Healthy Blue

Medical Policy

Subject:	Genetic Testing and Biochemical Markers for the Diagnosis of Alzheimer's Disease		
Document #:	GENE.00003	**Publish Date:**	12/16/2020
Status:	Reviewed	**Last Review Date:**	11/05/2020

Description/Scope

This document addresses the use of testing for genetic mutations, polymorphisms, or biochemical markers for either the diagnosis or screening of Alzheimer's disease.

Notes:

- This document does not address the testing of individuals with an existing diagnosis of Alzheimer's disease to identify candidates for an FDA approved treatment for Alzheimer's disease (for example: measurement of amyloid beta in cerebrospinal fluid to identify candidates for Aduhelm [Aducanumab]).
- This document does not address imaging services including MRI and PET. For criteria related to MRI and PET, refer to applicable guidelines used by the plan.

Position Statement

Investigational and Not Medically Necessary:

Genetic testing (including both genetic polymorphisms and genetic mutations) or measurements of biochemical markers (including but not limited to tau protein, AB-42, neural thread protein) is considered **investigational and not medically necessary** as a diagnostic technique for individuals with symptoms suggestive of Alzheimer's disease.

Genetic testing or measurements of biochemical markers as a screening technique in asymptomatic individuals with or without a family history of Alzheimer's disease is considered **investigational and not medically necessary.**

Rationale

Diagnosis of Alzheimer's disease (AD) by exclusion is challenging for both physicians and individuals. There has been considerable research interest in identifying an accurate and conclusive laboratory test to bolster the clinical diagnosis.

Genetic Testing

AD is commonly associated with a family history; 40% of individuals with AD have at least one other afflicted first-degree relative. At present, the following four genes have been associated with AD and have been investigated as a possible diagnostic test: (1) Apolipoprotein E gene, (2) Amyloid AB precursor gene, (3) Presenilin 1 gene, and (4) Presenilin 2 gene. Genetic testing has been investigated both in individuals with probable AD and in asymptomatic family members.

Susceptibility Polymorphism at the Apolipoprotein E (ApoE) Gene
The ApoE lipoprotein is a carrier of cholesterol and is produced in the liver and brain glial cells. Epsilon 2, 3, and 4 are the three principal types of apolipoprotein in humans. Every person carries two ApoE alleles. The presence of at least one epsilon 4 allele is associated with an increased risk of AD in the range of 1.2 to 3 fold, depending on ethnic group. For those homozygous for epsilon 4, the risk of AD is higher. It should be noted that the epsilon 4 allele represents a susceptibility polymorphism and not a genetic mutation, discussed below.

Genetic Mutations
Early onset AD occurs before age 65 but can occur as early as age 30 years. Some families may show an autosomal dominant pattern of inheritance. Three genes have been identified by linkage analysis of affected families: amyloid AB precursor gene (APP), presenilin 1 gene (PSEN1), and presenilin 2 (PSEN2) genes. A variety of mutations within these genes have been associated with AD; mutations in presenilin 1 appear to be the most common. However, only 2%-10% of those with AD have early onset AD, and genetic mutations have only been identified in 30%-50% of those individuals. Overall, identifiable genetic mutations are rare causes of AD.

Chen and colleagues (2012) conducted a meta-analysis to evaluate the association of PSEN2 polymorphisms, rs8383 and 5'indel, with the risk of sporadic AD. Overall, the meta-analysis included six case-control studies for each polymorphism with 2186 confirmed AD cases and 2507 healthy controls in total. The analysis suggested a significant association between SNP rs8383 polymorphism and AD risk with no evidence of between-study heterogeneity or publication bias. In contrast, the authors did not find any evidence supporting the association between the 5'indel polymorphism and the risk of AD. The stratified analyses of apolipoprotein ε4 status or ethnicity also failed to reveal a statistically significant association between the 5'indel polymorphism of PSEN2 and AD risk. The authors concluded that PSEN2 rs8383 polymorphism is associated with an increased risk of sporadic AD. The authors also acknowledged that larger scale studies are needed to confirm these findings and to define potential gene-gene interactions.

Biochemical Markers
Abnormal levels of the tau and amyloid beta proteins in the cerebrospinal fluid have been seen in individuals with known AD and have been investigated for their diagnostic utility. Neural thread protein is a protein that is associated with neurofibrillary tangles. Both CSF and urine levels of this protein have been investigated as a potential biochemical marker of AD. While genetic testing for Alzheimer’s disease has been investigated in both symptomatic and asymptomatic at-risk individuals, biochemical markers have only been investigated in those who are symptomatic.

Researchers are also exploring the use of skin fibroblast testing as a means to detect and differentiate AD from other dementias. The Discern™ Alzheimer's disease test (NeuroDiagnostics, Rockville, MD) examines skin fibroblast cells to identify and quantify three biomarkers (the phosphorylated Erk1 and Erk2, quantitatively measure skin fibroblast networks and protein kinase C_ϵ levels), each of which is reported to independently identify and differentiate AD. At the time of this review, peer-reviewed studies assessing the analytical validity of this test were limited (Chirila, 2013; Chirila, 2014; Nelson, 2017). Large, randomized, controlled trials demonstrating this test is as accurate as autopsy results (the gold standard in the definitive diagnosis of AD) are needed in order to assess the clinical utility of the test.

Based on the 2011 guidelines from the National Institute on Aging (NIAA) and the Alzheimer's Association (AA), the diagnosis of AD is a clinical diagnosis, focusing on the exclusion of other causes of senile dementia. However, ancillary imaging studies such as computed tomography [CT], magnetic resonance imaging [MRI], single-photon emission CT [SPECT], or positron emission tomography [PET]) and laboratory tests may be used. These tests help rule out other possible causes for dementia (for example, cerebrovascular disease, cobalamin [vitamin B12] deficiency, syphilis, and thyroid disease). According to the NIA-AA, the core clinical criteria for AD dementia will continue to be the foundation of the diagnosis in clinical practice, however, "further studies are needed to prioritize biomarkers and to determine their value and validity in practice and research settings" (McKahn, 2011).

In 2018, the National Institute on Aging and Alzheimer's Association (NIA-AA) published an updated biological definition of AD that focuses on the underlying pathological activities of the disease, which can be identified either in living individuals (via biomarkers) or during autopsy. The NIA-AA framework proposes using three groups of biomarkers (β amyloid deposition, pathologic tau, and neurodegeneration) that can be measured by obtaining spinal fluid and/or special radiological imaging tests. The new definition is intended for research purposes only (to identify and stage research participants) and is meant to provide a flexible framework amenable to new (yet discovered) biomarker tests. The definition is not intended to be used in routine clinical care, and further investigation is required to establish the role and utility of the biomarker definition (Jack Jr., 2018).

Symptomatic Individuals
There is inadequate data to suggest that the addition of either genetic testing or biochemical markers improves the clinical diagnosis of AD. The majority of available studies focus on those with probable AD, for whom the clinical diagnosis has a sensitivity of 85%. There is inadequate data regarding the use of these tests in individuals with possible AD where the diagnosis is less certain. Additionally, there is no data to suggest that the use of the above tests would change clinical management in terms of either altering the diagnostic work up or therapy. There are currently no published data suggesting that either biochemical or genetic testing of individuals with possible or probable AD affects the conventional diagnostic work up, treatment or clinical outcomes.

Asymptomatic Individuals
There is inadequate data regarding the role of genetic or biochemical testing in asymptomatic individuals and no data regarding how test results may alter their medical management, treatment or clinical outcomes.

Background/Overview

AD is a progressive and ultimately fatal dementia that can be familial or idiopathic (no family history). The majority of AD is late-onset, but there is also a less common early-onset form of AD, which appears before the age of 65 and is associated with a rapid decline, cognitive and behavioral changes, and severe neurochemical and neuropathological changes. Researchers continue to explore the use of genetic testing and biomarkers as an accurate and conclusive means to diagnose AD.

Definitions

Alzheimer's disease: A progressive neurological condition, including dementia, which primarily affects memory.

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

When services are Investigational and Not Medically Necessary:
For the following procedure and diagnosis codes, or when the code describes a procedure indicated in the Position Statement section as investigational and not medically necessary.

CPT

81401	Molecular pathology procedure, Level 2 (eg, 2-10 SNPs, 1 methylated variant, or 1 somatic variant [typically using nonsequencing target variant analysis], or detection of a dynamic mutation disorder/triplet repeat) [when specified as the following]: • *APOE (apolipoprotein E)* (eg, hyperlipoproteinemia type III, cardiovascular disease, Alzheimer disease), common variants (eg, *2, *3, *4)
81405	Molecular pathology procedure, Level 6 (eg, analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons, regionally targeted cytogenomic array analysis) [when specified as the following]: • *PSEN1 (presenilin 1)* (eg, Alzheimer disease), full gene sequence
81406	Molecular pathology procedure, Level 7 (eg, analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons, cytogenomic array analysis for neoplasia) [when specified as the following]: • *APP (amyloid beta [A4] precursor protein)* (eg, Alzheimer disease), full gene sequence • *PSEN2 (presenilin 2 [Alzheimer disease 4])* (eg, Alzheimer disease), full gene sequence
83520	Immunoassay for analyte other than infectious agent antibody or infectious agent antigen; quantitative, not otherwise specified [when specified as tau protein, amyloid beta peptide testing]
84999	Unlisted chemistry procedure [when specified as tau protein, amyloid beta peptide or neural thread protein biochemical testing]

ICD-10 Diagnosis

F03.90-F03.91	Unspecified dementia
G30.0-G30.9	Alzheimer's disease
G31.1	Senile degeneration of brain, not elsewhere classified
R41.0	Disorientation, unspecified
R41.3	Other amnesia (memory loss NOS)
R41.81	Age-related cognitive decline

When services are also Investigational and Not Medically Necessary:

CPT

0206U	Neurology (Alzheimer disease); cell aggregation using morphometric imaging and protein kinase C-epsilon (PKCe) concentration in response to amylospheroid treatment by ELISA, cultured skin fibroblasts, each reported as positive or negative for Alzheimer disease DISCERN™, NeuroDiagnostics, NeuroDiagnostics
0207U	Neurology (Alzheimer disease); quantitative imaging of phosphorylated ERK1 and ERK2 in response to bradykinin treatment by in situ immunofluorescence, using cultured skin fibroblasts, reported as a probability index for Alzheimer disease DISCERN™, NeuroDiagnostics, NeuroDiagnostics

HCPCS

S3852	DNA analysis for APOE epsilon 4 allele for susceptibility to Alzheimer's disease

ICD-10 Diagnosis

All diagnoses

References

Peer Reviewed Publications:

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Index

Alzheimer's Disease
ApoE
Apolipoprotein E
C_2N Diagnostics
Discern™
Epsilon 4 Allele
Neural Thread Protein
PrecivityAD™
Tau Protein

The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.

Document History

Status	Date	Action
	06/23/2021	Added notes to the Description/Scope section to clarify this document does not address imaging services and does not address the testing of individuals with an existing diagnosis of Alzheimer's disease to identify candidates for an FDA approved treatment for Alzheimer's disease.
Reviewed	11/05/2020	Medical Policy & Technology Assessment Committee (MPTAC) review. Updated the Rationale, References, Index and History sections. Updated Coding section, added PLA codes 0206U, 0207U.
Reviewed	02/20/2020	MPTAC review. Updated the Background/Overview, Rationale, References and History sections.
Reviewed	03/21/2019	MPTAC review. Updated the References and History sections.
Reviewed	03/22/2018	MPTAC review. The document header wording updated from "Current Effective Date" to "Publish Date." Updates the References and History section. Deleted the Websites for Additional Information section.
Reviewed	05/04/2017	MPTAC review. Updated Background/Overview and History sections.
Reviewed	05/05/2016	MPTAC review. Updated Rationale and Reference sections. Removed ICD-9 codes from Coding section.
Reviewed	05/07/2015	MPTAC review. Updated References and History sections.
	01/01/2015	Updated Coding section with 01/01/2015 HCPCS changes; removed S3855 deleted 12/31/2014.
Reviewed	05/15/2014	MPTAC review. Updated Rationale, References, Index and History sections.
	01/01/2014	Updated Coding section with 01/01/2014 CPT descriptor changes.
Reviewed	05/09/2013	MPTAC review. Updated the Rationale and References sections.
	01/01/2013	Updated Coding section with 01/01/2013 CPT changes; removed 83890-83914, 88384-88386 deleted 12/31/2012; removed 81228, 81229, 88245-88249, 88261-88264, 88271-88275, 88280-88291 (not applicable).
Reviewed	05/10/2012	MPTAC review. Updated Review Date, Rationale, References and History sections.
	01/01/2012	Updated Coding section with 01/01/2012 CPT changes.

Reviewed	05/19/2011	MPTAC review. Updated Review Date, References and History sections.
Reviewed	05/13/2010	MPTAC review. Updated review date, References and History sections.
Reviewed	05/21/2009	MPTAC review. No change to position statement. Updated References section.
Reviewed	05/15/2008	MPTAC review. Revised second investigational and not medically necessary position statement to add the following italicized text: "with *or without* a family history". Updated references.
	02/21/2008	The phrase "investigational/not medically necessary" was clarified to read "investigational and not medically necessary." This change was approved at the November 29, 2007 MPTAC meeting.
Reviewed	05/17/2007	MPTAC review. No changes to position statement.
	01/01/2007	Updated Coding section with 01/01/2007 CPT/HCPCS changes.
Reviewed	06/08/2006	MPTAC review. No changes to position statement; minor wording revisions; updated references.
	01/01/2006	Updated Coding section with 01/01/2006 CPT/HCPCS changes
Revised	07/14/2005	MPTAC review. Revision based on Pre-merger Anthem and Pre-merger WellPoint Harmonization.

Pre-Merger Organizations	**Last Review Date**	**Document Number**	**Title**
Anthem, Inc.	04/28/2004	GENE.00001	Genetic Molecular Testing for Inherited Disorders
WellPoint Health Networks, Inc.	04/28/2004	2.01.16	Genetic Testing and Biochemical Markers for the Diagnosis of Alzheimer's Disease