

Evidence Based Guideline

Biochemical Markers of Alzheimer's Disease

File Name:	biochemical_markers_of_alzheimer's_disease
Origination:	8/2010
Last CAP Review:	11/2011
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Last Review:	11/2011

Description of Procedure or Service

Alzheimer's disease (AD) is almost always clinically diagnosed, focusing on the exclusion of other causes of dementia. Because diagnosis of AD can be difficult, there has been considerable interest in identifying an accurate laboratory test for AD—particularly for use early in the course of disease. Abnormal cerebrospinal fluid (CSF) levels 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. Other potential CSF peptide markers have also been explored. The tau protein is a microtubule-associated molecule that is found in the neurofibrillary tangles that are typical of AD. 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 is a subtype of amyloid beta peptide that is produced following the metabolism of amyloid precursor protein. AB-42 is the key peptide deposited in the amyloid plaques characteristic of AD. Low levels of AB-42 in the CSF have been associated with AD, perhaps because AB-42 is deposited in amyloid plaques instead of remaining in solution. Finally, investigators have suggested a Tau/AB-42 ratio, a potentially more accurate diagnostic marker than either alone.

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

In 1984, the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA) developed clinical criteria for the diagnosis of AD. Three categories were defined: possible, probable, and definite AD. The diagnosis of definite AD requires pathologic confirmation of the presence of characteristic neurofibrillary tangles. In approximately 85% of those with a diagnosis of probable AD, pathological findings are subsequently found to be consistent.

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

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to documented decline or having a causative AD genetic mutation. Additionally, a category "Probable AD dementia with evidence of the AD pathophysiological process" has been added. Evidence of the AD pathophysiological process is supported by detection of low CSF Aβ₄₂, 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.

Related Policy:

Genetic Testing for Familial Alzheimer's Disease

*****Note: This Evidence Based Guideline is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.**

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Not applicable.

Medical Evidence regarding Biochemical Markers of Alzheimer's Disease indicates it is not recommended in the following situations

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

Measurement of urinary biomarkers of Alzheimer's disease is not recommended, including but not limited to neural thread proteins.

Evidence that testing for AD-related biomarkers can improve health outcomes is lacking. A majority of studies derive from select samples and optimally defined test cutoffs without validation; generalizability of results is unclear. For the diagnosis of AD, evidence does not demonstrate incremental improvement in diagnostic accuracy over a clinical diagnosis. For predicting conversion from MCI to AD, limited evidence 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.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

Billing/Coding/Physician Documentation Information

This guideline may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable codes: 83520, 83912

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There are no specific codes used for testing for neural thread protein.

Scientific Background and Reference Sources

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.04.14, 11/2009

Medical Director – 8/2010

Specialty Matched Consultant Advisory Panel – 11/2010

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.04.14, 5/2011

Medical Director – 8/2011

Specialty Matched Consultant Advisory Panel – 11/2011

Policy Implementation/Update Information

- 9/14/10 New evidence based guideline written. Reviewed by Medical Director 8/10/10. “Biochemical markers of Alzheimer’s disease using measurement of cerebrospinal fluid biomarkers, including but not limited to tau protein, amyloid beta peptides, or neural thread proteins, is not recommended.” “Measurement of urinary biomarkers of Alzheimer’s disease is not recommended, including but not limited to neural thread proteins.” (btw)
- 12/21/10 Specialty Matched Consultant Advisory Panel review 11/29/2010. No changes to guideline. Medical Director review 8/6/2011. Reference added. (btw)
- 8/30/11 “Description” section revised. No change to evidence based guideline intent. Reference added. (btw)
- 12/20/11 Specialty Matched Consultant Advisory Panel review 11/30/2011. “Description” section revised. No change to guideline intent. (btw)

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