Biochemical Markers of Alzheimer Disease

Description

A variety of biochemical changes have been associated with Alzheimer disease pathology and are being evaluated to aid in the diagnosis of Alzheimer disease (AD). Some of the most commonly studied biomarkers are amyloid-β peptide 1-42 (AB-42), and total or phosphorylated tau protein (T-tau or P-tau) in cerebrospinal fluid (CSF).

Background

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

Mild cognitive impairment (MCI) may be diagnosed when there is a change in cognition, but not sufficient impairment for the diagnosis of dementia. (2) MCI is characterized by impairment in 1 or more cognitive domains but preserved functional independence. In some patients, MCI may be a predementia phase of AD. Patients with MCI or suspected AD may undergo ancillary testing (eg, neuroimaging, laboratory studies, and neuropsychological assessment) to rule out vascular, traumatic, and medical causes of cognitive decline and to evaluate genetic factors. Because clinical diagnosis can be difficult, particularly early in the course of disease, there has been considerable interest in developing an accurate laboratory test for AD. Several potential biomarkers of AD are associated with AD pathology (ie, beta amyloid plaques and 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 AB-42. Other potential CSF (3, 4) and serum (5) peptide markers have also 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. AB-42 is the key peptide that is produced from metabolism of amyloid precursor protein. AB-42 is the key peptide deposited in the amyloid plaques characteristic of AD. Low levels of AB-42 in the CSF have been associated with AD, perhaps because AB-42 is deposited in amyloid plaques instead of remaining in fluid. Investigators have suggested that the tau/AB-42 ratio may be a more accurate diagnostic marker than either alone. (6) A variety of kits are commercially available to measure AB-42 and tau proteins. Between-laboratory variability in CSF biomarker measurement is large. (7, 8)

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.

**Regulatory Status**

No biochemical marker tests for Alzheimer disease are currently approved by the U.S. Food and Drug Administration (FDA). Commercially available tests include:

- AlzheimAlert™ (Nymox Pharmaceutical Corporation; Hasbrouck Heights, NJ)
- Innotest® assays for T-tau, P-tau, and aB-42 (Fujirebio [previously Innogenetics]; Malvern, PA)
- AdMark® CSF analysis

These are laboratory-developed tests. 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, FDA has chosen not to require any regulatory review of these tests.

Nymox Pharmaceutical Corporation previously offered AD7C testing as an LDT but no longer lists the test on its web site.

**Related Policies**

2.04.13 Genetic Testing for Familial Alzheimer Disease
6.01.55 Beta Amyloid Imaging with Positron Emission Tomography (PET) for Alzheimer Disease

**Policy**

*This policy statement applies to clinical review performed for pre-service (Prior Approval, Precertification, Advanced Benefit Determination, etc.) and/or post-service claims.*

Measurement of cerebrospinal fluid biomarkers of Alzheimer disease, including but not limited to tau protein, amyloid beta peptides, or neural thread proteins, is considered not medically necessary.

Measurement of urinary biomarkers of Alzheimer disease is considered not medically necessary, including but not limited to neural thread proteins.
Rationale

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

Evidence of health benefit or clinical utility from testing requires demonstrating:

- incremental improvement in diagnostic or prognostic accuracy over current practice and
- that incremental improvements lead to improved health outcomes (eg, by informing clinical management decisions), and
- generalizability

A framework for evaluating evidence supporting health benefit following testing requires consideration of the following: appropriate reference standard, requirements for predicting conversion from MCI to AD, how better diagnostic accuracy or prediction of conversion would lead to improved health outcomes; appropriate data analysis including assay cutoffs; patient sample composition (inclusion and exclusion criteria), and validation of accuracy or prediction in independent samples as evidence of generalizability.

Criterion Standard: Accuracy of clinical AD diagnostic criteria has been established by comparison to autopsy, the criterion standard. Therefore, comparison with autopsy is most appropriate to validly assess incremental diagnostic improvement of biomarkers.

Predicting Conversion from MCI to AD: Predicting conversion from MCI to AD may rely on clinical diagnosis, albeit with some attendant error and misclassification, because the prediction of interest is conversion and not the criterion 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. (9) Alternative approaches such as classical receiver operating characteristic (ROC) analyses, while providing insight, do not allow one to directly translate improvements in diagnostic or prognostic accuracy to changes in health outcomes. (10)

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, in turn overstating test accuracy.

Sample Definition: Clear description of whether samples included consecutive patients or were selective is required to evaluate potential bias—including verification bias (exclusion of cases without postmortem autopsy) (11) - and generalizability.

Validation: Validation in independent samples is required to establish generalizability of markers.
Diagnostic Accuracy of CSF Markers Versus Clinical Diagnosis

Most studies have relied on clinically diagnosed AD as the criterion standard. These studies are described next, and results are summarized in Table 1.

Rosa et al (2014) conducted a systematic review with meta-analysis of studies of CSF AB-42 in patients with clinically-diagnosed AD. (12) Literature was searched to May 2013, and 41 prospective or retrospective, cohort, case-control, and cross-sectional studies were included (total N=5086 2932 AD, 2154 non-demented controls). 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% confidence interval [CI], 81 to 85) and 79% (95% CI, 77 to 81), respectively. Positive and negative likelihood ratios were 4.5 (95% CI, 3.7 to 5.4) and 0.18 (95% CI, 0.14 to 0.22), respectively, and their ratio, the diagnostic odds ratio, was 29 (95% CI, 21 to 40). Statistical heterogeneity was substantial (I²=68%); studies varied in test cutoffs used and severity of AD across patient samples. Eleven studies (total N=1459 [830 AD, 629 controls]) reported AB-42 CSF levels. Mean (SD) CSF AB-42 was 467 pg/mL (189) in patients with AD and 925 pg/mL (414) in controls (weighted mean difference, 450 pg/mL [95% CI, –600 to –289]; p<0.001). However, statistical heterogeneity was considerable (I²=99%).

Ferreira et al (2014) published a meta-review of systematic reviews with meta-analyses to assess the use of CSF biomarker tests for AD after publication of revised AD diagnostic criteria (13) in 2011. (14) Literature was searched in September 2013, and 7 systematic reviews were included. None were 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. Results for both the systematic reviews and the individual studies are summarized in Table 1. For differentiating AD from non-demented controls, positive and negative likelihood ratios for all 3 biomarkers ranged from 4-8 and from 0.1-0.3, respectively. For differentiating AD from other dementias, 1 systematic review of 7 studies reported positive and negative likelihood ratios of 46 and 0.09, respectively, for differentiating AD (n=175) from Creutzfeldt–Jakob disease (n=110). (15) With this systematic review excluded, positive and negative likelihood ratios ranged from 2-7 and from 0.15-0.4, respectively.

A 2011 meta-analysis included 119 studies on biomarkers and diagnostic imaging in AD. (16) Sensitivity and specificity were calculated for distinguishing AD from non-demented controls, and for distinguishing AD from non-AD dementias with and without MCI, if available. The included studies of CSF biomarkers used a variety of thresholds, with clinical diagnosis or autopsy as the reference standard. Twenty studies of the AB-42 CSF marker were included; pooled analysis resulted in sensitivity of 76% and specificity of 77%. CSF total tau was evaluated in 30 studies with a resulting sensitivity of 79% and specificity of 85%. CSF P-tau was evaluated in 24 studies resulting in a pooled sensitivity of 78% and specificity of 81%. Six studies evaluated CSF P-tau as a biomarker to distinguish AD patients from patients with MCI, with a pooled sensitivity of 73% and specificity of 69%. The combination of total tau and AB-42 was evaluated in 12 included studies with a pooled sensitivity of 80% and specificity of 76%. In comparison of CSF biomarkers, the area under the ROC curve was highest for P-tau alone (0.85). 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%) and lower specificity (57%).

In a 2006 review of studies using clinical diagnosis as the criterion standard, Formichi et al (17) identified studies examining diagnostic accuracy of the following cerebrospinal fluid (CSF) markers for AD: total tau protein (T-tau) (41 studies; 2287 AD patients and 1384 controls; sensitivity, 52%-100%; specificity, 50%-100%), phosphorylated tau protein (P-tau) (12 studies; 760 AD patients and 396 controls; sensitivity, 37%-100%; specificity, 80%-100%), and amyloid beta peptide 1-42 (AB-42) (14 studies; 688 AD patients and 477 controls; sensitivity, 55%-100%; specificity, 80%-100%). Although primarily a descriptive review, test accuracies varied widely and only 1 study included a majority of autopsy-confirmed AD diagnoses.

Table 1. CSF Biomarkers Performance for Distinguishing AD From Controls

<table>
<thead>
<tr>
<th></th>
<th>Non-Demented Controls</th>
<th>Controls with Dementia (*)</th>
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<tbody>
<tr>
<td></td>
<td>Sensitivity</td>
<td>Specificity</td>
</tr>
<tr>
<td>AB-42</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ferreira 2014 (14) SR</td>
<td>80% (73 to 85)</td>
<td>82% (74 to 88)</td>
</tr>
<tr>
<td>Ferreira 2014 (14) IS</td>
<td>63%-97%</td>
<td>67%-92%</td>
</tr>
<tr>
<td>Rosa 2013 (12)</td>
<td>84% (81 to 85)</td>
<td>79% (77 to 81)</td>
</tr>
<tr>
<td>Mattson 2011 (16)</td>
<td>76%</td>
<td>77%</td>
</tr>
<tr>
<td>Formichi 2006 (17)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>T-tau</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ferreira 2014 (14) SR</td>
<td>82% (76 to 87)</td>
<td>90% (86 to 93)</td>
</tr>
<tr>
<td>Ferreira 2014 (14) IS</td>
<td>61%-91%</td>
<td>53%-97%</td>
</tr>
<tr>
<td>Mattson 2011 (16)</td>
<td>79%</td>
<td>85%</td>
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<tr>
<td>Formichi 2006 (17)</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td>P-tau</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ferreira 2014,14 SR</td>
<td>78%-80%</td>
<td>83%-88%</td>
</tr>
<tr>
<td>Ferreira 2014,14 IS</td>
<td>61%-89%</td>
<td>37%-92%</td>
</tr>
<tr>
<td>Mattson 201116</td>
<td>78%</td>
<td>81%</td>
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<tr>
<td>Formichi 200617</td>
<td>NR</td>
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</tbody>
</table>

Values in parentheses are 95% confidence intervals unless otherwise noted.
IS: individual studies; NR: not reported; P-tau: phosphorylated tau protein; SR: systematic review; T-tau: total tau protein

a Or unspecified

Section Summary: Several studies have examined the diagnostic performance of CSF biomarkers for distinguishing probable AD from non-demented controls and from patients with other types of dementia. The range of reported sensitivities and specificities is broad; in systematic reviews with meta-analyses, sensitivity and specificity were 80%-82% and 82%-90%, respectively, for differentiating AD from non-demented controls, and 73% and 67%, respectively, for differentiating AD from other dementias. Positive and negative likelihood ratios were 2-8 and 0.2-0.4, respectively, in either setting. This evidence does not indicate that CSF biomarkers improve the accuracy of clinical diagnostic criteria.
Engelborghs et al (2008) assayed P-tau and AB-42 in banked CSF. (18) Samples were examined from 100 patients with and 100 without dementing illness seen between 1992 and 2003. All dementia diagnoses were autopsy proven (67 pure AD, 6 mixed, 27 non-AD dementias). Details of the sample selection were not provided; whether CSF testing was routine or selective was not indicated. Of those with dementia, 76 were evaluated in a memory clinic and the remainder in referring centers; all underwent clinical, neuropsychological, and imaging evaluations. The non-demented group was substantially younger (age, 47 vs 76 years). Laboratory technicians performing assays were blinded to clinical diagnoses. Samples from 52 subjects required retesting due to questionable results. Sensitivity and specificity of clinical evaluation for a pure AD diagnosis was 83% with 75% respectfully; and of P-tau and AB-42 in combination, 80% and 93%, respectively. In logistic regression models, CSF biomarkers did not provide incremental diagnostic accuracy over the clinical diagnosis; as stated by the authors,—“[a]lthough biomarkers did not perform significantly better comparing all unique clinical diagnoses, they were also not significantly worse, and could therefore add certainty to an established diagnosis.” Four of 7 listed authors were employees of the test manufacturer (Innogenetics [now Fujirebio; Ghent, Belgium).

Clark et al (2003) examined CSF from 106 patients with autopsy-confirmed dementia who were evaluated at 10 referral clinics and 73 controls (4 pathologically examined). (19) Laboratory technicians were blinded to clinical diagnoses. An optimal cutoff of 234 pg/mL for total tau had sensitivity and specificity of 85% and 84%, respectively, for distinguishing those with AD (n=73) from cognitively normal individuals (n=74); AB-42 offered no incremental diagnostic value to total tau in ROC analyses. An optimal cutoff of 361 pg/mL had sensitivity and specificity of 72% and 69%, respectively, for distinguishing AD (n=74) from frontotemporal dementia (FTD) (n=3) and dementia with Lewy bodies (DLB) (n=10).

Bian et al (2008) assembled a sample from 2 institutions including 30 patients with FTD (19 autopsy-proven and 11 with known causal genetic mutations) and autopsy proven AD (n=19). (20) Using an optimal cutoff of 403 pg/mL, total tau had sensitivity and specificity of 68% and 90%, respectively, for distinguishing FTD from AD. A tau/AB-42 ratio of 1.06 had 97% specificity for distinguishing FTD from AD.

Cure et al (2014) conducted a systematic review with meta-analysis of CSF and imaging studies for the diagnosis of definite AD (autopsy-confirmed). (21) Literature was searched in January 2012, and 3 studies of CSF markers (P-tau, T-tau, AB-42, and AB-40) 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 (non-demented patients 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.

Section Summary: There is limited existing evidence examining incremental diagnostic accuracy of CSF biomarkers for AD diagnosis employing autopsy as a criterion standard. Current evidence does not demonstrate improvement over a clinical diagnosis, or whether diagnosis using CSF biomarkers would lead to improved health outcomes.
CSF Markers in Combination

As previously noted, for patients with clinically diagnosed AD, some have suggested that the tau/AB-42 ratio is a more accurate predictor than either alone. For example, using optimal cutoffs, de Jong et al (2006) reported sensitivity and specificity of 95% and 90% in a sample with clinically diagnosed AD (n=61) and vascular dementia (VaD) (n=61). (22) In contrast, Le Bastard et al (2007) found the P-tau/AB-42 ratio lacked specificity to distinguish AD from VaD in a sample of 85 patients (VaD [n=64] or AD [n=21]; 76/85 autopsy-confirmed diagnoses); specificity was 52% and sensitivity, 91%-95%. (23)

CSF AB-42 level normalized to CSF AB-40 (ie, the AB-42/AB-40 ratio) is being investigated as a marker for patients with uncertain clinical diagnosis. Because AB-40 is not incorporated into amyloid plaques, CSF levels are more stable than those of AB-42. Sauvee et al (2014) examined the AB-42/AB-40 ratio in 122 patients with atypical dementia who had discordant CSF biomarker results (ie, tau, P-tau, and AB-42). (24) Using 0.05 as the ratio threshold, biological profiles were clarified in 72 (59%) of 122 patients with the addition of the AB-42/AB-40 ratio. However, of 35 patients diagnosed with AD by biological profile, 9 (26%) did not meet clinical criteria for AD or mixed dementia.

Section Summary: Clinical utility of CSF biomarkers used in combination has not been demonstrated.

Neural Thread Protein

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. (25) Nine studies were included (total N=841 patients with probable or possible AD, 37 patients with MCI, 992 non-AD demented or non-demented controls). 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.

Kahle et al (2000) reported on the diagnostic potential of CSF levels of total tau protein and neural thread protein in a group of 35 patients with dementia (30 with probable or definite AD), 5 patients with Lewy body disease, 29 patients with Parkinson’s disease, and 16 elderly healthy control patients. (26) Levels of both tau and neural thread protein were elevated in patients with AD compared with controls; sensitivity and specificity were (63% and 93%), respectively, for tau, and 70% and 80%, respectively, for neural thread protein.

In a prospective multicenter study conducted at 8 sites, Goodman et al (2007) enrolled 168 patients with recent referral to memory clinics. (27) The urinary neural thread test was 91.4% sensitive for a diagnosis of probable AD (32/35) and 90.1% specific among healthy patients. However, it was unclear whether the marker changed management or what the potential consequences of a 9.9% false-positive rate might be.

Section Summary: Data on neural thread protein as a marker for AD are limited. In 2 studies and 1 meta-analysis, estimated sensitivity and specificity ranged from 70%-91% and from 80%-90%, respectively. Clinical utility of neural thread protein testing has not been demonstrated.
CSF Markers and Progression of Mild Cognitive Impairment (MCI)

Studies have also evaluated the prognostic value of markers for progression of MCI and conversion to clinically manifest AD.

Ritchie et al (2014) published a Cochrane review of CSF amyloid beta protein (primarily AB-42) for detecting which patients with MCI would progress to AD or other dementias. (28) Literature was searched in December 2012, and 14 prospective or retrospective cohort studies of AD, including 1 discussed next, (29) were included (total N=1349 patients with MCI). Studies that enrolled patients less than 50 years of age or with less than 2 years of follow-up were excluded. Risk of bias was moderate to high in most studies. AD, diagnosed by clinical criteria, developed in 436 (32%) of 1349 patients. Sensitivity ranged from 36%-100%, and specificity from 29%-91%. Due to heterogeneity of thresholds used, summary sensitivity and specificity were not calculated. However, a summary ROC curve was generated using the median specificity of 64%; pooled sensitivity was 81% (95% CI, 72 to 87). Positive and negative likelihood ratios were 2.2 (95% CI, 2.0 to 2.5) and 0.31 (95% CI, 0.21 to 0.48), respectively. Analysis of the pre- and post-test probabilities of conversion to AD among patients with MCI in primary and secondary care settings showed little incremental value of AB-42 testing in either setting.

The 2014 meta-review of systematic reviews by Ferriera et al (discussed above) included studies of CSF biomarkers for differentiating patients with MCI who progress to AD from those who do not. (14) In systematic reviews with meta-analyses, sensitivity and specificity of AB-42 were 67% (95% CI, 59 to 75) and 71% (95% CI, 65-78), respectively; for T-tau, 82% (95% CI, 76 to 86) and 70% (95% CI, 65 to 85), respectively; and for P-tau, 81% (69 to 91) and 65%-76%, respectively. Positive and negative likelihood ratios for all 3 tests ranged from 2-3 and from 0.3-0.5, respectively.

Mattsson et al (2009) recruited individuals from 12 U.S. and European centers with MCI (n=750), AD (n=529), and controls (n=304). (30) Those with MCI were followed up a minimum of 2 years or to progression. Development of probable AD was associated with lower CSF AB-42, and higher T-tau and P-tau. Using cutoffs defined in the AD and control groups for a diagnostic sensitivity of 85%, combining AB-42/P-tau and T-tau yielded sensitivity for AD conversion of 83% (95% CI: 78% to 88%), specificity 72% (95% CI: 68% to 76%), positive predictive value 62%; and negative predictive value 88%. Type of MCI (amnestic or nonamnestic) was not specified.

Herukka et al (2007) reported on a sample of 106 patients evaluated at a university neurology department and 33 “from an ongoing prospective population-based study”; selection criteria other than agreeing to a lumbar puncture were not further described. (31) Seventy-nine patients were diagnosed with MCI, 47 with amnestic type, 33 converting to dementia; 60 were included as controls. Average follow-up ranged from 3.5 years (MCI converters), 3.9 years (controls), to 4.6 years (stable MCI). CSF AB-42, P-tau, and total tau were measured. Graphical representation of AB-42, P-tau, and total tau suggested considerable overlap between controls, those with stable MCI, and progressive MCI. Test accuracy was not reported.

Hansson et al (2006) obtained 137 CSF samples from a larger group of 180 consecutive individuals with MCI evaluated at a referral memory clinic between 1998 and 2001. (32) CSF was also obtained
From 39 controls. In the analytical sample (n=137) patients were 50 to 86 years of age at baseline and 55% were female. Median follow-up was 5.2 years; 57 (42%) progressed to AD. Using a predictor comprising T-tau and AB-42/P-tau with optimal cutoffs, sensitivity and specificity for progression to clinical AD were 95% (95% CI, 86 to 98) and 87% (95% CI, 78 to 93), respectively. Patients were not categorized by the presence of amnestic MCI conferring increased risk of conversion to AD. (33)

From 4 international clinical research centers, Ewers et al (2007) retrospectively assembled a sample of 88 patients with amnestic MCI based on both the availability of CSF samples and at least 1 follow-up between 1 and 3 years after initial evaluation; 57 healthy controls with baseline evaluations only also were included. (34) Forty-three patients (49%) in the MCI group converted to AD over an average 1.5-year follow-up. Using a cutoff of 27.3 pg/mL, sensitivity and specificity of P-tau for conversion were 87% (95% CI, 73 to 93) and 73% (95% CI, 55 to 84) respectively. It should be noted that the conversion rate to AD in the sample was between 2- and 3-fold higher than the typical 15% found in amnestic MCI.

Andreasen et al (2005) studied 32 controls and 44 patients with MCI who, after a 1-year follow-up, had progressed to probable AD. (35) At the start of the study, the investigators evaluated total and P-tau and AB-42 levels. At baseline, 79.5%, 70.4%, and 77.3% had abnormal levels of total tau, P-tau, and AB-42, respectively. These results would have been more informative if patients with MCI who did not progress to AD were included for comparison.

Bouwman et al (2007) followed 59 patients with MCI a mean of 19 months (range, 4 - 45), obtaining baseline of CSF AB-42 and tau. (36) Abnormal AB-42 (<495 pg/mL) and total tau (>356 pg/mL) were accompanied by increased, but imprecise, relative risks for progression to AD (5.0 [95% CI, 1.4 to 18.0] and 5.3 [95% CI, 1.5 to 19.2]), respectively).

Parnetti et al (2006) examined 55 patients with MCI. (29) Baseline CSF AB-42, total tau, and P-tau were measured; 38% had abnormal values. After 1 year, 4 (12%) of 33 stable patients had abnormal markers. Of 11 patients who progressed to AD, Lewy body disease, or familial frontotemporal dementia (FTD), 10 (91%) had 2 or more abnormal markers. Although results from these studies are consistent with potential prognostic utility of markers, sample sizes were small. Additionally, the type of MCI (amnestic or nonamnestic) was not specified but has important predictive value for progression to dementia.

Section Summary: Evidence suggests that biomarker testing may identify increased risk of conversion from MCI to AD. Evidence that earlier diagnosis leads to improved health outcomes through delay of AD onset or improved quality of life is lacking.

**Alzheimer Disease Neuroimaging Initiative (ADNI)**

Initiated in 2003, the ADNI is a public-private effort designed to aid researchers and clinicians to develop new treatments and monitor their effectiveness, as well as lessen the time and cost of clinical trials. Participants have been recruited across the U.S. and Canada with follow-up every 6 months for approximately 10 years. Participants undergo neuropsychological testing, imaging and biomarker evaluations to determine whether these measures can be combined to monitor the progression of MCI...
and AD. Ongoing results from several studies span diagnostic and prognostic questions addressed here.

In a 2011 report, Gomar et al evaluated the value of neuropsychological testing, neuroimaging, and biomarkers (CSF AB and tau) for diagnosing AD in all participants in the ADNI database who had a lumbar puncture. (37) This included 105 normal controls, 179 individuals with MCI, and 91 with AD. Neuropsychological testing and magnetic resonance imaging (MRI) were found to be the most informative techniques, with 84% and 82% correct classification, respectively. CSF assessments had 73% correct classification and did not add diagnostic information when all the techniques were combined. CSF assessments were less informative in patients aged 75 years and older (70% correct classification vs. 77% for patients ≤75).

Two reports from 2009 compared MRI scans and CSF biomarkers for diagnosis and prognosis among 399 participants undergoing both exams (109 normal, 192 amnestic MCI, and 98 AD). (38, 39) In ROC analyses, the c-statistics for MRI as diagnostic of probable AD compared with normal and for P-tau/AB-42 were 0.90 and 0.84, respectively. (38) In the longitudinal evaluation both MRI and biomarkers were associated with conversion to AD; c-indices were 0.69 for MRI and 0.62 for T-tau/AB-42. (39) Reclassification measures were not reported. In these studies, MRI appeared to provide greater diagnostic (for probable AD) and prognostic information.

In a 2012 report, Schmand et al evaluated the value of neuropsychological testing, neuroimaging, and biomarkers (AB and tau in CSF) for predicting the conversion to AD in 175 patients with MCI. (40) With a mean follow-up of 2.7 years (range, 0.5-4.6), 81 patients (46%) had converted to AD. Neuropsychological testing and MRI predicted conversion with 63%-67% classification success both in patients younger and older than 75 years. CSF biomarkers correctly classified 64% of patients younger than 75 years and 60% of patients ≥75 years of age. Difference in prediction for markers in combination (70%) was not significantly better than the individual markers.

Landau et al (2010) examined predictors of conversion to clinically diagnosed AD and cognitive decline in 85 patients with amnestic MCI in the ADNI. (41) Twenty-eight patients developed AD over a mean 1.9-year follow-up. In multivariate models, CSF markers (P-tau, T-tau, P-tau/AB-42, T-tau/AB-42) were not associated with conversion to AD.

De Meyer et al (2010) developed a model using biomarkers (CSF AB-42/P-tau) in the US-ADNI sample (114 cognitively normal, 200 MCI, and 102 AD patients). (42) Sensitivity and specificity in the development set were 90% and 64%, respectively; one-third of cognitively normal individuals had false-positive results. The model was then validated in a Belgian data set of 73 subjects with autopsy-confirmed dementia and correctly identified 64 (94%) of 68 AD patients. In a separate data set of 57 patients with MCI, the model identified all patients progressing to AD.

Ewers et al (2012) evaluated CSF AB-42, amyloid PET, fluorodeoxyglucose-posterior emission testing (FDG-PET), and MRI in 211 ADNI patients with at least 1 detected amyloid biomarker. (43) Using the most recent diagnostic criteria, in 92 patients undergoing all tests, AB-42 had 94% sensitivity for a positive FDG-PET or MRI. The authors concluded, "[m]ore correlation and validation studies of
biomarkers in the AD population will be essential to understand biomarker performance and correlation with autopsy data.”

In 181 ADNI patients with MCI, Richard et al (2013) found neither MRI nor CSF biomarkers improved classification of patients developing AD with a brief memory test. (44) Net reclassification improvement obtained by adding MRI results to the memory test was 1.1% and for CSF AB-42/P-tau, 2.2%.

Improved Health Outcomes (Clinical Utility): Although not without controversy because of modest efficacy, cholinesterase inhibitors are used to treat mild-to-moderate AD. (45, 46) Memantine, an N-methyl-d-aspartate (NMDA) receptor antagonist, appears to provide a small benefit in those with moderate-to-advanced disease. (45, 47) 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 AD. (48-51)

Practice Guidelines and Position Statements

National Institute of Neurological and Communicative Disorders and Stroke (NINCDS)-Alzheimer Disease and Related Disorders Association (ADRDA)

In 1984, the NINCDS and ADRDA developed clinical criteria for the diagnosis of AD. (52) Although evidence to date has used NINCDS/ADRDA’s AD classification, in 2011, the National Institute on Aging and the Alzheimer’s Association workgroup revised diagnostic criteria for diagnosis of dementia due to Alzheimer disease. (13)

In the 1984 guidelines, diagnostic categories were defined as follows in the 1984 guidelines:

Possible Alzheimer disease

Clinical diagnosis of possible AD:

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

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

Probable Alzheimer Disease

The criteria for the clinical diagnosis of probable AD include:
a) Dementia, established by clinical examination and documented by the Mini-Mental State Examination, the Blessed Dementia Scale, or some similar examination and confirmed by neuropsychological tests;
b) Deficits in 2 or more areas of cognition;
c) Progressive worsening of memory and other cognitive functions;
d) No disturbance of consciousness;
e) Onset between ages 40 and 90 years, most often after the age of 65 years; and
f) Absence of systemic disorders or other brain diseases that in and of themselves could account for the progressive deficits in memory and cognition.

The diagnosis of probable AD is supported by:

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

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

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

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

a) Sudden apoplectic onset;
b) Focal neurological findings such as hemiparesis, sensory loss, visual field deficits, and incoordination early in the course of the illness; and
c) Seizures or gait disturbances at the onset or very early in the course of the illness.

Definite Alzheimer Disease

Criteria for diagnosis of definite AD are:

a) Clinical criteria for probable Alzheimer disease AND
b) Histopathologic evidence obtained from a biopsy or autopsy.

**National Institute on Aging and the Alzheimer’s Association**

As of 2011, probable AD is now defined by the National Institute on Aging and the Alzheimer’s Association workgroup according to the following diagnostic criteria (13):

“We meets criteria for dementia described ... and in addition, have the following characteristics:

A. Insidious onset. Symptoms have a gradual onset over months to years, not sudden over hours or days;

B. Clear-cut history of worsening of cognition by report or observation; and

C. The initial and most prominent cognitive deficits are evident on history and examination in one of the following categories.

a) Amnestic presentation: It is the most common syndromic presentation of AD dementia. The deficits should include impairment in learning and recall of recently learned information. There should also be evidence of cognitive dysfunction in at least one other cognitive domain, as defined earlier in the text.

b) Nonamnestic presentations: Language presentation: The most prominent deficits are in word-finding, but deficits in other cognitive domains should be present. Visuospatial presentation: The most prominent deficits are in spatial cognition, including object agnosia, impaired face recognition, simultanagnosia, and alexia. Deficits in other cognitive domains should be present. Executive dysfunction: The most prominent deficits are impaired reasoning, judgment, and problem solving. Deficits in other cognitive domains should be present.

D. The diagnosis of probable AD dementia should not be applied when there is evidence of:

a) Substantial concomitant cerebrovascular disease, defined by a history of a stroke temporally related to the onset or worsening of cognitive impairment; or the presence of multiple or extensive infarcts or severe white matter hyperintensity burden; or

b) Core features of Dementia with Lewy bodies other than dementia itself; or

c) Prominent features of behavioral variant frontotemporal dementia; or

d) Prominent features of semantic variant primary progressive aphasia or nonfluent/agrammatic variant primary progressive aphasia; or

e) Evidence for another concurrent, active neurological disease, or a non-neurological medical comorbidity or use of medication that could have a substantial effect on cognition.”

All probable AD by NINCDS-ADRDA criteria are subsumed in the revised probable AD criteria. Revised criteria include a category of “Probable AD dementia with increased level of certainty” due to documented decline or having a causative AD genetic mutation. Additionally, a category “Probable AD dementia with evidence of the AD pathophysiological process” has been added. Evidence of the AD pathophysiological process is supported by detection of low (CSF) AB-42, positive positron emission
tomography (PET) amyloid imaging, or elevated CSF tau, and decreased 18-F fluorodeoxyglucose uptake on PET in the temporo-parietal cortex with accompanying atrophy by magnetic resonance imaging (MRI) in relevant structures. Detection of the “pathophysiological process” is further divided according to when in the disease natural history markers are expected to be detectable.

Note on Revised 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”. (13) However, the diagnostic criteria workgroup publication noted that “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.” (13)

Alzheimer's Association

In 2009, the Alzheimer’s Association initiated a quality control program for CSF markers, noting that “Measurements of CSF AD biomarkers show large between laboratory variability, likely caused by factors related to analytical procedures and the analytical kits. Standardization of laboratory procedures and efforts by kit vendors to increase kit performance might lower variability, and will likely increase the usefulness of CSF AD biomarkers”. (8) In 2012, the Alzheimer's Biomarkers Standardization Initiative published consensus recommendations for standardization of preanalytical aspects (eg, fasting, tube types, centrifugation, storage time and temperature) of CSF biomarker testing. (53)

In 2013, the Alzheimer’s Association published recommendations for operationalizing the detection of cognitive impairment during the Medicare annual wellness visit in primary care settings. (54) 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 (eg, CSF tau and beta amyloid proteins) “was not considered as these measures are not currently approved or widely available for clinical use.”

The 4th Canadian Consensus Conference on Diagnosis and Treatment of Dementia (CCCDTD4)

CCCDTD4 published updated evidence-based consensus recommendations in 2012. (55, 56) There was consensus that plasma AB-42 measurement is unreliable and is not recommended for clinical practice. There was lack of consensus for measurement of CSF AB-42 and tau levels in patients with atypical dementia. Conference participants concluded that “for now, measurement of CSF AB1-42 and tau have no clinical utility in Canada, although they are part of research protocols in observational and therapeutic studies.”
In 2012, EFNS-ENS published updated evidence-based consensus guidelines on the diagnosis and management of disorders associated with dementia. (57) A Level B recommendation (probably effective based on Class 3 [unblinded] evidence) that CSF AB-42/tau/p-tau assessment helps to differentiate AD was included.

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

Testing for biochemical markers is not a preventive service.

**Summary**

Evidence that testing for Alzheimer disease (AD)-related biomarkers in patients with dementia can improve health outcomes is lacking. A majority of studies derive from select samples and define optimal test cutoffs without validation; thus generalizability of results is uncertain. For the diagnosis of AD, evidence does not demonstrate incremental improvement in diagnostic accuracy over a clinical diagnosis. For predicting conversion from mild cognitive impairment (MCI) to AD, limited evidence suggests that testing might define increased risk. Whether earlier diagnosis leads to improved health outcomes through delay of AD onset or quality of life is lacking. Guidelines align with these conclusions. Therefore, biochemical testing for AD is considered not medically necessary.

**Medicare National Coverage**

There is no national coverage determination (NCD).

**References**


Neural thread Protein, Alzheimer Disease
Tau Protein, Alzheimer Disease
AB 1-42, AB-42, AB42, AlzheimAlert™, Biomarkers

This policy was approved by the FEP® Pharmacy and Medical Policy Committee on December 5, 2014 and is effective January 15, 2015.

Signature on File
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