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Medical Policy Manual

Topic: Biochemical Markers of Alzheimer's Disease

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IMPORTANT REMINDER

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

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

DESCRIPTION

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

I. Possible Alzheimer's Disease

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

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

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

II. Probable Alzheimer's Disease

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

1. Dementia, established by clinical examination and documented by the Mini-Mental State Examination, the Blessed Dementia Scale, or some similar examination and confirmed by neuropsychological tests
2. Deficits in two or more areas of cognition
3. Progressive worsening of memory and other cognitive functions
4. No disturbance of consciousness
5. Onset between ages 40 and 90, most often after the age of 65
6. Absence of systemic disorders or other brain diseases that in and of themselves could account for the progressive deficits in memory and cognition

B. The diagnosis of probable AD is supported by:

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

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

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

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

1. Sudden apoplectic onset
2. Focal neurological findings such as hemiparesis, sensory loss, visual field deficits, and incoordination early in the course of the illness

3. Seizures or gait disturbances at the onset or very early in the course of the illness

III. Definite Alzheimer's Disease

A. Clinical criteria for probable Alzheimer's disease AND

B. Histopathologic evidence obtained from a biopsy or autopsy

While 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.[1] All probable AD by NINCDS-ADRDA criteria are subsumed in the revised probable AD criteria, which is now defined by the following:

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

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

The diagnosis of probable AD dementia should not be applied when there is evidence of (a) substantial concomitant cerebrovascular disease, defined by a history of a stroke temporally related to the onset or worsening of cognitive impairment; or the presence of multiple or extensive infarcts or severe white matter hyperintensity burden; or (b) core features of Dementia with Lewy bodies other than dementia itself; or (c) prominent features of behavioral variant frontotemporal dementia; or (d) prominent features of semantic variant primary progressive aphasia or nonfluent/agrammatic variant primary progressive aphasia; or (e) evidence for another concurrent, active neurological disease, or a non-neurological medical comorbidity or use of medication that could have a substantial effect on cognition."

Diagnosis by exclusion is frustrating for physicians, patients and families, and there has been considerable research interest in identifying an inclusive laboratory test for AD, particularly for use early in the course of disease. Abnormal levels in cerebrospinal fluid (CSF) of the tau protein (phosphorylated [P-tau] or with a threonine moiety [T-tau]) or an amyloid beta (AB) peptide such as AB-42, have been found in patients with AD, and thus these proteins have been investigated for their diagnostic utility. The tau protein is a microtubule-associated molecule that is found in the neurofibrillary tangles that are typical of Alzheimer's disease. This protein is thought to be related to degenerating and dying neurons, and high levels of tau proteins in the CSF have been associated with AD. AB-42 stands for a subtype of amyloid beta peptide that is produced following the metabolism of an 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 the AB-42 is deposited in the amyloid plaques instead of remaining in solution.

Neural thread protein is another protein that is associated with neurofibrillary tangles of Alzheimer's disease. Both CSF and urine levels of this protein have been investigated as a biochemical marker of

Alzheimer's disease. Urine and CSF tests for neural thread protein may be referred to as the AD7C™ test, as developed by Nymox Pharmaceutical Corporation.

MEDICAL POLICY CRITERIA

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

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

SCIENTIFIC EVIDENCE

The purposes of testing for Alzheimer's disease (AD)-related biomarkers are to:

- Improve diagnostic accuracy
- Predict conversion from mild cognitive impairment (MCI) to AD

Evidence of clinical utility (i.e., improved health outcomes) requires that the testing being evaluated demonstrate all of the following:

- Incremental improvement in diagnostic or prognostic accuracy over current practice

  Incremental improvements lead to improved health outcomes (e.g., by informing clinical management decisions)

- Generalizability

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

- Reference Standard

  The gold standard for definitive diagnosis of Alzheimer’s disease (AD) is autopsy. The accuracy of testing for AD is best established by comparison with this gold standard; therefore, the gold standard must be employed to accurately assess incremental diagnostic improvement.

- Predicting Conversion from mild cognitive impairment (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.[2] Alternative approaches such as classical ROC analyses, while providing some insight, do not allow directly translating improvements in diagnostic or prognostic accuracy to changes in health outcomes.[3]

- Improved Health Outcomes (Clinical Utility)

  Although not without controversy because of modest efficacy, cholinesterase inhibitors are used to treat mild-to-moderate Alzheimer's disease.[2] Memantine, a NMDA receptor antagonist, appears to provide a small benefit in those with moderate-to-advanced disease.[4] Given available therapies, in principle more accurate diagnosis might allow targeting treatment to those most likely to benefit. However, clinical trial entry criteria and benefit have been based on clinical diagnosis. While the possibility that more accurate diagnosis might lead to improved outcomes is plausible, it is not based on current evidence. Pharmacologic interventions for MCI have not demonstrated benefit in reducing progression to Alzheimer's disease.[5-8]

- Test Cutoffs

  Almost all studies employ optimal (data-driven) test cutoffs to define test accuracy (sensitivity and specificity). This approach is typically accompanied by a degree of optimism and potentially overstates test accuracy.

- Sample Definition

  Clear description of whether samples included consecutive patients or were selective is required to evaluate potential bias—including verification bias[9] — and generalizability but almost absent in this literature.

- Validation

  Validation in independent samples is required to establish generalizability of markers but has been scant.

The following article summaries are representative of current published literature. Few studies have included autopsy confirmation; instead, they employed clinical AD diagnosis as the referent standard. Although not directly informative of potential benefit, they are of some interest primarily from revealing possible inaccuracies.

In a recent systematic review, authors assessed the weight and quality of the evidence available from primary diagnostic test accuracy studies for Alzheimer's disease.[10] Authors identified 142 longitudinal studies relating to the biomarkers of interest, which included subjects who had objective cognitive impairment but no dementia at baseline. Authors concluded the body of evidence for biomarkers was not large and was variable across the different types of biomarkers. Authors suggest that important information is missing from many study reports, highlighting the need for standardization of methodology and reporting to improve the rigor of biomarker validation.

A 2011 meta-analysis included 119 studies on biomarkers and diagnostic imaging in Alzheimer's disease (AD).[11] 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, and the reference standard could be either clinical diagnosis or autopsy. When comparing CSF biomarkers, the area under the ROC curve was highest for the test of P-tau alone (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%).

Diagnostic Accuracy of CSF Markers with AD Autopsy Confirmation

Examples of non-randomized observational studies which have used CSF markers (confirmed with autopsy) are detailed below:

- Engelborghs and colleagues assayed P-tau and AB-42 in banked CSF.[12] 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, 8 mixed, 37 non-AD dementias). Details of the sample selection were not provided; neither was it indicated whether CSF testing was routine or selective. 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 CSF 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 and colleagues 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.[13] 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% for distinguishing AD (n=74) from frontotemporal dementia (FTD) (n=3) and DLB (n=10). Bian and colleagues 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).[14] Using an optimal cutoff total tau had sensitivity and specificity of 68% and 90%, respectively, for distinguishing FTD from AD. While the tau/AB-42 ratio appeared 100% sensitive distinguishing FTD from AD, it lacked specificity (53%).

- As previously noted, among patients with clinically diagnosed AD some have suggested the tau/AB-42 ratio a more accurate measure than either alone. For example, using optimal cutoffs de Jong and colleagues reported sensitivities and specificities for the ratio of 95% and 90% in a sample with clinically diagnosed AD (n=61) and VaD (n=61).[15] In contrast, Le Bastard and colleagues suggested the p-tau/AB-42 ratio lacked specificity distinguishing AD from vascular dementia (VaD) in a sample of 85 subjects (VaD [n=64] or AD [n=21]; 76/85 autopsy-confirmed diagnoses)—specificity 52% at a sensitivity of 91% to 95%.[16]

Conclusion

There is limited existing evidence examining incremental diagnostic accuracy of CSF biomarkers for AD diagnosis employing autopsy as a referent standard. The evidence does not demonstrate improvement over a clinical diagnosis, or whether diagnosis using CSF biomarkers would lead to improved net health outcomes.

Neural Thread Protein

Data have been limited on neural thread protein as a marker for AD, and consist mainly of non-randomized observational studies. Examples of such studies include:

- Kahle and colleagues 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 Lewy body disease, 29 patients with Parkinson's disease, and 16 elderly healthy control patients.[17] Levels of both tau and neural thread protein were elevated in patients with AD compared to controls—sensitivities and specificities for tau (63% and 93%) and neural thread protein (70% and 80%).

- In a prospective multicenter study conducted at eight sites, Goodman and colleagues enrolled 168 patients with recent referral to memory clinics.[18] The urinary neural thread test was 91.4% sensitive for a diagnosis of probable AD (32/35) and 90.1% specific among healthy subjects. However, it was unclear whether the marker changed management or what the potential consequences of a 9.9% false-positive rate might be.

Conclusion

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

CSF Markers and Progression of Mild Cognitive Impairment

There have been a number of studies of patients with mild cognitive impairment (MCI) for whom the distinction between early stage AD and other etiologies may be more important.

Several observational research trials have been published, examples of which are detailed below:

- In the largest case series to date, Mattsson and colleagues studied sensitivity, specificity, positive and negative likelihood ratios (LRs) of CSF AB-42, T-tau, and P-tau for identifying incipient AD in patients with MCI.[19] A total of 750 consecutive patients with MCI, 529 with AD, and 304 healthy controls were included in the study. Individuals with MCI were followed up for at least 2 years or until symptoms had progressed to clinical dementia. Reported sensitivity was 83% (95% CI, 78%-88%), specificity 72% (95% CI, 68%-76%), positive predictive value 62%, and negative predictive value 88%, which is less accurate than reported in prior smaller studies. While this was reported as good accuracy, the authors noted that this testing is not appropriate for routine clinical use because there is currently not a treatment that alters the development of AD. Therefore, early detection of risk would not impact treatment planning or health outcomes. Other limitations of the

study included considerable variability in biomarker levels between the 12 centers participating in the study, short follow-up period, The authors also note that, "if these biomarkers are to be used throughout the world, external control programs that help laboratories harmonize their measurements with each other will be essential."

- Okonkwo and colleagues reported an association of AB-42 abnormalities in CSF with increased rate of cognitive decline, disease progression, and risk of conversion to AD in 195 patients with MCI.[20] This association was not found for tau abnormalities in CSF. Andreasen and colleagues studied 32 controls and 44 patients with mild cognitive impairment who, after a 1-year follow-up, had progressed to probable AD.[21] At the start of the study, the investigators evaluated total and p-tau and beta amyloid levels. At baseline, 79.5%, 70.4%, and 77.3% had abnormal levels of total tau, P-tau, and AB, respectively. More relevant results would have derived from including patients with mild cognitive development that did not progress to AD.

- Hansson and colleagues obtained 137 CSF samples from a larger group of 180 consecutive individuals with MCI evaluated at a referral memory clinic between 1998 and 2001.[22] CSF was also obtained from 39 controls. In the analytical sample (n=137) patients were 50 to 86 years of age at baseline, 55% were 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-tau181 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.[23] Bouwman and colleagues followed up 59 patients with MCI a mean of 19 months (range 4 to 45 months) obtaining baseline of CSF AB-42 and tau.[24] Abnormal levels for AB-42 (<495 pg/mL) and 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 and colleagues examined 55 patients with MCI.[25] 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 or frontotemporal dementia, 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.[23]

- Herrukka and colleagues 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.[26] Of the 106 patients, 79 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. From four international clinical research centers, Ewers and colleagues 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.[27] 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%). It should be noted that the conversion rate to AD in the sample was between two- and threefold the typical 15% found in amnestic MCI.

- The Alzheimer's Disease Neuroimaging Initiative (ADNI) is a public-private effort designed to improve AD clinical trials. Participants have been recruited across the U.S. and undergo clinical, imaging and biomarker evaluations. Studies to date consist of non-randomized trials of the ADNI cohort (a mixture of normal, amnestic MCI, and AD patients) and are mainly focused in identifying an association with 1 or more biomarkers and risk of conversion to AD (through single or multivariate statistical models) over time[28-30] or at a single point in time.[31] Although these studies add to the body of research on the technical feasibility of these biomarkers, interpretation of these results is limited by the lack of clearly defined patient samples.

Conclusion

The existing evidence examining incremental diagnostic accuracy of CSF biomarkers for progression of mild cognitive impairment is limited. Currently, the evidence does not demonstrate that clinical management alters or is improved with the addition of CSF biomarkers or that using these markers leads to improved health outcomes. Moreover, evidence that earlier diagnosis leads to improved health outcomes through delay of AD onset or improved quality of life is lacking.

Alzheimer's 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 2-3 years. The participants undergo neuropsychological tests, imaging and biomarker evaluations to determine whether these measures can be combined to measure the progression of MCI and AD. Ongoing results from the study 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.[32] The study 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.
- 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.[33] With a mean follow-up of 2.7 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.
- In 2013, Lowe et al. evaluated CSF AB-42, amyloid PET, FDG-PET, and MRI 211 in ADNI patients with at least one detected amyloid biomarker.[34] Using the most recent diagnostic criteria, in the 92 patients undergoing all tests, AB-42 had a 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."

- Richard and others, found neither MRI nor CSF biomarkers improved classification of patients developing AD over a brief memory test in 181 ADNI patients with MCI.[35] 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%. The authors concluded that after administration of a brief test of memory, MRI or CSF do not substantially affect diagnostic accuracy for predicting progression to Alzheimer's disease in patients with MCI.

Conclusion

Evidence suggests the prediction in the combined markers (neuropsychologic tests, neuroimaging, and biomarkers) was not better than individual markers. Evidence that additional diagnostic information leads to improved health outcomes or improved quality of life is lacking.

Clinical Practice Guidelines

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

American Academy of Neurology (AAN)[36]

The AAN does not address laboratory testing for the clinical evaluation of dementia, including AD.

National Institute on Aging (NIA) and the Alzheimer's Association (AA)[1]

- Recommendations from the National Institute on Aging-Alzheimer's Association workgroup on diagnostic guidelines for Alzheimer's disease include a category entitled, "Probable AD dementia with evidence of the AD pathophysiological process." 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. This recommendation is tempered by the following statement from the NIA-AA workgroup:

  "However, 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."

Therefore, although biomarkers are included in these guidelines for diagnosis, their use is not routinely recommended to aid in the diagnosis of probable AD.

American Psychiatric Association (APA)[37]

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

Summary

Current evidence is insufficient to determine whether testing for Alzheimer's disease (AD)-related biomarkers can improve health outcomes. 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 testing might define increased risk; however, further validation studies are needed. Whether earlier diagnosis leads to improved health outcomes through delay of AD onset or quality of life is also unknown. Therefore, the use of AD-related biomarkers for diagnosis of AD, or for prediction of conversion from MCI to AD, is considered investigational.

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CROSS REFERENCES

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

CODES	NUMBER	DESCRIPTION
The following CPT code are used to identify the steps in testing for tau protein and amyloid beta peptides. There are no specific codes used for testing for neural thread protein.		

CODES	NUMBER	DESCRIPTION
CPT	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
HCPCS	No code	