-42; CSF: cerebrospinal fluid; SR: systematic review; IS: individual studies; NR: not reported; pTau: 6andomized66ed 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.[19] 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 Aß42/pTau ratio, tTau/Aß42 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).[20] Literature was searched in January 2012, and 3 studies of CSF markers (pTau, tTau, Aβ42, Aβ40) were identified (total n=337 patients). Pooled sensitivity of all CSF tests was 82% (95% CI, 72% to 92%), and pooled specificity was 75% (95% CI, 60% to 90%). Statistical heterogeneity was not reported, but studies varied by AD definitions, controls (nondemented patients or patients with dementia due to other causes), and test thresholds. The summary area under receiver operating characteristic curve, constructed using multiple test thresholds, was 0.84.

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 (Aß42/pTau or

tTau/Aß42) 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

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

Systematic Reviews

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

Study	Dates	Studies	Participants	N (Range)	Design	Duration
Olsson (2016)[21]	1995-2014	231	Patients with AD or MCI due to AD.	AD=15,699 Controls=13,018 Total=27,717 (Range=20-1087)	Not specified	Not specified
Ritchie (2017)[22]	2006-2013	15	Patients with MCI at baseline.	N=1282	Longitudinal cohort	2 mo-11.8 y
Ritchie (2014)[23]	2003-2013	17	Participants with cognitive decline but no dementia condition at baseline.	Total=2228 (Range=37-588)	Longitudinal cohort	2 mo-12 y

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

Table 4. Results of Key Meta-Analyses

Study	Aβ42	tTau	pTau
Olsson (2016)[21]			
Average ratio (95% CI)	0.56 (0.55 to 0.58)	2.54 (2.44 to 2.64)	1.88 (1.79 to 1.97)
p value	<.001	<.001	<.001
Ritchie (2017)[22]			
Sensitivity range, %	-	51-90	40-100
Specificity range, %	-	48-88	22-86
Median specificity, %	-	72	47.5
Sensitivity at median specificity, % (95% CI)	-	75 (67 to 85)	81 (64 to 91)
Ritchie (2014)[23]			
Sensitivity range, %	36-100	-	-
Specificity range, %	29-91	-	-
Median specificity, %	64	-	-
Sensitivity at median specificity, % (95% CI)	81 (72 to 87)	-	-

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

Subsection Summary: Clinical Validity of Cerebrospinal Fluid Biomarker Testing for Prognosis for Progression of Mild Cognitive Impairment
The evidence suggests that biomarker testing may identify an increased risk of conversion from MCI to AD. Studies primarily include clinical diagnosis as a reference standard and varying cutoffs for predicting conversion.

Clinically Useful
Possible clinical uses of CSF biomarker testing could include confirming the diagnosis of AD to begin medications at an earlier stage or ruling out AD, which could lead to further diagnostic testing to determine the etiology of dementia and/or avoidance of unnecessary 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.[24,25] 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.[24,26] 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.[27-30] The chain of evidence of clinical utility is incomplete.

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

Urinary Biomarker Testing

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

Zhang et al (2014) conducted a systematic review and meta-analysis of urinary AD-associated neural thread protein for diagnosing AD in patients with suspected AD.[31] 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 1 study. 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 1 to 11.1) and 0.12 (95% CI, 0.09 to 0.16), respectively.

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

Section Summary: Urinary Marker Testing
A systematic review and meta-analysis that evaluated urinary AD-associated NTP with regard to diagnosing AD in patients with suspected AD concluded that, for probable AD, pooled sensitivity and specificity were 89% (95% CI, 86% to 92%) and 90% (95% CI, 88% to 92%), respectively. Pooled positive and negative likelihood ratios were 8.9 (95% CI, 7.1 to 11.1) and 0.12 (95% CI, 0.09 to 0.16), respectively.

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

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

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

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

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

In the pivotal trials for the amyloid beta plaque targeting therapy aducanumab, enrolled patients had an early stage of AD; MCI due to AD; or mild AD dementia based on an entry criteria of baseline Mini-Mental State Examination (MMSE) score of 24 to 30, baseline Clinical Dementia Rating (CDR) global score of 0.5 and Repeatable Battery for the Assessment of Neurological Status (RBANS) delayed memory index score ≤85. Patients were also clinically staged based on the National Institute on Aging-Alzheimer's criteria (Table 1). The National Institute on Aging-Alzheimer's Association has provided guidance on the clinical diagnosis of MCI and dementia due to AD.[32,33,34] This includes utilizing a battery of cognitive tests versus a single test to identify individuals with MCI due to AD (stage 3) or mild dementia due to AD (stage 4). The tests should evaluate multiple domains such as cognition and function and specific tests may vary.

Interventions
The test being considered is the CSF biomarker amyloid beta-42/40 ratio. The amyloid beta-42/40 ratio test quantifies the amount of amyloid beta-42 and 40 proteins in a CSF sample (collected via lumbar puncture) and computes the ratio of those proteins, intended to be an indication of AD pathology. Ratios <0.058 indicate a higher likelihood of a patient having a clinical diagnosis of AD. The ratio, as compared with CSF amyloid beta-42 alone, corrects for interindividual variability in the overall amyloid beta production and CSF turnover, changes in global levels of all amyloid beta isoforms owing to non-AD-related abnormal findings, and variability owing to preanalytical factors.[35] This concentration ratio has also been suggested to be superior to the concentration of amyloid beta-42 alone when identifying patients with AD.[36] The test is indicated for patients being evaluated for MCI or mild dementia clinical stages of AD who are under consideration for targeted therapy.

Comparators
Comparators of interest include the amyloid beta PET scan. Amyloid beta PET imaging is a neuroimaging technique with standardized tracer-specific visual reading procedures and documented high reproducibility across PET centers.[37] It allows non-invasive, in-vivo detection of amyloid plaques with very high sensitivity (96%; 95% CI, 80 to 100) and specificity (100%, 95% CI, 78 to 100) as determined by correlation in patients with confirmed AD who had an autopsy within 1 year of PET imaging. Trials of amyloid beta targeting therapy have traditionally used clinical criteria along with amyloid beta PET imaging to select appropriate patients for participation.

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

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

Review of Evidence
Overall, both PET imaging and CSF biomarkers provide overlapping, and in part complementary, diagnostic information with agreement between CSF and PET amyloid results usually good.[37] There are various studies that evaluate concordance between CSF biomarkers and PET imaging; however, studies that specifically evaluate the CSF biomarker amyloid beta-42/40 in comparison to amyloid PET imaging are limited.

The diagnostic accuracy of CSF biomarkers and amyloid beta PET for diagnosing early-stage AD were compared using data from the prospective, longitudinal Swedish BioFINDER study that consecutively enrolled patients without dementia with mild cognitive symptoms.[38] This was the first study to compare the accuracy of regional amyloid beta PET (using the [18F]-flutemetamol) and different CSF assays or ratios of CSF biomarkers, including amyloid beta-

42/40, for this diagnostic purpose. The study included 34 patients with MCI who developed AD dementia within 3 years and 122 healthy elderly controls. Overall, the best CSF measures for the identification of MCI-AD were amyloid-beta 42/total tau (t-tau) and amyloid beta-42/hyperphosphorylated tau (p-tau), with an area under the curve (AUC) of 0.93 to 0.94. The best PET measures (i.e., anterior cingulate, posterior cingulate/percuneus, and global neocortical uptake) performed similarly (AUC 0.92 to 0.93). The AUC for CSF amyloid beta-42/40 was numerically poorer as compared to the majority of PET variables; however, the differences were non-significant (p=.09 to.40). The combination of CSF and PET was not better than using either biomarker separately. The results were replicated in 146 controls and 64 patients with MCI-AD from the Alzheimer's Disease Neuroimaging Initiative (ADNI) study that utilized another CSF assay (amyloid beta-42, t-tau and p-tau) and PET (18F-florbetapir) tracer. In the ADNI cohort, amyloid-beta 42/t-tau and amyloid beta-42/p-tau ratios similarly had higher AUCs that amyloid beta-42 alone.

Lewczuk et al (2017) evaluated whether amyloid beta-42 alone or the amyloid beta-42/40 ratio corresponded better with amyloid beta PET status.[39] The investigators collected CSF from a mixed cohort (N=200) of cognitively normal and abnormal subjects who had undergone amyloid beta PET within 12 months. Of these, 150 were PET-negative and 50 were PET-positive according to a previously published cutoff. The collected CSF was assayed for amyloid beta-42 alone and the amyloid beta-42/40 ratio. Results revealed that the amyloid beta-42/40 ratio corresponded better than amyloid beta-42 alone with PET results, with a higher proportion of concordant cases (89.4% vs. 74.9%; p<.0001) and a larger AUC (0.936 vs. 0.814; p<.0001) associated with the ratio.

Clinically Useful

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

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without specific tests. Because these are intervention studies, the preferred evidence would be from randomized controlled trials (RCTs). No direct evidence to support the clinical utility of the CSF biomarker testing (amyloid beta-42/40 ratio) alone or in conjunction with amyloid beta PET scans to initially select appropriate patients for treatment with an amyloid beta plaque targeting therapy (e.g., aducanumab) is available. Additionally, there are no data on the serial use of these tests to determine if there are changes in biomarker results that correlate with clinical cognitive and functional status and/or amyloid beta imaging to inform continuation of amyloid beta plaque targeting therapy. Prior to the approval of aducanumab, the only approved treatments for AD were for symptoms. Rabinovici et al (2019) published results from a large scale (N=16,008 patients) multicenter study in the United States, revealing that knowledge of amyloid PET scans was associated with significant changes in diagnosis and patient management, including the administration of medications approved for the symptomatic treatment of AD, other relevant medications addressing dementia risk factors, counseling, and future planning (e.g., medical and financial decision making). Disease-specific morbidity or mortality were not evaluable.[40]

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

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

SUMMARY OF EVIDENCE

For individuals who have AD or mild cognitive impairment (MCI) who receive CSF biomarker testing for AD, the evidence includes systematic reviews . These studies assess using CSF biomarkers for diagnosis of AD or for the prognosis of progression of MCI to AD. Relevant outcomes includes diagnosis accuracy correct treatment, avoiding unnecessary subsequent testing, harms of invasive testing, and quality of life. 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 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 that the technology results in an improvement in the net 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 prospective and retrospective studies. Relevant outcomes diagnosis accuracy, correct treatment, avoiding unnecessary subsequent testing, harms of invasive testing, and quality of life. Clinical validity studies have included normal healthy controls and defined optimal test cutoffs without validation; thus, clinical validity is uncertain. Whether 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.

For individuals who have MCI or mild dementia due to AD who are being considered for initial treatment with an approved amyloid beta plaque targeting therapy, the evidence includes multisite longitudinal studies and an analysis of a mixed cohort. Two of these studies assess the correlation between CSF biomarkers and PET amyloid scans and another assesses the clinical utility of amyloid PET in cognitively impaired patients who met appropriate use criteria for clinical amyloid PET. Relevant outcomes include test validity, symptoms, change in disease status, functional outcomes, health status measures, and QOL. Overall, the diagnostic accuracy of CSF biomarkers versus amyloid PET scans to identify MCI-AD was found to be similar but there are no data to support the clinical utility of CSF biomarker use as a component of determining appropriate initiation of amyloid beta targeting therapy. Prior to the availability of amyloid beta targeting therapy, additional data exist suggesting that amyloid

beta PET scan results impacted diagnosis of dementias and patient management including use of symptomatic treatment. Further research is required to determine whether use of CSF biomarkers alone or in conjunction with amyloid PET scans is associated with improved clinical outcomes. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have MCI or mild dementia due to AD, who are being treated with an amyloid beta plaque targeting therapy and are being evaluated for therapy continuation, the evidence includes multisite longitudinal studies and an analysis of a mixed cohort. Two of these studies assess the correlation between CSF biomarkers and PET amyloid scans and another assesses the clinical utility of amyloid PET in cognitively impaired patients who met appropriate use criteria for clinical amyloid PET. Relevant outcomes include test validity, symptoms, change in disease status, functional outcomes, health status measures, and QOL. The diagnostic accuracy of CSF biomarkers versus amyloid beta PET scans to identify MCI-AD was found to be similar. Prior to the availability of amyloid beta targeting therapy, additional data exist suggesting that amyloid beta PET scan results impacted diagnosis of dementias and patient management including use of symptomatic treatment. Further research is required to determine whether use of CSF biomarkers alone in conjunction with amyloid beta PET scans are useful for determining whether or not amyloid beta targeting therapy should be continued. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

SUPPLEMTAL INFORMATION

PRACTICE GUIDELINES AND POSITION STATEMENTS

National Institute of Neurological and Communicative Disorders et al

2011 Revised Diagnostic Criteria

As of 2011, probable AD is defined by the National Institute on Aging [34]

“Meets criteria for dementia described... and in addition, has the following characteristics:

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

a. substantial concomitant cerebrovascular disease, defined by a history of a stroke temporally related to the onset or worsening of cognitive impairment; or the presence of multiple or extensive infarcts or severe white matter hyperintensity burden; or
b. core features of Dementia with Lewy bodies other than dementia itself; or
c. prominent features of behavioral variant frontotemporal dementia; or
d. prominent features of semantic variant primary progressive aphasia or nonfluent/agrammatic variant primary progressive aphasia; or
e. evidence for another concurrent, active neurological disease, or a non-neurological medical comorbidity or use of medication that could have a substantial effect on cognition."

The diagnosis for possible AD dementia should meet the follow 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 2011Revised AD Criteria and Biomarkers
The biomarkers reviewed in this policy are included in a category among revisions to the 2011 updated AD diagnostic criteria—"probable AD dementia with evidence of the AD pathophysiological process." However, the diagnostic criteria workgroup publication 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 three circumstances: investigational studies, clinical trials, and as optional clinical tools for use where available and when deemed appropriate by the clinician."[34]

Alzheimer's Association
In 2009, the Alzheimer's Association (AA) 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".[16] 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.[41]

In 2013, AA published recommendations for operationalizing the detection of cognitive impairment during the Medicare annual wellness visit in primary care settings.[42] The recommended algorithm for cognitive assessment was based on "current validated tools and commonly used rule-out assessments." Guideline authors noted that use of biomarkers (e.g., CSF tau and β-amyloid proteins) "was not considered as these measures are not currently approved or widely available for clinical use."

The Alzheimer's Association (2018) published appropriate use criteria for lumbar puncture and CSF testing for AD.[43] Table 5 summarizes the indications for these practices. In 2021, the Alzheimer's Association also published international guidelines for the appropriate handling of CSF for routine clinical measurements of amyloid beta and tau.[44]

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

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

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

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.[45] 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.

ONGOING AND UNPUBLISHED CLINICAL TRIALS

A search of ClinicalTrials.gov identified some currently ongoing and unpublished trials that might influence this review that are listed in Table 6.

Table 6. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT05020106	Study on the Diagnostic Cut-off Value for Core Biomarkers in Cerebrospinal Fluid and Blood of Alzheimer's Disease	3200	Sep 2022
NCT03136679	Discovery of novel biomarkers that will lead to the early detection of Alzheimer's disease	220	Dec 2022
NCT02612376	Rocky mountain Alzheimer's disease center longitudinal biomarker and clinical phenotyping study	800	Jan 2024
NCT03860857	MRI and PET Biomarkers for Cognitive Decline in Older Adults	200	Dec 2024
NCT04575337	Study on Body Fluid, Gene and Neuroimaging Biomarkers for Early Diagnosis of Alzheimer's Disease	6000	Jun 2025
Unpublished			
NCT01642420	Quantitative electroencephalography, cerebrospinal fluid biomarkers, linear CT analyses and timed up and go dual task as diagnostic tools in dementia and their ability to predict disease progression	115	Feb 2017 (estimated)

NCT: national clinical trial.

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.[46] 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.

Government Regulations

National/Local:

There is no national or local coverage determination published on this topic.

The current Physician Fee Schedule does not price the following codes: 81099, 84999, 83520, and 86849.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

Genetic Testing for Familial Alzheimer's Disease

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The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through January 2022, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
11/1/13	8/22/13	8/27/13	Topic split out from former combined policy, "Genetic Testing and Biochemical Markers for Alzheimer's Disease" and renamed "Biochemical Markers of Alzheimer's Disease." Deleted procedure code 83912; added NOC code 84999, Unlisted chemistry procedure [when specified as tau protein, amyloid beta peptide or neural thread protein biochemical testing]
5/1/15	2/17/15	2/27/15	Routine maintenance. Updated background, rationale and references.
5/1/16	2/16/16	2/16/16	Routine maintenance
5/1/17	2/21/17	2/21/17	Added codes 81099 and 86849 as unlisted codes suggested for use on AlzheimAlert™ website. Title changed to Cerebrospinal Fluid and Urinary Biomarkers of Alzheimer Disease. Reference sections updated (12-15, 25, 29 and 37), rationale section reorganized-- individual studies that were included in meta-analyses were removed. No change in policy statement.
5/1/18	2/20/18	2/20/18	Routine policy maintenance, added references # 20, 23 and 27. No change in policy status.
5/1/19	2/19/19		Routine policy maintenance, added references # 26, 28-30 and 34. No change in policy status.
5/1/20	2/18/20		Updated rationale section, added reference #49 and 50. No change in policy status.

5/1/21	2/16/21		Rationale updated, reference # 22, 35 and 36 added. No change in policy status.
5/1/22	2/15/22		Separated MPS E/I status for cognitive impairment, mild dementia due to Alzheimer dx, target therapy in Alzheimer, evaluation of initial tx, continuation of therapy. Extensive editing to rationale and description section.

Next Review Date: 1st Qtr. 2023

Joint BCBSM/BCN Medical Policy History

Previous Policy: Genetic Testing and Biochemical Markers for Alzheimer's Disease

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
7/21/03	7/21/03	7/7/03	Joint policy for Biochemical Markers of Alzheimer's Disease established
2/26/05	2/26/05	1/14/05	Routine maintenance
1/1/07	1/18/07	10/20/06	Genetic Testing for Alzheimer's Disease and Biochemical Markers for Alzheimer's Disease combined with change in medical policy statement.
9/1/07	7/3/07	8/29/07	Routine maintenance
1/1/09	10/13/08	12/30/08	Routine maintenance
5/1/12	2/21/12	2/21/12	Pulled out of retirement to clarify coverage guidelines; references updated. Policy enhanced to mirror BCBSA policy. Added codes 83520 and 83912 to policy for coding urinary and CSF biomarker testing.

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: CEREBROSPINAL FLUID AND URINARY BIOMARKERS OF ALZHEIMER'S DISEASE

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Not covered
BCNA (Medicare Advantage)	See government section
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

N/A