Medical Policy Manual Laboratory, Policy No. 22

Biochemical and Cellular Markers of Alzheimer's Disease

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IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Biochemical and cellular biomarkers may predict risk of Alzheimer's disease (AD); however, the clinical value of this testing is uncertain.

MEDICAL POLICY CRITERIA

I. Measurement of cerebrospinal fluid or blood biomarkers of Alzheimer's disease, including but not limited to tau protein, amyloid beta peptides, or neural thread proteins, is considered **investigational**.

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

III. Skin cell (fibroblast) testing for biomarkers of Alzheimer's disease, including but not limited to the DISCERN™ test, is considered **investigational**.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

CROSS REFERENCES

1. Genetic Testing for Familial Alzheimer's Disease, Genetic Testing, Policy No. 01

BACKGROUND

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. According to 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.[1] The cumulative dementia incidence was 14.9% in individuals with MCI over 65 years of age followed for two years.

Data from the National Institute on Aging have shown that Black Americans are approximately 1.5 to 2 times more likely to develop AD and related dementias as compared to Whites.[2] Additionally, Black participants in AD research studies were 35% less likely to be diagnosed with AD and related dementias and were found to have more risk factors for the disease as well as greater cognitive impairment and symptom severity than White participants. Findings from two national surveys conducted by the Alzheimer's Association also found that people of color face discrimination when seeking health care for AD and related dementias with the highest level of discrimination in dementia health care reported by Black Americans (50%) followed by Native (42%), Asian (34%), and Hispanic (33%) Americans. Non-Hispanic White Americans reported a discrimination rate of 9%.[3]

The diagnosis of Alzheimer's disease (AD) is typically a clinical diagnosis, focusing on the exclusion of other causes of dementia. In 1984 the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's and Related Disorders Association (ADRDA) published clinical criteria for the diagnosis of AD. These organizations defined three categories: possible, probable, and definite AD. The only difference between probable and definite AD is that the definite category requires a brain biopsy confirming the presence of characteristic neurofibrillary tangles. Therefore, definite AD is typically identified only at autopsy. The categories are defined as follows:

I. Possible Alzheimer's Disease

   A. May be made on the basis of the dementia syndrome in the absence of other neurological, psychiatric, or systemic disorders sufficient to cause dementia, and in the presence of variations in the onset, in the presentation, or in the clinical course

   B. May be made in the presence of a second systemic or brain disorder sufficient to produce dementia, which is not considered to be the cause of the dementia

   C. Should be used in research studies when a single gradually progressive severe cognitive deficit is identified in the absence of other identifiable cause

II. Probable Alzheimer's Disease

   A. The criteria for the clinical diagnosis of probable AD include:

      1. Dementia, established by clinical examination and documented by the Mini-Mental State Examination, the Blessed Dementia Scale, or some similar examination and confirmed by neuropsychological tests

2. Deficits in two or more areas of cognition
3. Progressive worsening of memory and other cognitive functions
4. No disturbance of consciousness
5. Onset between ages 40 and 90, most often after the age of 65
6. Absence of systemic disorders or other brain diseases that in and of themselves could account for the progressive deficits in memory and cognition

B. The diagnosis of probable AD is supported by:

1. Progressive deterioration of specific cognitive functions such as language (aphasia), motor skills (apraxia), and perception (agnosia)
2. Impaired activities of daily living and altered patterns of behavior
3. Family history of similar disorders, particularly if confirmed neuropathologically
4. Laboratory results: normal lumbar puncture as evaluated by standard techniques, normal pattern or non-specific changes in the EEG, and evidence of cerebral atrophy on CT scanning with progression documented by serial observation

C. Other clinical features consistent with the diagnosis of probable AD, after exclusion of causes of dementia other than AD, include:

1. Plateaus in the course of progression of the illness;
2. Associated symptoms of depression, insomnia, incontinence, delusions, illusions, hallucinations, sexual disorders, weight loss, and catastrophic verbal, emotional, or physical outbursts
3. Other neurologic abnormalities in some patients, especially with more advanced disease and including motor signs such as increased muscle tone, myoclonus, or gait disorder
4. Seizures in advanced disease CT normal for age

D. Features that make the diagnosis of probable AD uncertain or unlikely include:

1. Sudden apoplectic onset
2. Focal neurological findings such as hemiparesis, sensory loss, visual field deficits, and incoordination early in the course of the illness
3. Seizures or gait disturbances at the onset or very early in the course of the illness

III. Definite Alzheimer's Disease

A. Clinical criteria for probable Alzheimer's disease AND

B. Histopathologic evidence obtained from a biopsy or autopsy

In 2011, the National Institute on Aging and the Alzheimer's Association workgroup revised diagnostic criteria for diagnosis of dementia due to Alzheimer's disease. All probable AD by NINCDS-ADRDA criteria are subsumed in the revised probable AD criteria, which is now defined by the following:

"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.

    1. 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.

    2. 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.

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."

Diagnosis by exclusion is frustrating for physicians, patients and families, and there has been considerable research interest in identifying an inclusive laboratory test for AD, particularly for use early in the disease process. Abnormal levels in cerebrospinal fluid (CSF) of the tau protein (total tau [T-tau] or phosphorylated [P-tau]) or an amyloid beta (Aβ) peptide such as Aβ42, have been found in patients with AD, and thus these proteins have been investigated for their diagnostic utility. The tau protein is a microtubule-associated molecule that is found in the neurofibrillary tangles that are typical of Alzheimer's disease. This 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 an amyloid precursor protein. Aβ42 is the key peptide deposited in the amyloid plaques that are characteristic of AD. Low levels of Aβ42 in the CSF have been associated with AD, perhaps because the Aβ42 is deposited in the amyloid plaques instead of remaining in solution.

Neural thread protein (NTP) is another protein that is associated with neurofibrillary tangles of Alzheimer's disease. Both CSF and urine levels of this protein have been investigated as a biochemical marker of Alzheimer's disease. Urine and CSF tests for neural thread protein may be referred to as the AD7C™ test.

In 2024, the Alzheimer's Association workgroup published revised diagnostic criteria for diagnosis of dementia due to Alzheimer's disease and proposed that amyloid PET and certain CSF or blood-based biomarkers could be used for diagnosis.[4] These guidelines have been controversial, as they may lead to AD diagnosis in individuals with no cognitive changes. For example, the American Geriatrics Society published a response letter to the draft guidelines, which stated that they were "concerned that the proposed expansion of the NIA-AA guidelines to include usage in clinical care will place many older and multimorbid people at risk of overdiagnosis, which in turn could lead to initiation of treatments with limited benefit and high potential for harm in this population"[5] Among their concerns, they noted substantial conflicts of interest among the authors and questioned the reduced level of involvement of the National Institute on Aging (NIA), noting that earlier versions of the guidelines were intended to provide a research framework, "a usage that is consistent with the mission of the NIA," and not clinical guidelines.[5] The NIA removed their name from the title of the final publication.

REGULATORY STATUS

The Lumipulse® G ß-Amyloid Ratio (1-42/1-40) Test (Fujirebio Diagnostics) and the Elecsys® CSF assays for P-tau181/Aβ42 andT-tau/Aβ42 (Roche) have received 510(k) marketing clearance from the U.S. Food and Drug Administration (FDA).

Many biomarker tests for AD do not have FDA approval or clearance, including:

- AlzheimAlert™ (Nymox Pharmaceutical Corp.)
- Innotest® assays for T-tau, P-tau, and Aβ42 (Fujirebio Diagnotics)
- AdMark® CSF analysis
- DISCERN™ (Neurodiagnostics) skin sample fibroblast testing
- AD-Detect (Quest Diagnostics)

These are laboratory-developed tests (LDTs). Clinical laboratories may develop and validate tests inhouse and market them as a laboratory service; LDTs must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA). Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing.

EVIDENCE SUMMARY

Validation of the clinical use of any prognostic test focuses on three main principles:

1. The analytic validity of the test, which refers to the technical accuracy of the test in detecting a disease marker of interest that is present or in excluding a disease marker that is absent;
2. The clinical validity of the test, which refers to the diagnostic performance of the test (sensitivity, specificity, positive and negative predictive values) in detecting clinical disease; and
3. The clinical utility of the test, i.e., how the results of the diagnostic test will be used to change management of the patient and whether these changes in management lead to

clinically important improvements in health outcomes. The clinical utility of both positive and negative tests must be established.

This evidence review focuses on clinical validity and utility.

Evaluation of evidence of clinical utility requires consideration of the following:

- Reference/criterion standard: The gold standard for definitive diagnosis of AD is autopsy. The accuracy of testing for AD is best established by comparison with this gold standard; therefore, the gold standard must be employed to accurately assess incremental diagnostic improvement.
- Predicting conversion from MCI to AD: Predicting conversion from MCI to AD may rely on a clinical diagnosis, albeit with some attendant error and misclassification, because the prediction of interest is conversion and not the gold standard diagnosis.
- Incremental diagnostic improvement: Incremental diagnostic or prognostic improvement is best demonstrated through evidence that the proposed predictor can correctly reclassify individuals with and without AD, or those with MCI who will and will not progress to AD.[6] Alternative approaches such as classical receiver operating characteristic (ROC) analyses, while providing some insight, do not allow directly translating improvements in diagnostic or prognostic accuracy to changes in health outcomes.[7]
- Improved health outcomes (clinical utility): In order to establish clinical utility, AD biomarkers would need to provide information which improves treatment decisions and health outcomes beyond that of clinical diagnosis.
- Test cutoffs: Almost all studies employ optimal (data-driven) test cutoffs to define test accuracy (sensitivity and specificity). This approach is typically accompanied by a degree of optimism and potentially overstates test accuracy.
- Sample definition: Clear description of whether samples included consecutive patients or were selective is required to evaluate potential bias—including verification bias[8] — and generalizability but almost absent in this literature.
- Validation: Validation in independent samples is required to establish generalizability of markers but has been scant.

Studies were selected for inclusion in the evidence review based on the following criteria:

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

CEREBRAL SPINAL FLUID BIOMARKER TESTING

Clinical Validity

Diagnosis of AD

Systematic Reviews

Most studies have relied on clinically diagnosed AD as the criterion standard. Results from several systematic reviews are summarized in Table 1. Studies included in these systematic reviews are not individually reviewed.

A Cochrane review by Kokkinou (2021) evaluated the accuracy of plasma and CSF Aβ42 measurement to distinguish Alzheimer's disease from other forms of dementia.[9] A literature search was performed through February 2020, and 39 studies with a total of 7,246 patients were included in the analysis. No suitable studies of plasma were identified; thus, the review was focused on CSF measures. None of the studies was rated as having a low risk of bias based on the QUADAS-2 instrument. The pooled sensitivity and specificity estimates for CSF Aβ42 to differentiate Alzheimer's disease from other dementia subtypes were 79% (95% CI 0.73 to 0.85) and 60% (95% CI 0.52 to 0.67), respectively, based on data from 13 studies (1,704 patients, 880 with Alzheimer's disease). The authors concluded that while CSF Aβ42 may help to distinguish Alzheimer's disease from other dementia subtypes, the test tends to misdiagnose those with non-Alzheimer's dementia as having Alzheimer's and should not be used alone for dementia classification.

Fink (2020) conducted a systematic review of biomarker accuracy for diagnosing neuropathologically defined AD in older patients with dementia.[10] The analysis included literature published between January 2012 and November 2019, with nine 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/P-tau ratio, T-tau/Aß42 ratio, and P-tau compared with T-tau alone.

Olsson (2016) published a systematic review and meta-analysis on the diagnostic performance of the three core CSF biomarkers for the diagnosis of Alzheimer's disease (Aβ42, T-tau, and P-tau).[11] The investigators included 231 cross-sectional cohort and longitudinal studies that contained a cohort with Alzheimer's disease and a control cohort, or a cohort with mild cognitive impairment due to Alzheimer's disease and a stable mild cognitive impairment cohort (n=15,699 Alzheimer's patients and 13,018 controls). Biomarker performance was reported as the ratio between biomarker concentration in patients with Alzheimer's disease and controls (fold change) or the ratio between biomarker concentration in those with mild cognitive impairment due to Alzheimer's disease and those with stable mild cognitive impairment who had no further cognitive decline in minimum of two years. In the CSF, T-tau was able to differentiate clinically diagnosed Alzheimer's disease from controls with good performance (average ratio 2.54, 95% confidence interval [CI] 2.44 to 2.64, $p<0.0001$), with similar effect sizes reported for the emerging biomarker neurofilament light chain protein (NFL) (2.35, 1.90 to 2.91, $p<0.0001$). CSF P-tau (1.88, 1.79 to 1.97, $p<0.0001$) and plasma T-tau (1.95, 1.12 to 3.38, $p=0.02$) also had large effect sizes when differentiating between controls and patients with Alzheimer's disease. All other markers, including CSF Aβ42, had only marginal effect sizes. Limitations of this review include the fact that only five of the included studies were considered to be of good quality; and substantial publication bias for all three core biomarkers.

Table 1. CSF Biomarkers Performance for Distinguishing AD from Controls

	Controls without Dementia		Controls with Dementia[a]	
	Sensitivity, %	**Specificity, %**	**Sensitivity, %**	**Specificity, %**
Aβ42				
Ferreira (2014)[12]	80 (73 to 85)	82 (74 to 88)	73 (67 to 78)	67 (62 to 72)
Rosa (2014)[13]	84 (81 to 85)	79 (77 to 81)	NR	NR
Bloudek (2011)[14]	80 (73 to 85)	82 (74 to 88)	73 (67 to 78)	67 (62 to 72)
Formichi (2006)[15]	NR	NR	55%-100%	80%-100%
Vogelsgang (2018)[16]	NR	NR	NR	NR
T-tau				
Ferreira (2014)[12]	82 (76 to 87)	90 (86 to 93)	73 to 91	75 to 98
Bloudek (2011)[14]	82 (76 to 87)	90 (86 to 93)	78 (72 to 83)	75 (68 to 81)
Formichi (2006)[15]	NR	NR	52 to 100	50 to 100
P-tau				
Ferreira (2014)[12]	78 to 80	83 to 88	72 to 88	78 to 83
Bloudek (2011)[14]	80 (70 to 87)	83 (75 to 88)	79 (72 to 84)	80 (71 to 86)
Formichi (2006)[15]	NR	NR	37 to 100	80 to 100%
BACE1				
Alexopoulos (2018)[17]	NR	NR	NR	NR
α-synuclein				
Wang (2018)[18]	NR	NR	NR	NR

Values in parentheses are 95% confidence intervals unless otherwise noted.
CSF: cerebrospinal fluid; NR: not reported; P-tau: phosphorylated tau protein; T-tau: total tau protein.

Ferreira (2014) published a meta-review of systematic reviews with meta-analyses to assess the use of CSF biomarker tests for AD after publication of revised AD diagnostic criteria[19] in 2011.[12] Literature was searched in September 2013, and seven systematic reviews were included. None was published after introduction of the revised AD diagnostic criteria, so primary studies were searched. Twenty-six prospective or retrospective case-control, cross-sectional, or longitudinal studies were included. Most included studies used clinical criteria for AD diagnosis or did not specify. For differentiating AD from controls without dementia, positive and negative likelihood ratios for all three biomarkers ranged from 4 to 8 and from 0.1 to 0.3, respectively.

Rosa (2014) conducted a systematic review with meta-analysis of studies of CSF Aβ42 in patients with clinically diagnosed AD.[13] Literature was searched to May 2013, and 41 prospective or retrospective, cohort, case-control, and cross-sectional studies were included (total n=5,086: 2,932 AD, and 2,154 controls without dementia). Patients with MCI were excluded. Seventy-six percent of studies satisfied all quality domains of the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool. Publication bias was detected. A summary ROC curve was generated from all reported thresholds. Pooled sensitivity and specificity were 84% (95% CI 81 to 85) and 79% (95% CI 77 to 81), respectively. Positive and negative likelihood ratios were 4.5 (95% CI 3.7 to 5.4) and 0.18 (95% CI 0.14 to 0.22), respectively, and their ratio, the diagnostic odds ratio, was 29 (95% CI 21 to 40). Statistical heterogeneity was substantial (I^2=68%); studies varied in test cutoffs used and severity of AD across patient samples. Eleven studies (total n=1,459: 830 AD, 629 controls) reported AB42 CSF levels. Mean (standard deviation [SD]) CSF AB42 was 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, p<0.001). However, statistical heterogeneity was considerable (I^2=99%).

Cure (2014) published 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 three studies of CSF markers (P-tau, T-tau, Aβ42, Aβ40) were identified (total n=337). 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 in AD definitions, controls (patients without dementia or patients with dementia due to other causes), and test thresholds. Area under the summary ROC curve constructed using multiple test thresholds was 0.84.

In a systematic review by Noel-Storr (2013), authors assessed the weight and quality of the evidence available from primary diagnostic test accuracy studies for Alzheimer's disease.[21] Authors identified 142 longitudinal studies relating to the biomarkers of interest, which included subjects who had objective cognitive impairment but no dementia at baseline. Authors concluded the body of evidence for biomarkers was not large and was variable across the different types of biomarkers. Authors suggest that important information is missing from many study reports, highlighting the need for standardization of methodology and reporting to improve the rigor of biomarker validation.

A meta-analysis by Bloudek (2011) included 119 studies on biomarkers and diagnostic imaging in AD.[14] 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 with and without 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 total tau was evaluated in 30 studies with a resulting sensitivity of 79% (95% CI 75% to 83%) and specificity of 85% (95% CI 81% to 89%). CSF P-tau 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 P-tau as a biomarker to distinguish patients with AD from patients with MCI, with a pooled sensitivity of 73% (95% CI 54% to 86%) and specificity of 69% (95% CI 53% to 82%). The combination of total tau and Aβ42 was evaluated in 12 studies, with a pooled sensitivity of 80% (95% CI 72% to 85%) and specificity of 76% (95% CI 57% to 88%). Comparison of CSF biomarkers, area under the receiver operating characteristic curve was highest for P-tau 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 P-tau resulted in slightly higher sensitivity (82%, 95% CI 75% to 87%) and lower specificity (57%, 95% CI 37% to 75%).

A systematic review by van Harten (2011) of seven studies using CSF biomarkers to differentiate AD from other dementias, reporting positive and negative likelihood ratios of 46 and 0.09, respectively, for differentiating AD (n=175) from Creutzfeldt-Jakob disease (n=110).[22] With this systematic review excluded, positive and negative likelihood ratios ranged from 2 to 7 and from 0.15 to 0.4, respectively.

Prognosis for Progression of Mild Cognitive Impairment

Systematic Reviews

Ritchie (2014, 2017) published Cochrane reviews assessing the evidence to determine the accuracy of CSF biomarkers for detecting which patients with MCI would progress to AD or other dementias. The two systematic reviews analyzed many of the same studies and reached the same conclusion.[23, 24] In the 2017 review, literature was searched in January 2013 and 15 prospective and retrospective studies (1,172 participants with MCI had analyzable data) were included. Only studies that applied a reference standard for Alzheimer's disease dementia diagnosis were included. There were 430 patients that converted to Alzheimer's disease dementia and 130 that converted to other forms of dementia. The sensitivity of T-tau values ranged from 51% to 90% and the specificity from 48% to 88%. Sensitivities for P-tau ranged from 40% to 100% and specificities ranged from 22% to 86%. In the five studies that evaluated the CSF P-tau/Aβ ratio, the sensitivities were between 80% and 96% and the specificities were between 33% and 95%. Eight of 15 studies were of poor methodological quality, and in the majority of studies there was an unclear risk of bias. The authors conclude that the biomarkers analyzed lack the accuracy to identify patients who will progress from MCI to AD.

The 2014 meta-review of systematic reviews by Ferreira summarized above included studies of CSF biomarkers for differentiating patients with MCI who progress to AD from those who do not.[12] In systematic reviews with meta-analyses, sensitivity and specificity of Aβ42 were 67% (95% CI 59 to 75) and 71% (95% CI 65 to 78), respectively; for T-tau, 82% (95% CI 76 to 86) and 70% (95% CI 65 to 85), respectively; and for P-tau, 81% (95% CI 69% to 91%) and 65% to 76%, respectively. Positive and negative likelihood ratios for all three tests ranged from 2 to 3 and from 0.3 to 0.5, respectively.

Prognosis for Progression of Mild Cognitive Impairment

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.[25] This was the first study to compare the accuracy of regional amyloid beta PET (using the [^{18}F]-flutemetamol) and different CSF assays or ratios of CSF biomarkers, including amyloid beta-42/40, for this diagnostic purpose. The study included 34 patients with MCI who developed AD dementia within 3 years and 122 healthy elderly controls. Overall, the best CSF measures for the identification of MCI-AD were amyloid-beta 42/total tau (t-tau) and amyloid beta-42/hyperphosphorylated tau (p-tau), with an AUC of 0.93 to 0.94. The best PET measures (i.e., anterior cingulate, posterior cingulate/precuneus, 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 nonsignificant (p=0.09 to.40). The combination of CSF and PET was not better than using either biomarker separately. The results were replicated in 146 controls and 64 patients with MCI-AD from the Alzheimer's Disease Neuroimaging Initiative (ADNI) study that utilized another CSF assay (amyloid beta-42, t-tau and p-tau) and PET (^{18}F-florbetapir) tracer. In the ADNI cohort, amyloid-beta 42/t-tau and amyloid beta-42/p-tau ratios similarly had higher AUCs that amyloid beta-42 alone.

Lewczuk (2017) evaluated whether amyloid beta-42 alone or the amyloid beta-42/40 ratio corresponded better with amyloid beta PET status.[26] 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. 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<0.0001) and a larger AUC (0.936 vs. 0.814, p<0.0001) associated with the ratio.

Nisenbaum (2022) compared CSF biomarkers to amyloid PET in the EMERGE and ENGAGE phase 3 RCTs of anti-amyloid therapy, aducanumab.[27] EMERGE and ENGAGE participants had MCI due to AD or mild AD with pathology confirmed amyloid-beta pathology by amyloid PET scan. A population of 350 participants who were screened for the RCTs (EMERGE, n=208; ENGAGE, n=142) were included in a CSF substudy. Amyloid PET imaging was performed using any of the FDA-approved amyloid PET tracers. Expert central readers classified the amyloid PET scans as positive or negative. CSF samples were tested for p-tau, t-tau, amyloid beta-42 and amyloid beta-40 via the Lumipulse® system. The mean age for participants in the substudy was 70 years (SD=7). Nearly half (46%) of the participants were female, 93% of participants were White, 1% were Black and 1% were Asian, 37% of participants were ApoE ε4 noncarriers, 47% were heterozygous and 17% were homozygous. The AUC (95% CI) for the amyloid beta-42/40 ratio was 0.90 (0.83 to 0.97, p<0.001) with a positive percent agreement of 94% (91 to 97) and a negative percent agreement of 88% (74 to 96). The AUC of t-tau/amyloid beta-42 ratio was 0.92 (0.86 to 0.97, p<0.001) with positive percent agreement of 92% (89 to 95) and negative percent agreement of 82% (66 to 92).

Clinical Utility

Although not without controversy because of modest efficacy, cholinesterase inhibitors are used to treat mild-to-moderate Alzheimer's disease.[6] Memantine, an NMDA receptor antagonist, appears to provide a small benefit in those with moderate-to-advanced disease.[28] Given available therapies, in principle more accurate diagnosis might allow targeting treatment to those most likely to benefit. However, clinical trial entry criteria and benefit have been based on clinical diagnosis. While the possibility that more accurate diagnosis might 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 Alzheimer's disease.[29-33]

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 (2019) published results from a large scale (n=16,008) 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).[34] Disease-specific morbidity or mortality were not evaluable.

BLOOD BIOMARKER TESTING

Due to the limited published evidence regarding the impact of blood biomarker testing on patient health outcomes, this evidence review is focused on CSF testing.

Clinical Validity

Systematic Reviews

The systematic review by Olsson (2016) discussed above also evaluated blood biomarkers to determine which may be useful to distinguish patients with AD from controls and patients with MCI due to AD from those with stable MCI.[11] In total, 231 articles comprising 15,699 patients with AD and 13,018 controls were included in the analysis. Among blood biomarkers, plasma T-tau was the only biomarker found to discriminate patients with AD from controls (p=0.02). No differences in plasma concentrations of amyloid beta-42 and amyloid beta-40 biomarkers in individuals with AD as compared to controls were seen in this systematic review; however, these results were reported before the development of more highly sensitive assays and technologies.

Cohort Studies

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

Janelidze (2020) evaluated the diagnostic and prognostic usefulness of plasma pTau181 in three cohorts totaling 589 individuals (patients with MCI, AD dementia, non-AD neurodegenerative diseases, and cognitively unimpaired individuals).[36] Results revealed plasma pTau181 to be increased in patients with preclinical AD and further elevated in the MCI and dementia disease stages. Plasma pTau181 also differentiated AD dementia from non-AD neurodegenerative diseases with an accuracy similar to PET Tau and CSF pTau181 and detected AD neuropathology in an autopsy-confirmed cohort.

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

Clinical Utility

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

URINARY BIOMARKER TESTING

Clinical Validity

Systematic Reviews

Zhang (2014) conducted a systematic review and meta-analysis of urinary AD–associated neural thread protein for diagnosing AD in patients with suspected AD.[38] Nine studies were included (total n=841 patients with probable or possible AD, 37 patients with MCI, 992 non-AD controls with or without dementia). 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 7.11 to 11.1) and 0.12 (95% CI 0.09 to 0.16), respectively.

Clinical Utility

As above, there is no direct evidence or indirect chain of evidence to support the clinical utility of urinary markers for diagnosing AD.

Section Summary

At present, the diagnostic accuracy of neural thread protein for diagnosis of AD has not been established. Neither have studies of clinical utility been identified. Additional research on both diagnostic and clinical validity of this biomarker is needed before conclusions can be made about the effectiveness of its use.

SKIN CELL (FIBROBLAST) TESTING

Two small case-control studies have linked various characteristics of fibroblast cell cultures to AD. Chirila (2013) compared skin fibroblast samples between individuals diagnosed with AD (n=10), individuals diagnosed with Parkinson's disease and/or Huntington disease (n=7) and age-matched controls without dementia (n=11), and reported significant differences in various markers of cell culture network formation, aggregation, and migration.[39] Chirila (2014) reported on differences in cellular aggregation measures between fibroblast samples from AD patients and controls without dementia in samples that overlapped substantially with the previous study (29/38).[40] It is not clear how the measures in these studies compare to the DISCERN™ test that is commercially available. No studies evaluating the performance of this test were identified.

PRACTICE GUIDELINE SUMMARY

Several clinical practice guidelines address the use of biomarkers in the diagnosis of Alzheimer's disease (AD). Among those which are proponents of their use, support is conditioned on further study, or use within research settings alone.

AMERICAN ACADEMY OF NEUROLOGY

The American Academy of Neurology (AAN) does not address laboratory testing for the clinical evaluation of dementia in their Practice Parameter for the diagnosis of dementia, including AD.[1] In their practice guideline "Update: Mild Cognitive Impairment," they state that "there are no biomarkers clearly shown to predict progression in patients with MCI."

THE ALZHEIMER'S ASSOCIATION

The 2024 updated consensus recommendations from the Alzheimer's Association Workgroup on diagnostic guidelines for Alzheimer's disease propose that "the following can be diagnostic of AD: amyloid PET; CSF Aβ 42/40, CSF p-tau 181/Aβ 42, CSF t-tau/Aβ 42; or 'accurate' plasma assays where 'accurate' can be defined as accuracy that is equivalent to approved CSF assays in detecting abnormal amyloid PET in the intended-use population."[4] However, they also note that not all assays of these biomarkers have sufficient accuracy for diagnostic purposes. Additional biomarkers, including other phosphorylated tau forms, tau PET, and NFL, were recommended as potentially useful for confirming AD pathology and/or staging, but were not recommended as primary diagnostic tests, as they not be used to rule out AD.

AMERICAN PSYCHIATRIC ASSOCIATION

A 2007 guideline on the treatment of patients with AD and other dementias by the American Psychiatric Association (APA) workgroup on AD stated, “Except in rare circumstances (notably the use of CSF-14-3-3 protein when Creutzfeldt-Jakob disease is suspected and recent stroke or viral encephalitis can be excluded), these techniques remain investigational, and there is insufficient evidence for their utility in routine clinical practice.”[41]

ALZHEIMER’S ASSOCIATION

In 2013, recommendations from the Alzheimer’s Association (AA) 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.” 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.”[42]

SUMMARY

There is not enough research to show that testing for Alzheimer disease (AD)-related biomarkers improves health outcomes for people who have AD, dementia, or mild cognitive impairment (MCI). No clinical guidelines based on research recommend the use of AD biomarkers. Therefore, the use of cerebral spinal fluid, blood, urinary, and skin cell biomarkers for diagnosis of AD, or for prediction of conversion from MCI to AD, is considered investigational.

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CODES

NOTE: Some of the following CPT codes may be used to identify the steps in testing for tau protein and amyloid beta peptides. There are no specific codes used for testing for neural thread protein.

Codes	Number	Description
CPT	0206U	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
	0207U	Neurology (Alzheimer disease); quantitative imaging of phosphorylated ERK1 and ERK2 in response to bradykinin treatment by in situ immunofluorescence, using cultured skin fibroblasts, reported as a probability index for Alzheimer disease (List separately in addition to code for primary procedure)
	~~0346U~~	~~Beta amyloid, Aβ40 and Aβ42 by liquid chromatography with tandem mass spectrometry (LC-MS/MS), ratio, plasma~~ (Deleted 01/01/2025)
	0358U	Neurology (mild cognitive impairment), analysis of β-amyloid 1-42 and 1-40, chemiluminescence enzyme immunoassay, cerebral spinal fluid, reported as positive, likely positive, or negative
	0412U	Beta amyloid, Aβ42/40 ratio, immunoprecipitation with quantitation by liquid chromatography with tandem mass spectrometry (LC-MS/MS) and qualitative ApoE isoform specific proteotyping, plasma combined with age, algorithm reported as presence or absence of brain amyloid pathology
	0445U	β-a Amyloid Beta (Abeta42) and phospho tau (181P) (pTau181), electrochemiluminescent immunoassay (ECLIA), cerebral spinal fluid, ratio reported as positive or negative for amyloid pathology
	0459U	B-amyloid (Abeta42) and total tau (tTau), electrochemiluminescent immunoassay (ECLIA), cerebral spinal fluid, ratio reported as positive or negative for amyloid pathology
	0479U	Tau, phosphorylated, pTau217

	0503U	Neurology (Alzheimer disease), beta amyloid (Aβ40, Aβ42, Aβ42/40 ratio) and tau-protein (ptau217, np-tau217, ptau217/nptau217 ratio), blood, immunoprecipitation with quantitation by liquid chromatography with tandem mass spectrometry (LC-MS/MS), algorithm score reported as likelihood of positive or negative for amyloid plaques
	0551U	Tau, phosphorylated, pTau217, by single-molecule array (ultrasensitive digital protein detection), using plasma
	81099	Unlisted urinalysis procedure
	82233	Beta-amyloid; 1-40
	82234	Beta-amyloid; 1-42
	83520	Immunoassay for analyte other than infectious agent antibody or infectious agent antigen; quantitative; not otherwise specified
	84393	Tau, phosphorylated
	84394	Tau, total
	86849	Unlisted immunology procedure
HCPCS	None	

Date of Origin: *October 1999*