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Medical Policy Manual

Topic: Genetic Testing for Familial Alzheimer's Disease

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Section: Genetic Testing

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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

Alzheimer's disease is the most common cause of dementia in elderly patients. Early-onset Alzheimer's disease is much less common, but can occur in non-elderly individuals. For late-onset Alzheimer's disease, there is a component of risk that runs in families, suggesting the contribution of genetic factors. Early-onset Alzheimer's has a stronger component of family risk, with clustering in families, thus suggesting an inherited genetic mutation.

Alzheimer's disease (AD) is commonly associated with a family history; 40% of patients with AD have a 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.[1]

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. Among those homozygous for epsilon 4 (about 2% of the population), the risk of AD is higher than for those heterozygous for epsilon 4. The mean age of onset of AD is about 68 years for epsilon 4 homozygotes, about 77 years for heterozygotes, and about 85 years for those with no epsilon 4 alleles. About half of patients with sporadic AD carry an epsilon 4 allele. However, not all patients with the allele develop AD. The epsilon 4 allele represents a risk factor

for AD rather than a disease-causing mutation. 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.[2] There is evidence of possible interactions between epsilon 4 alleles, other risk factors for AD (e.g., risk factors for cerebrovascular disease such as smoking, hypertension, hypercholesterolemia, and diabetes[3]), and a higher risk of developing AD. However, it is not clear that all risk factors have been taken into account in such studies, including the presence of polymorphisms in other genes that may increase the risk of AD.

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 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.[4,5] 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 epsilon 4 allele, although it occurs less frequently.

Clinical Diagnosis of AD

Currently, the clinical diagnosis of AD is established by the presence of a consistent history and by excluding treatable 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) developed clinical criteria for the diagnosis of AD.[6] Three categories were defined: possible, probable, and definite AD. The diagnosis of definite AD requires a brain biopsy confirming the presence of characteristic neurofibrillary tangles. While definite AD is almost always diagnosed by autopsy, in approximately 85% of those with a diagnosis of probable AD, pathological

findings are found to be consistent.

Biomarker evidence has been integrated into the diagnostic criteria for probable and possible AD for use in research settings.[7] Other proposed diagnostic tests for AD include cerebrospinal (CSF) fluid levels of Tau protein or beta-amyloid precursor protein. These CSF tests are addressed in a separate medical policy (see Cross References below).

Regulatory Status

No U.S. Food and Drug Administration (FDA)-cleared genotyping tests were found. The 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 ("home-brew") and market them as a laboratory service. Such tests must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA). The laboratory offering the service must be licensed by CLIA for high-complexity testing.

MEDICAL POLICY CRITERIA

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 (APOE) epsilon 4 allele, presenilin (PSEN) genes, amyloid precursor protein (APP) gene, or triggering receptor expressed on myeloid cells 2 **(**TREM2) gene.

SCIENTIFIC EVIDENCE

Validation of the clinical use of any genetic test focuses on 3 main principles:

- The analytic validity of the test, which refers to the technical accuracy of the test in detecting a mutation that is present or in excluding a mutation that is absent;
- The clinical validity of the test, which refers to the diagnostic performance of the test (sensitivity, specificity, positive and negative predictive values) in detecting clinical disease; and
- The clinical utility of the test, i.e., how the results of the diagnostic test will be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes.

Literature Appraisal

There are a number of studies reporting associations between risk of AD and more than 20 genes; however, they fail to demonstrate how test results alter and improve treatment or predict therapeutic response to treatment (thereby improving health outcomes).[8-13] The possibility that earlier diagnosis of AD might lead to improved outcomes, while plausible, is not based on current evidence. To date, pharmacologic interventions for mild cognitive impairment have failed to demonstrate benefit in reducing progression to AD.[14]

Technology Assessment

A BlueCross BlueShield Association Technology Evaluation Center (TEC) Assessment published in

1999 concluded that the addition of APOE genetic testing does not improve the sensitivity and only marginally improves the specificity of clinical criteria for the diagnosis of AD.[15,16] The sensitivity and specificity of clinical diagnostic criteria were 93% and 55%, respectively. The sensitivity and specificity for the presence of at least one APOE epsilon 4 allele for pathogenically diagnosed AD were 65% and 68%, respectively.

Because of the significant number of false positive tests, the TEC Assessment concluded that APOE genetic testing does not eliminate additional recommended diagnostic testing to rule out other treatable causes of dementia. No data were available to assess whether AD could be prevented among individuals who carried an epsilon 4 allele, nor were specific therapies developed on the basis of APOE genotype status. Finally, the evidence did not suggest that APOE epsilon testing was of value in determining rate of progression to AD or mortality from AD.

Systematic Reviews

A 2012 systematic review on the psychological and behavioral impact of genetic testing for AD found few studies on the impact of testing for early onset familial AD.[17] The authors reported that existing studies generally had small sample sizes and retrospective designs, and the research was conducted in different countries, which may limit the generalizability of the findings.

Clinical Trials

There are a number of studies reporting associations between risk of AD and more than 20 genes; however, they failed to demonstrate how test results alter and improve treatment or predict therapeutic response to treatment (thereby improving health outcomes).[4,5,8-13] The possibility that earlier diagnosis of AD might lead to improved outcomes, while plausible, is not based on current evidence. In addition, the sensitivity and specificity of these genes is low or unknown for diagnosing AD, and test results have not been shown to add value to the management of clinically-diagnosed AD.

Clinical Practice Guidelines

- Several consensus statements regarding APOE genotyping universally concluded that APOE genotyping in asymptomatic patients as a technique of risk assessment is not recommended.[18-22]

- Statements regarding the use of genetic testing as a diagnostic test in symptomatic patients are mixed:

    - Diagnostic guidelines for AD released in 2011 by the National Institute on Aging-Alzheimer's Association workgroup recommended testing for APP, PSEN1, or PSEN2 mutations as confirmation of probable AD dementia.[7] This recommendation is not accompanied by references to scientific literature; it is not clear how evidence relating to the clinical utility of this type of testing was appraised in making this recommendation.

    - An evidence and consensus-based practice guideline from the American Psychiatric Association (APA) published in 2007 recommended genetic testing for AD in limited instances.[22] However, the guidelines state that this type of testing has not been widely instituted in current clinical practice (due in part to the lack of preventative treatment, among other concerns).

- An evidence-based practice parameter for the diagnosis of dementia by the American Academy of Neurology stated that routine use of APOE or other genetic markers in the diagnosis of AD is not recommended.[23,24]

- In a 2011 joint practice guideline the American College of Medical Genetics and the National Society of Genetic Counselors published practice guidelines recommending testing for mutations to aid in diagnosis of both symptomatic patients and predictive testing of asymptomatic patients.[2] However, the guidelines cite the difficulty in interpreting test results: if the test is negative, it does not rule out the potential influence of as yet unidentified mutations which may lead to AD; if it is positive, the lack of “clear genotype-phenotype correlations” may likewise hinder interpretation of the result.

- In 1997 a National Study Group, supported by the NIH and composed of AD geneticists, policy experts, and ethicists, stated "The use of APOE genetic testing as a diagnostic adjunct in patients already presenting with dementia may prove useful but it remains under investigation."[19]

- In contrast, a report by the Working Group on Molecular and Biochemical Markers of Alzheimer's Disease stated that APOE genotyping can add "confidence to the clinical diagnosis of AD..." but "...the sensitivity and specificity of the epsilon 4 allele alone are low, indicating that this measure cannot be used as the sole diagnostic test for AD."[21]

- In 1998, the Alzheimer Disease Working Group of the Stanford Program in Genomics, Ethics, and Society[25] suggested that “predictive or diagnostic genetic testing for highly penetrant mutations (e.g., APP, PSEN1, PSEN2) may be appropriate for individuals from families with a clear autosomal dominant pattern of inheritance, particularly those with a family history of early onset of symptoms.” Such families generally have three affected members in two generations. In the case of diagnostic testing of clearly symptomatic individuals, testing would do little to change diagnostic confidence; however, it might assist excluding other causes of early onset dementia, as potentially treatable contributory causes would still require exploring. In cases of early detection of questionably symptomatic individuals (i.e., those with mild cognitive impairment, mutation identification might secure a diagnosis and lead to early treatment. The possibility that earlier diagnosis might lead to improved outcomes, while plausible, is not based on current evidence. Pharmacologic interventions for mild cognitive impairment have not demonstrated benefit in reducing progression to AD.[14]

Summary

There are no published clinical utility studies which demonstrate how genetic testing for the diagnosis or risk assessment for Alzheimer’s disease (AD) guides prevention or treatment, or results in improved health outcomes. The lack of effective methods to prevent the onset of AD or to target AD treatments based on genetic characteristics limits the clinical benefit for such genetic testing. In addition, the sensitivity and specificity (clinical validity) of these genes is low or unknown for diagnosing AD. Therefore, genetic testing for the diagnosis or risk assessment for AD is considered investigational. This includes, but is not limited to, testing for the apolipoprotein E epsilon (APOE) 4 allele, presenilin (PSEN1, PSEN2) genes, amyloid precursor (APP) gene, or triggering receptor expressed on myeloid cells 2 (TREM2) gene.

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CROSS REFERENCES

Genetic and Molecular Diagnostic Testing, Genetic Testing, Policy No. 20

Biochemical Markers of Alzheimer's Disease, Laboratory, Policy No. 22

CODES	NUMBER	DESCRIPTION
CPT	81401	Molecular pathology procedure, Tier 2, Level 1
	81405	Molecular pathology procedure, Tier 2, Level 6
	81406	Molecular pathology procedure, Tier 2, Level 7
	88363	Examination and selection of retrieved archival (ie, previously diagnosed) tissue(s) for molecular analysis (eg, KRAS mutational analysis)
HCPCS	S3852	DNA analysis for APOE epsilon 4 allele for susceptibility to Alzheimer’s disease

CODES	NUMBER	DESCRIPTION
	S3855	Genetic testing for detection of mutations in the presenilin-1 gene