This Protocol considers this test or procedure investigational. If the physician feels this service is medically necessary, preauthorization is recommended.

The following Protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient’s contract at the time the services are rendered.

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Description

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

Summary of Evidence

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), CR1, 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 are 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.
Policy
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 (APOE), presenilin genes (PSEN), amyloid precursor gene (APP), or triggering receptor expressed on myeloid cells 2 (TREM2).

Policy Guidelines
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, MA).

Genetic Counseling
Genetic counseling is primarily aimed at patients who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual’s family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

Background
Alzheimer 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.1

Susceptibility Polymorphism at the Apolipoprotein E Gene
The apolipoprotein E (APOE) lipoprotein is a carrier of cholesterol produced in the liver and brain glial cells. The APOE gene has three alleles—ε2, 3, and 4—with the epsilon 3 allele being the most common. Individuals carry two APOE alleles. The presence of at least one ε4 allele is associated with a 1.2 to three-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 at 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-causing mutation. In the absence of APOE testing, first-degree relatives of an individual with sporadic or familial AD are estimated to have a two- to four-fold greater risk of developing AD than the general population.2 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, diabetes3), 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 years 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 three genes have been identified in affected families: amyloid-beta precursor protein...
(APP) gene, 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% to 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 of 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 Gene**

Recent studies identified rs75932628-T, a rare functional substitution for R47H of 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 ε4 allele, although it occurs less frequently.

**Diagnosis of AD**

The diagnosis of 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. These criteria require evidence of a specific pattern of cognitive impairment, a typical clinical course, and exclusion of other potential etiologies, as follows:

- **Cognitive impairment**
  - Cognitive impairment established by history from patient and a knowledgeable informant, plus objective assessment by bedside mental status examination or neuropsychological testing
  - Cognitive impairment involving a minimum of two of the following domains:
    - Impaired ability to acquire and remember new information
    - Impaired reasoning and handling of complex tasks, poor judgment
    - Impaired visuospatial abilities
    - Impaired language functions
    - Changes in personality, behavior, or comportment
  - Initial and most prominent cognitive deficits are one of the following:
    - Amnestic presentation
Nonamnestic presentations, either a language presentation with prominent word-finding deficits; a visuospatial presentation with visual cognitive defects; or a dysexecutive presentation with prominent impairment of reasoning, judgment, and/or problem solving.

- **Clinical course**
  - Insidious onset
  - Clear-cut history of worsening over time
  - Interference with ability to function at work or usual activities
  - Decline from previous level of functioning and performing

- **Exclusion of other disorders**
  - Cognitive decline not explained by delirium or major psychiatric disorder
  - No evidence of other active neurologic disease, including substantial cerebrovascular disease or dementia with Lewy bodies.
  - Lack of prominent features of variant frontotemporal dementia or primary progressive aphasia.
  - No medication use with substantial effects on cognition.

A diagnosis of possible AD dementia is made when the patient meets most of the AD criteria, but has an atypical course or an etiologically mixed presentation. This may consist of an atypical onset (e.g., sudden onset) or atypical progression. A diagnosis of possible AD is also made when there is another potentially causative systemic or neurologic disorder that is not thought to be the primary etiology of dementia.

Mild cognitive impairment (MCI) is a precursor of AD in many instances. MCI may be diagnosed when there is a change in cognition, but not sufficient impairment for the diagnosis of dementia. Features of MCI are evidence of impairment in one or more cognitive domains and preservation of independence in functional abilities. In some patients, MCI may be a predementia phase of AD. Patients with MCI may undergo ancillary testing (e.g., neuroimaging, laboratory studies, neuropsychological assessment) to rule out vascular, traumatic, and medical causes of cognitive decline and to evaluate genetic factors.

Biomarker evidence has been integrated into the diagnostic criteria for probable and possible AD for use in research settings. Other diagnostic tests for AD include CSF levels of tau protein or beta amyloid precursor protein, as well as positron emission tomography amyloid imaging.

**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 Act (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 this test.

Services that are the subject of a clinical trial do not meet our Technology Assessment Protocol criteria and are considered investigational. For explanation of experimental and investigational, please refer to the Technology Assessment Protocol.

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced
procedures. Some of this Protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.

References

We are not responsible for the continuing viability of web site addresses that may be listed in any references below.


