Corporate Medical Policy

Genetic Testing for Alzheimer’s Disease

File Name: genetic_testing_for_alzheimers_disease

Origination: 8/2010
Last CAP Review: 10/2017
Next CAP Review: 10/2018
Last Review: 10/2017

**Description of Procedure or Service**

Alzheimer’s disease (AD) is commonly associated with a family history; 40% of patients with AD have at least one other afflicted first-degree relative. Numerous genes have been associated with late-onset AD, while variants in chromosomes 1, 14, and 21 have been associated with early onset familial AD.

**Genetic Variants**

Individuals with early onset familial AD (i.e., before age 65 but as early as 30 years) form a small subset of AD patients. AD within families of these patients may show an autosomal dominant pattern of inheritance. Pathogenic variants in 3 genes have been identified in affected families: the amyloid-beta precursor protein gene (APP), presenilin 1 (PSEN1) gene, and presenilin 2 (PSEN2) gene. APP and PSEN1 variants have 100% penetrance absent death from other causes, while PSEN2 has 95% penetrance. A variety of variants within these genes has been associated with AD; variants in PSEN1 appear to be the most common. While only 3%–5% of all patients with AD have early onset disease, pathogenic variants have been identified in 70% or more of these patients. Identifiable genetic variants are, therefore, rare causes of AD.

Testing for the apolipoprotein ε4 allele (APOE*E4) among patients with late-onset AD and for APP, PSEN1, or PSEN2 pathogenic variants in the rare patient with early onset AD have been investigated as an aid in diagnosis in patients presenting with symptoms suggestive of AD, or as a technique for risk assessment in asymptomatic patients with a family history of AD. Pathogenic variants in PSEN1 and PSEN2 are specific for AD; APP variants are also found in cerebral hemorrhagic amyloidosis of the Dutch type, a disease in which dementia and brain amyloid plaques are uncommon.

The APOE lipoprotein is a carrier of cholesterol produced in the liver and brain glial cells. The APOE gene has 3 alleles—ε2, 3, and 4—with the ε3 allele being the most common. Individuals carry 2 APOE alleles. The presence of at least one ε4 allele is associated with a 1.2- to 3-fold increased risk of AD, depending on the ethnic group. Among those homozygous for epsilon 4 (=2% of the population), the risk of AD is higher than for those heterozygous for ε4. Mean age of onset of AD is about age 68 years for ε4 homozygotes, about 77 years for heterozygotes, and about 85 years for those with no ε4 alleles. About half of patients with sporadic AD carry an ε4 allele. However, not all patients with the allele develop AD. The ε4 allele represents a risk factor for AD rather than a disease- associated variant. In the absence of APOE testing, first-degree relatives of an individual with sporadic or familial AD are estimated to have a 2- to 4-fold greater risk of developing AD than the general population. There is evidence of possible interactions between ε4 alleles, other risk factors for AD (e.g., risk factors for cerebrovascular disease such as smoking, hypertension, hypercholesterolemia, diabetes), and a higher risk of developing AD.
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However, it is not clear that all risk factors have been taken into account in such studies, including the presence of variants in other genes that may increase the risk of AD.

Recent studies identified rs75932628-T, a rare functional substitution for R47H on the triggering receptor expressed on myeloid cells 2 (TREM2), as a heterozygous risk variant for late-onset AD. On chromosome 6p21.1, at position 47 (R47H), the T allele of rs75932628, encodes a histidine substitute for arginine in the gene that encodes TREM2.

*TREM2* is highly expressed in the brain and is known to have a role in regulating inflammation and phagocytosis. *TREM2* may serve a protective role in the brain by suppressing inflammation and clearing it of cell debris, amyloids and toxic products. A decrease in the function of *TREM2* would allow inflammation in the brain to increase and may be a factor in the development of AD. The effect size of the *TREM2* variant confers a risk of AD that is similar to the *APOE*E4 allele, although it occurs less frequently.

**Diagnosis**

The diagnosis of Alzheimer’s disease (AD) is divided into three categories: possible, probable, and definite AD. A diagnosis of definite AD requires postmortem confirmation of AD pathology, documenting the presence of extracellular beta amyloid plaques and intraneuronal neurofibrillary tangles in the cerebral cortex. As a result, a diagnosis of definite AD cannot be made during life, and the diagnosis of probable or possible AD is made on clinical grounds. Probable AD dementia is diagnosed clinically when the patient meets core clinical criteria for dementia and has a typical clinical course for AD. Criteria for diagnosis of probable AD have been developed by the National Institute on Aging and the Alzheimer’s Association.

Other diagnostic tests for AD include cerebrospinal (CSF) fluid levels of Tau protein or beta-amyloid precursor protein.

Genetic testing for Alzheimer’s disease may be offered along with analysis of cerebral spinal fluid (CSF) levels of the Tau protein and amyloid-β peptide 1-42. This group of tests may be collectively referred to as the ADmark™ Profile, offered by Athena Diagnostics (Worcester, Mass.).

**Regulatory Status**

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). Lab tests are available under the auspices of CLIA. Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of these tests.

**Related Policies**

Beta Amyloid Imaging With Positron Emission Tomography (PET) for Alzheimer’s Disease

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

**Policy**

BCBSNC will cover genetic testing for Alzheimer’s Disease when it is determined to be medically necessary because the medical criteria and guidelines shown below are met.

**Benefits Application**
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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.

When Genetic Testing for Alzheimer’s Disease is covered

Targeted genetic testing for a known familial variant in the presenilin genes (*PSEN*) or amyloid-beta precursor protein (*APP*) gene associated with autosomal dominant early-onset Alzheimer’s disease may be considered medically necessary in an asymptomatic individual to determine future risk of disease when the following criteria are met:

- The individual has a close relative (i.e., first- or second-degree relative) with a known familial variant associated with autosomal dominant early-onset Alzheimer’s disease AND
- Results of testing will inform reproductive decision making.

Genetic testing for variants in presenilin genes (*PSEN*) or amyloid-beta precursor protein (*APP*) gene associated with autosomal dominant Alzheimer’s disease may be considered medically necessary in an asymptomatic individual to determine future risk of disease when the following criteria are met:

- The individual has a family history of dementia consistent with autosomal dominant Alzheimer’s disease for whom the genetic status of the affected family members is unavailable AND
- Results of testing will inform reproductive decision making.

When Genetic Testing for Alzheimer’s Disease is not covered

Genetic testing for the risk assessment of Alzheimer’s disease in asymptomatic individuals is considered investigational in all other situations. Genetic testing includes, but is not limited to, testing for the apolipoprotein E epsilon 4 allele or triggering receptor expressed on myeloid cells 2.

Policy Guidelines

For individuals who are asymptomatic and at risk for developing late-onset AD who receive genetic testing, the evidence includes studies on gene associations, test accuracy, and effects on health outcomes. Relevant outcomes are test accuracy and validity, change in disease status, health status measures, and quality of life. Many genes, including apolipoprotein E (*APOE*), *CRI*, *BIN1*, *PICALM*, and *TREM2*, are associated with late-onset AD. However, the sensitivity and specificity of genetic testing for indicating which individuals will progress to AD is low, and numerous other factors can affect progression. Overall, genetic testing has not been shown to add value to the diagnosis of AD made clinically. The current lack of effective methods to prevent the onset of AD or to target AD treatments based on genetic characteristics limits the clinical benefit for genetic testing. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who are asymptomatic, at risk for developing early-onset, autosomal dominant AD, and have a known familial variant who receive targeted genetic testing for a known familial variant, the evidence includes studies on gene associations and test accuracy. Relevant outcomes are test accuracy and validity, change in disease status, change in reproductive decision making, health status measures, and quality of life. Variants in the presenilin 1 and 2 (*PSEN1* and *PSEN2*) and amyloid-beta precursor protein (*APP*) genes are known to cause early-onset AD in an autosomal dominant pattern with almost complete penetrance. The clinical validity for autosomal dominant early-onset AD will be nearly certain when a familial pathogenic variant has previously been identified. Outside the reproductive
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setting when used for prognosis or prediction, there is insufficient evidence to draw conclusions on the benefits of genetic testing for pathogenic variants. Testing a prospective parent, when performed in conjunction with genetic counseling, provides more accurate information to guide reproductive planning than family history alone. Therefore, clinical utility for the purposes of reproductive decision making has been demonstrated for these tests. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who are asymptomatic, at risk for developing early-onset, autosomal dominant AD, and have no known familial variant who receive genetic testing, the evidence includes studies on gene associations and test accuracy. Relevant outcomes are test accuracy and validity, change in disease status, change in reproductive decision making, health status measures, and quality of life. Variants in the \textit{PSEN1}, \textit{PSEN2}, and \textit{APP} genes are known to cause early-onset AD in an autosomal dominant pattern with almost complete penetrance. The clinical validity for autosomal dominant early-onset AD will be reasonably certain when a variant found in the database of pathogenic \textit{PSEN1}, \textit{PSEN2}, and \textit{APP} variants is identified. Outside the reproductive setting when used for prognosis or prediction, there is insufficient evidence to draw conclusions on the benefits of genetic testing for pathogenic variants. Testing a prospective parent, when performed in conjunction with genetic counseling, provides more accurate information to guide reproductive planning than family history alone. Therefore, clinical utility for the purposes of reproductive decision making has been demonstrated for these tests. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

\section*{Billing/Coding/Physician Documentation Information}

This policy 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.

\textit{Applicable codes: 81401, 81405, 81406, G0452, S3852}

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

\section*{Scientific Background and Reference Sources}


Medical Director – 8/2010


Senior Medical Director – 10/2012

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For Policy titled Genetic Testing for Alzheimer’s Disease


Policy Implementation/Update Information

For Policy titled Genetic Testing for Familial Alzheimer’s Disease:

9/14/10 New evidence based guideline. Reviewed by Medical Director 8/10/2010. “Genetic testing for the diagnosis or risk assessment of Alzheimer’s disease not recommended. Genetic testing includes, but is not limited to, testing for the apolipoprotein E epsilon 4 allele, presenilin genes, or amyloid precursor gene.” (btw)


1/1/2012 Policy converted from Evidence Based Guideline to Corporate Medical Policy. Specialty Matched Consultant Advisory Panel review 11/30/2011. “Genetic testing for the diagnosis or risk assessment of Alzheimer’s disease is considered investigational. Genetic testing includes, but is not limited to, testing for the apolipoprotein E epsilon 4 allele, presenilin genes, or amyloid precursor gene.” Added new CPT code effective 1/1/2012, 81401, to “Billing/Coding” section. Notification given 1/1/2012. Policy effective 4/1/2012. (btw)


12/28/12 Added the following codes to the Billing/Coding section: 81405, 81406, and G0452. (btw)

11/12/13 Description section updated to include information related to TREM2. TREM2 added to investigational policy statement. Specialty Matched Consultant Advisory Panel review 10/16/2013. Reference added. (btw)

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12/30/14  Code S3855 deleted from Billing/Coding section. (sk)


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12/30/15 References added. Policy title changed to Genetic Testing for Alzheimer’s Disease.
Policy Guidelines updated. (sk)

11/22/16 Specialty Matched Consultant Advisory Panel review 10/26/2016. (sk)


Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.