Genetic Testing for Alzheimer’s Disease

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 mutations in chromosomes 1, 14, and 21 have been associated with early onset familial AD.

Susceptibility Polymorphism at the Apolipoprotein E (APOE) Gene

The APOE lipoprotein is a carrier of cholesterol produced in the liver and brain glial cells. The APOE gene has 3 alleles—epsilon 2, 3, and 4—with the epsilon 3 allele being the most common. Individuals carry 2 APOE alleles. The presence of at least 1 epsilon 4 allele is associated with a 1.2- to 3-fold increased risk of AD depending on the ethnic group. The epsilon 4 allele represents a risk factor for AD rather than a disease-causing mutation.

Genetic Mutations

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 mutations in 3 genes have been identified in affected families: amyloid-beta precursor protein gene (APP), presenilin 1 (PSEN1) gene, and presenilin 2 (PSEN2) gene. APP and PSEN1 mutations have 100% penetrance absent death from other causes, while PSEN2 has 95% penetrance. A variety of mutations within these genes has been associated with AD; mutations in PSEN1 appear to be the most common. While only 3%–5% of all patients with AD have early onset disease, pathogenic mutations have been identified in up to 70% or more of these patients. Identifiable genetic mutations are, therefore, rare causes of AD.

Testing for the APOE 4 allele among patients with late-onset AD and for APP, PSEN1, or PSEN2 mutations 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. Mutations in PSEN1 and PSEN2 are specific for AD; APP mutations are also found in cerebral hemorrhagic amyloidosis of the Dutch type, a disease in which dementia and brain amyloid plaques are uncommon.

Susceptibility Testing at the Triggering Receptor Expressed on Myeloid Cells 2 (TREM2) Gene

Recent studies identified rs75932628-T, a rare functional substitution for R47H of 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.
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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 epsilon 4 allele, although it occurs less frequently.

Diagnosis of Alzheimer’s Disease

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 cerebral spinal fluid (CSF) levels of the Tau protein and AB-42 peptide. This group of tests may be collectively referred to as the ADmark™ Profile, offered by Athena Diagnostics (Worcester, Mass.).

Regulatory Status

No U.S. Food and Drug Administration (FDA)-cleared genotyping tests were found. The U.S. Food and Drug Administration (FDA) has not regulated these tests to date. Thus, genotyping is offered as a laboratory-developed test. Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; such tests must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA).

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

Genetic testing for familial Alzheimer’s disease is considered investigational for all applications. BCBSNC does not provide coverage for investigational services or procedures.

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.

When Genetic Testing for Alzheimer’s Disease is covered
Not applicable.
Genetic Testing for Alzheimer’s Disease

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. Genetic testing includes, but is not limited to, testing for the apolipoprotein E epsilon 4 allele, presenilin genes, amyloid-beta precursor protein or triggering receptor expressed on myeloid cells 2.

Policy Guidelines

The evidence for genetic testing in individuals who are asymptomatic and at risk for developing Alzheimer disease (AD) includes studies on gene associations, test accuracy, and effects on health outcomes. Relevant outcomes are test accuracy, test validity, change in disease status, and health status measures. Many genes, including apolipoprotein E (APOE) 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. For individuals with early-onset AD, mutations in the presenilin 1 (PSEN1) and amyloid-beta precursor protein (APP) genes are found in a substantial number of patients. However, there is no direct or indirect evidence to establish that clinical outcomes are improved as a result of genetic testing for these mutations. 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.

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.

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.

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)


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


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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.