BlueCross BlueShield of Alabama

Name of Policy:

Biochemical Markers of Alzheimer Disease

Policy #: 200
Category: Laboratory

Latest Review Date: August 2014
Policy Grade: A

Background/Definitions:

As a general rule, benefits are payable under Blue Cross and Blue Shield of Alabama health plans only in cases of medical necessity and only if services or supplies are not investigational, provided the customer group contracts have such coverage.

The following Association Technology Evaluation Criteria must be met for a service/supply to be considered for coverage:

1. *The technology must have final approval from the appropriate government regulatory bodies;*
2. *The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes;*
3. *The technology must improve the net health outcome;*
4. *The technology must be as beneficial as any established alternatives;*
5. *The improvement must be attainable outside the investigational setting.*

Medical Necessity means that health care services (e.g., procedures, treatments, supplies, devices, equipment, facilities or drugs) that a physician, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury or disease or its symptoms, and that are:

1. *In accordance with generally accepted standards of medical practice; and*
2. *Clinically appropriate in terms of type, frequency, extent, site and duration and considered effective for the patient's illness, injury or disease; and*
3. *Not primarily for the convenience of the patient, physician or other health care provider; and*
4. *Not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.*

Description of Procedure or Service:

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

MCI may be diagnosed when there is a change in cognition but insufficient impairment for the diagnosis of dementia. 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 (e.g., neuroimaging, laboratory tests, neuropsychological assessment) to rule out vascular, traumatic, and medical causes of cognitive decline and to evaluate genetic factors. Because clinical diagnosis can be difficult, particularly early in the course of disease, there has been considerable interest in developing an accurate laboratory test for AD. Several potential biomarkers of AD are associated with AD pathophysiology (i.e., β-amyloid plaques and neurofibrillary tangles).

Elevated 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-β peptide such as AB-42. Other potential CSF and serum peptide markers also have been explored. Tau protein is a microtubule-associated molecule found in neurofibrillary tangles that are typical of AD. Tau protein is thought to be related to degenerating and dying neurons, and high levels of tau protein in the CSF have been associated with AD. AB-42 is a subtype of amyloid-β peptide that is produced from metabolism of amyloid precursor protein. AB-42 is the key peptide deposited in 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. A variety of kits are commercially available to measure AB-42 and tau proteins. Between-laboratory variability in CSF biomarker measurement is large.

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

Policy:

Measurement of cerebrospinal fluid biomarkers of Alzheimer disease, including but not limited to tau protein, amyloid beta peptides, or neural thread proteins, **does not meet** Blue Cross and Blue Shield of Alabama's medical criteria for coverage and is considered **investigational**.

Measurement of urinary biomarkers of Alzheimer disease, including but not limited to neural thread proteins, **does not meet** Blue Cross and Blue Shield of Alabama's medical criteria for coverage and is considered **investigational**.

Blue Cross and Blue Shield of Alabama does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Cross and Blue Shield of Alabama administers benefits based on the member's contract and corporate medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

Key Points:

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 (e.g., by informing clinical management decisions), and
- generalizability.

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

Criterion Standard

The accuracy of clinical AD diagnostic criteria has been established by comparison to autopsy or the gold standard. Therefore, comparison with autopsy is most appropriate to validly assess incremental diagnostic improvement accompanying biomarkers.

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. 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.

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—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 below.

Rosa et al (2014) conducted a systematic review with meta-analysis of studies of cerebrospinal fluid (CSF) amyloid-β peptide-1-42 (AB-42) in patients with clinically diagnosed AD. Literature was searched to May 2013, and 41 prospective or retrospective, cohort, case-control, and cross-sectional studies were included (total N=5086; 2932 AD, 2154 nondemented 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 (I^2=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 (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%).

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 in 2011. 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. Results for both the systematic reviews and the individual studies are

summarized in Table 1. For differentiating AD from nondemented controls, positive and negative likelihood ratios for all three biomarkers ranged from 4 to 8 and from 0.1 to 0.3, respectively. For differentiating AD from other dementias, one systematic review of seven studies reported positive and negative likelihood ratios of 46 and 0.09, respectively, for differentiating AD (n=175) from Creutzfeldt-Jakob disease (n=110). With this systematic review excluded, positive and negative likelihood ratios ranged from 2 to 7 and from 0.15 to 0.4, respectively.

A 2011 meta-analysis included 119 studies on biomarkers and diagnostic imaging in Alzheimer's disease (AD). 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 were included with the CSF marker AB-42; pooled analysis resulted in sensitivity of 76% and specificity of 77%. CSF total tau was evaluated in 30 included studies with a resulting sensitivity of 79% and specificity of 85%. CSF P-tau was evaluated in 24 included 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%. When comparing CSF biomarkers, the area under the ROC curve was highest for P-tau alone (0.85). Heterogeneity in the studies was considered to be due to the use of different thresholds, although differences in assay kits may also have contributed to the heterogeneity. Sensitivity analysis that only included 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. identified those examining diagnostic accuracy of cerebrospinal fluid (CSF) markers for AD: Total tau protein (T-tau) (41 studies; 2,287 AD patients and 1,384 controls; sensitivities 52% to 100%; specificities 50% to 100%), phosphorylated tau protein (P-tau) (12 studies; 760 AD patients and 396 controls; sensitivities 37% to 100%; specificities 80% to 100%), amyloid beta peptide 1-42 (AB-42) (14 studies; 688 AD patients and 477 controls; sensitivities 55% to 100%; specificities 80% to 100%). While primarily a descriptive review, test accuracies varied widely, and a single study included a majority of autopsy-confirmed AD diagnoses.

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% to 82% and 82% to 90%, respectively, for differentiating AD from nondemented controls, and 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. This evidence does not indicate that CSF biomarkers improve the accuracy of clinical diagnostic criteria.

Diagnostic Accuracy of CSF Markers with AD Autopsy Confirmation
Engelborghs et al assayed P-tau and AB-42 in banked CSF. Samples were examined from 100 patients with and 100 without dementing illness seen between 1992 and 2003. All dementia diagnoses were autopsy proven (65 pure AD, eight mixed, 37 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 (mean age 47 versus 76 years of age). Laboratory technicians performing assays were blinded to clinical diagnoses. Samples from 52 subjects required retesting due to questionable results. The sensitivity of clinical evaluation for a pure AD diagnosis was 83% with 75% specificity; of P-tau and AB-42 80% and 93%, respectively. In models, the CSF biomarkers did not provide incremental diagnostic accuracy over the clinical diagnosis—"[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 seven listed authors were employees of the test manufacturer.

Clark et al examined CSF from 106 patients with autopsy-confirmed dementia evaluated at 10 referral clinics and 73 controls (four pathologically examined). 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 assembled a sample from two institutions including 30 patients with FTD (19 autopsy-proven and 11 with known causal genetic mutations) and autopsy proven AD (n=19). Using an optimal cutoff of403 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). Literature was searched in January 2012, and three studies of CSF markers (P-tau, T-tau, AB-42, 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 (nondemented 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 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). 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], AD [n=21]; 76/85 autopsy-confirmed diagnoses); specificity was 52% and sensitivity ranged from 91% to 95%.

CSF AB-42 level normalized to CSF AB-40 (i.e., 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 (i.e., tau, P-tau, AB-42). 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

The 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. Nine studies were included (total N=841 patients with probable or possible AD, 37 patients with MCI, 992 non-AD demented or nondemented 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 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), five patients with DLB, 29 patients with Parkinson disease, and 16 elderly healthy control patients. 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 eight sites, Goodman et al (2007) enrolled 168 patients with recent referrals to memory clinics. The Urinary Neural Thread Protein 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 two studies and one meta-analysis, estimated sensitivity and specificity ranged from 70% to 91% and from 80% to 90%, respectively. The 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-protein (primarily AB-42) for detecting which patients with MCI would progress to AD or other dementias. Literature was searched in December 2012, and 14 prospective or retrospective cohort studies of AD, including one discussed next, were included (total N=1349 patients with MCI). Studies that enrolled patients younger than 50 years of age or with less than two 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% to 100%, and specificity from 29% to 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 posttest 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 (previously discussed) included studies of CSF biomarkers for differentiating patients with MCI who progress to AD from those who do not. In systematic reviews with meta-analyses, sensitivity and specificity of AB-42 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.

Mattsson et al recruited individuals from 12 U.S. and European centers with MCI (n=750), AD (n=529), and controls (n=304). Those with MCI were followed up a minimum of two years or to progression. Development of probable AD was associated with lower CSF AB-42, 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% confidence interval [CI]: 78% to 88%), specificity 72% (95% CI: 68% to 76%), positive predictive value 62%; and negative predictive value 88%. Amnestic MCI was not distinguished.

Herukka et al 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. Seventy-nine 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 obtained 137 CSF samples from a larger group of 180 consecutive individuals with MCI evaluated at a referral memory clinic between 1998 and 2001. 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% female. They were followed a median of 5.2 years and 57 (42%) progressed to AD. Using a predictor composed of T-tau and AB-42/P-tau employing 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.

From four international clinical research centers, Ewers et al retrospectively assembled a sample of 88 patients with amnestic MCI based on both the availability of CSF samples and at least one follow-up between one and three years after initial evaluation; 57 healthy controls with baseline evaluations only were also included. Forty-three patients (49%) in the MCI group converted to AD over an average 1.5-year follow-up. Using a cutoff of 27.32 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 two- and three-fold the typical 15% found in amnestic MCI.

Andreasen et al studied 32 controls and 44 patients with MCI who, after a one-year follow-up, had progressed to probable AD. 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. More informative results would have derived from including patients with MCI not progressing to AD.

Bouwman and colleagues followed 59 patients with MCI a mean of 19 months (range, 4 to 45 months), obtaining a baseline of CSF AB-42 and tau. 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 examined 55 patients with MCI. At baseline, CSF AB-42, total tau, and P-tau were measured—38% had abnormal values. After one year, four of 33 stable patients had abnormal markers. Of those progressing to AD, Lewy body disease, or familial frontotemporal dementia (FTD), 10 of 11 had two or more abnormal markers. While results from these studies are consistent with potential prognostic utility of markers, sample sizes were small. In addition, the type of MCI (amnestic or nonamnestic) was not distinguished but has important predictive value for progression to dementia.

Section Summary

Evidence suggests 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)

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 six months for approximately 10 years. Participants undergo neuropsychological tests, 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, Schmand et al evaluated the value of neuropsychologic tests, neuroimaging, and biomarkers (AB and tau in CSF) for diagnosing AD in all participants in the ADNI database who had a lumbar puncture. This included 105 normal controls, 179 individuals with MCI, and 91 with AD. Neuropsychologic tests and magnetic resonance imaging (MRI) were found to be the most informative techniques, with 84% and 82% correct classifications, respectively. CSF assessments had 73% correct classifications, respectively, 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). In ROC analyses, the c-statistic for MRI as diagnostic of probable AD compared to normal was 0.90, for P-tau/AB-42 0.84. In the longitudinal evaluation, both MRI and biomarkers were associated with conversion to AD, a c-index for MRI of 0.69 and for T-tau/AB-42 0.62. 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 neuropsychologic tests, neuroimaging, and biomarkers (AB and tau in CSF) for predicting the conversion to AD in 175 patients with MCI. With a mean follow-up of 2.7 years (range, 0.5 to 4.6 years), 81 patients (46%) had converted to AD. Neuropsychologic assessment and MRI variables predicted conversion with 63% to 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. The difference in prediction for the combined markers (70%) was not significantly better than the individual markers.

Landau et al examined predictors of conversion to clinically diagnosed AD and cognitive decline in 85 patients with amnestic MCI in the ADNI. 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 developed a model using biomarkers (CSF AB-42/P-tau) in the US-ADNI sample (114 cognitively normal, 200 MCI, and 102 AD patients). Sensitivity and specificity in the development set were 90% and 64%, respectively (1/3 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 correctly identifying 64 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-positron 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 found neither MRI nor CSF biomarkers improved classification of patients developing AD over a brief memory test. The 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. Memantine, an N-methyl-d-aspartate (NMDA) receptor antagonist, appears to provide a small benefit in those with moderate-to-advanced disease. 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.

Summary
Evidence that testing for 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 unclear. For the diagnosis of AD, evidence does not demonstrate incremental improvement in diagnostic accuracy over clinical testing. For predicting conversion from MCI to AD, limited evidence, including that from the ADNI, suggests 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 are consistent with these conclusions. Therefore, biochemical testing for AD is considered investigational.

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

The 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 two 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's 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 defined by the National Institute on Aging and the Alzheimer's Association workgroup according to the following diagnostic criteria:

"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.

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 pathophysiologic 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 AD diagnostic criteria—"probable AD dementia with evidence of the AD pathophysiological process". However, the diagnostic criteria workgroup publication noted

> "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."

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." In 2012, the Alzheimer's Biomarkers Standardization Initiative published consensus recommendations for standardization of preanalytical aspects (e.g., fasting, tube types, centrifugation, storage time, temperature) of CSF biomarker testing.

In 2013, AA published recommendations for operationalizing the detection of cognitive impairment during the Medicare annual wellness visit in primary care settings. The recommended algorithm for cognitive assessment was based on "current validated tools and commonly used rule-out assessments." 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 4th Canadian Consensus Conference on Diagnosis and Treatment of Dementia

The 4th Canadian Consensus Conference on Diagnosis and Treatment of Dementia published updated evidence-based consensus recommendations in 2012. 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."

European Federation of Neurological Societies-European Neurological Society

In 2012, European Federation of Neurological Societies and European Neurological Society published updated evidence-based consensus guidelines on the diagnosis and management of disorders associated with dementia. 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.

Key Words:

Biochemical marker, amyloid beta peptides, AB-42 Protein, Alzheimer's Disease, ADmark ProfileAD7C, Alzheimer's Disease, Beta-amyloid Protein, Neural thread Protein, Tau Protein, Alzheimer, Innotest, AlzheimAlert

Approved by Governing Bodies:

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

- AlzheimAlert™ (Nymox Pharmaceutical Corp.; 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 (LDTs). Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; 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 Corp. previously offered AD7C testing as an LDT but no longer lists the test on its website.

Benefit Application:

Coverage is subject to member's specific benefits. Group specific policy will supersede this policy when applicable.
ITS: Home Policy provisions apply
FEP contracts: FEP does not consider investigational if FDA approved and will be reviewed for medical necessity.

Current Coding:

CPT Codes:

81099	Unlisted urinalysis procedure
83520	Immunoassay for analyte other than infectious agent antibody or infectious agent antigen; quantitative; not otherwise specified
86849	Unlisted immunology procedure

References:

1. Albert MS, DeKosky ST, Dickson D et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 2011; 7(3):270-9.
2. Andreasen N, Vanmechelen E, Vanderstichele H et al. Cerebrospinal fluid levels of total-tau, phosho-tau and A beta 42 predicts development of Alzheimer's disease in patients with mild cognitive impairment. Acta Neurol Scand Suppl 2003;107:47-51.
3. Andreasen N and Blennow K. CSF biomarkers for mild cognitive impairment and early Alzheimer's disease. Clin Neurol Neurosurg 2005; 107(3): 165-173.
4. Arai H, Terajima M, Miura M et al. Tau in cerebrospinal fluid: a potential diagnostic marker in Alzheimer's disease. Ann Neurol 1995;38(4):649-52.
5. Bian H, Van Swieten JC, et al. CSF biomarkers in frontotemporal lobar degeneration with known pathology. Neurology, May 2008; 70(19 Pt 2): 1827-1835.
6. Blasko I, Lederer W, Oberbauer H, et al. Measurement of thirteen biological markers in CSF of patients with Alzheimer's disease and other dementias. Dement Geratr Cogn Disord 2006; 21(1): 9-15.
7. Bloudek LM, Spackman DE, Blankenburg M et al. Review and meta-analysis of biomarkers and diagnostic imaging in Alzheimer's disease. J Alzheimers Dis 2011; 26(4):627-45.
8. Bouwman FH, Schoonenboom SN, van der Flier WM, et al. CSF biomarkers and medial temporal lobe atrophy predict dementia in mild cognitive impairment. Neurobiol Aging 2007; 28(7): 1070-1074.
9. Bowler JV, Munoz DG, Merskey H et al. Fallacies in the pathological confirmation of the diagnosis of Alzheimer's disease. J Neurol Neurosurg Psychiatry 1998; 64(1):18-24.
10. Buerger K, Zinkowski R, Teipel SJ et al. Differential diagnosis of Alzheimer disease with cerebrospinal fluid levels of tau protein phosphorylated at threonine 231. Arch Neurol 2001;59(8):1267-72.
11. Chertkow H. Diagnosis and treatment of dementia: Introduction. CMAJ, January 29, 2008; 178(3): 316-321.
12. Clark CM, Xie S, Chittams J, et al. Cerebrospinal fluid tau and β-amyloid: how well do these biomarkers reflect autopsy-confirmed dementia diagnoses? Arch Neurol, December 2003, Vol. 60, pp. 1696-1702.
13. Cordell CB, Borson S, Boustani M, et al. Alzheimer's Association recommendations for operationalizing the detection of cognitive impairment during the Medicare Annual Wellness Visit in a primary care setting. Alzheimers Dement. Mar 2013;9(2):141-150.
14. Cure S, Abrams K, Belger M, et al. Systematic Literature review and meta-analysis of diagnostic test accuracy in Alzheimer's disease and other dementia using autopsy as standard of truth. J Alzheimers Dis. May 19 2014.
15. de Jong D, Jansen RW, et al. Cerebrospinal fluid amyloid beta42/phosphorylated tau ratio discriminates between Alzheimer's disease and vascular dementia. J Gerontol A Biol Sci Med Sci, July 2006; 61(7): 755-758.
16. De Meyer G, Shapiro F, Vanderstichele H et al. Diagnosis-independent Alzheimer disease biomarker signature in cognitively normal elderly people. Arch Neurol 2010; 67(8):949-56.

17. Dubois B, Feldman HH, Jacova C, et al. Research criteria for the diagnosis of Alzheimer's disease: Revising the NINCDS-ADRDA criteria. Lancet Neurol, August 2007; 6(8): 734-746.
18. Dumurgier J, Vercruysse O, Paquet C, et al. Intersite variability of CSF Alzheimer's disease biomarkers in clinical setting. Alzheimers Dement. Jul 2013;9(4):406-413.
19. Engelborghs S, De Vreese K, et al. Diagnostic performance of a CSF-biomarker panel in autopsy-confirmed dementia. Neurobiol Aging, August 2008; 29(8): 1143-1159.
20. Ewers M, Buerger K, Teipel SJ, et al. Multicenter assessment of CSF-phosphorylated tau for the prediction of conversion of MCI. Neurology, December 2007; 69(24): 2205-2212.
21. Ewers M, Walsh C, Trojanowski JQ, et al. Prediction of conversion from mild cognitive impairment to Alzheimer's disease dementia based upon biomarkers and neuropsychological test performance. Neurobiol Aging. Jul 2012;33(7):1203-1214.
22. Feldman HH, Ferris S, Winblad B et al. Effect of rivastigmine on delay to diagnosis of Alzheimer's disease from mild cognitive impairment: the InDDEx study. Lancet Neurol 2007; 6(6):501-12.
23. Ferreira D, Perestelo-Perez L, Westman E, et al. Meta-review of CSF core biomarkers in Alzheimer's disease: the state-of-the-art after the new revised diagnostic criteria. Front Aging Neurosci. 2014;6:47.
24. Formichi P, Battisti C, Radi E and Federico A. Cerebrospinal fluid tau, A beta, and phosphorylated tau protein for the diagnosis of Alzheimer's disease. J Cell Physiol, July 2006; 208(1): 39-46.
25. Galasko D, Clark C, Chang L et al. Assessment of CSF levels of tau protein in mildly demented patients with Alzheimer's disease. Neurology 1997;48(3):632-5.
26. Ganguli M, Dodge HH, Shen C and DeKosky ST. Mild cognitive impairment, amnestic type: An epidemiologic study. Neurology 2004; 63(1): 115-121.
27. Gauthier S, Patterson C, Chertkow H, et al. Recommendations of the 4th Canadian Consensus Conference on the Diagnosis and Treatment of Dementia (CCCDTD4). Can Geriatr J. Dec 2012;15(4):120-126.
28. Gever John. ICAD: Biomarkers, imaging ready for prime time in AD diagnosis. MedpageToday®, July 13, 2010. www.medpagetoday.com/MeetingCoverage/ICAD/21136.
29. Goodman I, Golden G, Flitman S, et al. A multi-center blinded prospective study of urine neural thread protein measurements in patients with suspected Alzheimer's disease. J Am Med Dir Assoc 2007; 8(1): 21-30.
30. Gomar JJ, Bobes-Bascaran MT, Conejero-Goldberg C, et al. Utility of combinations of biomarkers, cognitive markers, and risk factors to predict conversion from mild cognitive impairment to Alzheimer disease in patients in the Alzheimer's disease neuroimaging initiative. Arch Gen Psychiatry. Sep 2011;68(9):961-969.
31. Hampel H, Goernitz A, Buerger K. Advances in the development of biomarkers for Alzheimer's disease: from CSF total tau and Abeta (1-42) proteins to phosphorylated tau protein. Brain Res Bull 2003; 61(3):243-53.
32. Hansson O, Zetterberg H, Buchhave P, Londos E, et al. Association between CSF biomarkers and incipient Alzheimer's disease in patients with mild cognitive impairment: A follow-up study. Lancet Neurol, March 2006; 5(3): 228-234.

33. Herukka SK, Helisalmi S, Hallikainen M, et al. CSF Abeta42, Tau and phosphorylated Tau, APOE epsilon4 allele and MCI type in progressive MCI. Neurobiol Aging 2007; 28(4): 507-514.
34. Hort J, O'Brien JT, Gainotti G et al. EFNS guidelines for the diagnosis and management of Alzheimer's disease. Eur J Neurol 2010; 17(10):1236-48.
35. Hyman BT, Phelps CH, Beach TG et al. National Institute on Aging-Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease. Alzheimers Dement 2012; 8(1):1-13.
36. Ibach B, Binder H, Dragon M, et al. Cerebrospinal fluid tau and beta-amyloid in Alzheimer patients, disease controls and an age-matched random sample. Neurobiol Aging 2006; 27(9): 1202-1211.
37. Jia JP, Meng R, Sun YX, et al. Cerebrospinal fluid tau, Abeta 1-42 and inflammatory cytokines in patients with Alzheimer's disease and vascular dementia. Neurosci Lett 2005; 383(1-2): 12-16.
38. Kaduszkiewica H, Zimmermann T, Beck-Bornholdt HP, et al. Cholinesterase inhibitors for patients with Alzheimer's disease: Systematic review of randomized clinical trials. BMJ 2005; 33(7512): 321-7.
39. Kahle PJ, Jakowec M, Teipel SJ et al. Combined assessment of tau and neuronal thread protein in Alzheimer's disease CSF. Neurology 2000;54(7):1498-504.
40. Kanai M, Matsubara E, Isoe K et al. Longitudinal study of cerebrospinal fluid levels of tau, A beta1-40 and A beta1-42(43) in Alzheimer's disease: a study in Japan. Ann Neurol 1998;44(1):17-26.
41. Kapaki E, Liappas I, Paraskevas GP, et al. The diagnostic value of tau protein, beta-amyloid (1-42) and their ratio for the discrimination of alcohol-related cognitive disorders from Alzheimer's disease in the early stages. Int J Geratr Psychiatry 2005; 20(8): 722-729.
42. Knopman DS, DeKosky St, Cummings JL, et al. Practice parameter: Diagnosis of dementia (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2001; 56(9): 1143-1153.
43. Landau SM, Harvey D, Madison CM et al. Comparing predictors of conversion and decline in mild cognitive impairment. Neurology 2010; 75(3):230-8.
44. Le Bastard N, Van Buggenhout M, et al. LOW specificity limits the use of the cerebrospinal fluid AB1-42/P-TAU181P ratio to discriminate Alzheimer's disease from vascular dementia. J Gerontol A Biol Sci Med Sci, August 2007; 62(8): 923-924; author reply 24-5.
45. Locascio JJ, Fukumoto H, Yap L, et al. Plasma amyloid beta-protein and C-reactive protein in relation to the rate of progression of Alzheimer disease. Arch Neurol, June 2008 ; 65(6) : 776-785.
46. Lowe VJ, Peller PJ, Weigand SD et al. Application of the National Institute on Aging-Alzheimer's Association AD criteria to ADNI. Neurology 2013; 80(23):2130-7.
47. Maddalena A, Papassotiropoulos A, Muller-Tillmanns B et al. Biochemical diagnosis of Alzheimer disease by measuring the cerebrospinal fluid ratio of phosphorylated tau protein to beta-amyloid peptide42. Arch Neurol 2003;60(9):1202-6.
48. Mattsson N, Andreasson U, Persson S et al. The Alzheimer's Association external quality control program for cerebrospinal fluid biomarkers. Alzheimers Dement 2011; 7(4):386-95 e6.

49. Mattsson N, Zetterberg H, et al. CSF biomarkers and incipient Alzheimer disease in patients with mild cognitive impairment. JAMA 2009; 302(4): 385-393.
50. McKhann G, Drachman D, Folstein M, et al. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology 1984; 34: 939.
51. McKhann GM, Knopman DS, Chertkow H et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging and the Alzheimer's Association workgroup. Alzheimers Dement 2011; 7(3):263-9.
52. McShane R, Areosa Sastre A and Minakaran N. Memantine for dementia. Cochrane Database Syst Rev, April 2006;(2): CD003154.
53. Motter R, Vigo-Pelfrey C, Kholodenko D et al. Reduction of beta-amyloid peptide 42 in the cerebrospinal fluid of patients with Alzheimer's disease. Ann Neurol 1995;38(4):643-8.
54. Parnetti L, Lanari A, Silverstrelli G, et al. Diagnosing prodromal Alzheimer's disease: Role of CSF biochemical markers. Mech Ageing Dev 2006; 127(2): 129-132.
55. Pencina MJ, D'Agostino Sr RB, D'Agostino Jr RB and Vasan RS. Evaluating the added predictive ability of a new marker: From area under the ROC curve to reclassification and beyond. Stat Med, January 2008; 27(2): 157-172; discussion 207-12.
56. Petersen RC, Thomas RG, Grundman M et al. Vitamin E and donepezil for the treatment of mild cognitive impairment. N Engl J Med 2005; 352(23):2379-88.
57. Raina P, Santaguida P, Ismaila A, et al. Effectiveness of cholinesterase inhibitors and memantine for treating dementia: evidence review for a clinical practice guideline. Ann Intern Med. Mar 4 2008;148(5):379-397.
58. Raschetti R, Albanese E, et al. Cholinesterase inhibitors in mild cognitive impairment: A systematic review of randomized trials. PLOS Medicine, November 2007, vol. 4, Issue 11, pp. 1818-1828.
59. Richard E, Schmand BA, Eikelenboom P et al. MRI and cerebrospinal fluid biomarkers for predicting progression to Alzheimer's disease in patients with mild cognitive impairment: a diagnostic accuracy study. BMJ Open 2013; 3(6).
60. Riemenschneider M, Lautenschlager N, Wagenpfeil S et al. Cerebrospinal fluid tau and beta-amyloid 42 proteins identify Alzheimer disease in subjects with mild cognitive impairment. Arch Neurol 2002;59(11):1729-34.
61. Ringman JM, Younkin SG, et al. Biochemical markers in persons with preclinical familial Alzheimer disease. Neurology 2008; 71: 85-92.
62. Ritchie C, Smailagic N, Noel-Storr AH, et al. Plasma and cerebrospinal fluid amyloid beta for the diagnosis of Alzheimer's disease dementia and other dementias in people with mild cognitive impairment (MCI). Cochrane Database Syst Rev. 2014;6:CD008782.
63. Rosa MI, Perucchi J, Medeiros LR, et al. Accuracy of cerebrospinal fluid Abeta(1-42) for Alzheimer's disease diagnosis: a systematic review and meta-analysis. J Alzheimers Dis. 2014;40(2):443-454.
64. Rosa-Neto P, Hsiung GY, Masellis M. Fluid biomarkers for diagnosing dementia: rationale and the Canadian Consensus on Diagnosis and Treatment of Dementia recommendations for Canadian physicians. Alzheimers Res Ther. Nov 25 2013;5(Suppl 1):S8
65. Sauvee M, DidierLaurent G, Latarche C, et al. Additional use of abeta42/abeta40 ratio with cerebrospinal fluid biomarkers p-tau and abeta42 increases the level of evidence of Alzheimer's disease pathophysiological process in routine practice. J Alzheimers Dis. 2014;41(2):377-386.

66. Schmand B, Eikelenboom P, van Gool WA. Value of neuropsychological tests, neuroimaging, and biomarkers for diagnosing Alzheimer's disease in younger and older age cohorts. J Am Geriatr Soc 2011; 59(9):1705-10.
67. Schmand B, Eikelenboom P, van Gool WA. Value of diagnostic tests to predict conversion to Alzheimer's disease in young and old patients with amnestic mild cognitive impairment. J Alzheimers Dis 2012; 29(3):641-8.
68. Schneider LS, Mangialasche F, Andreasen N, et al. Clinical trials and late-stage drug development for Alzheimer's disease: an appraisal from 1984 to 2014. J Intern Med. Mar 2014;275(3):251-283.
69. Schoonenboom NS, van der Flier WM, Blankenstein MA, et al. CSF and MRI markers independently contribute to the diagnosis of Alzheimer's disease. Neurobiol Aging 2008; 29(5): 669-675.
70. Sorbi S, Hort J, Erkinjuntti T, et al. EFNS-ENS Guidelines on the diagnosis and management of disorders associated with dementia. *Eur J Neurol.* Sep 2012;19(9):1159-1179.
71. Sunderland T, Linker G, Mirza N et al. Decreased beta-amyloid 1-42 and increased tau levels in cerebrospinal fluid of patients with Alzheimer disease. JAMA 2003;289(16):2094-13.
72. Sunderland T, Gur RE and Arnold SE. The use of biomarkers in the elderly: Current and future challenges. Biol Psychiatry 2005; 58(4): 272-276.
73. Vanderstichele H, Bibl M, Engelborghs S, et al. Standardization of preanalytical aspects of cerebrospinal fluid biomarker testing for Alzheimer's disease diagnosis: a consensus paper from the Alzheimer's Biomarkers Standardization Initiative. Alzheimers Dement. Jan 2012;8(1):65-73.
74. van Harten AC, Kester MI, Visser PJ, et al. Tau and p-tau as CSF biomarkers in dementia: a meta-analysis. Clin Chem Lab Med. Mar 2011;49(3):353-366.
75. Vemuri P, Wiste HJ, Weigand SD, Shaw LM, et al. MRI and CSF biomarkers in normal, MCI, and AD subjects: Diagnostic discrimination and cognitive correlations. Neurology, July 2009; 73(4): 287-293.
76. Vemuri P, Wiste HJ, Weigand SD, Shaw LM, et al. MRI and CSF biomarkers in normal, MCI and AD subjects: Predicting future clinical change. Neurology, July 2009; 73(4): 294-301.
77. Vickers Andrew J. Decision analysis for the evaluation of diagnostic tests, prediction models and molecular markers. Am Stat 2008; 6294): 314-320.
78. Waldemar G, Dubois B, Emre M, et al. Recommendations for the diagnosis and management of Alzheimer's disease and other disorders associated with dementia: EFNS guideline. Eur J Neurol, January 2007; 14(1): e1-26.
79. Winblad B, Gauthier S, Scinto L et al. Safety and efficacy of galantamine in subjects with mild cognitive impairment. Neurology 2008; 70(22):2024-35.
80. Zhang J, Peng M, Jia J. Plasma amyloid-beta oligomers and soluble tumor necrosis factor receptors as potential biomarkers of AD. Curr Alzheimer Res. Mar 16 2014.
81. Zhang J, Zhang CH, Li RJ, et al. Accuracy of urinary AD7c-NTP for diagnosing Alzheimer's disease: a systematic review and meta-analysis. J Alzheimers Dis. 2014;40(1):153-159.

Policy History:

Medical Policy Group, August 2004 **(4)**
Medical Policy Administration Committee, August 2004
Available for comment August 24-October 7, 2004
Medical Policy Group, August 2006 **(1)**
Medical Policy Group, August 2008 **(1)**
Medical Policy Group, August 2010 **(1):** Description and Key Points Updated, No change in policy coverage
Medical Policy Group, May 2011 **(1):** Update to Description, Key Points and References
Medical Policy Panel, September 2012
Medical Policy Group, September 2012 **(1):** Update to Key Points and References; no change to policy statement
Medical Policy Group, December 2012 **(3):** 2013 Code Updates – Deleted 83912
Medical Policy Panel, August 2013
Medical Policy Group, September 2013 **(1):** Update to Key Points and References; removed codes 83912 and G0452, unlisted codes 81099 and 86849 added to policy; no change to policy statement
Medical Policy Panel, August 2014
Medical Policy Group, August 2014 **(1):** Update to Key Points, Key Words, Governing Bodies and References; no change to policy statement

---