### Genetic Testing for Familial Alzheimer’s Disease

**Medical Benefit**

Effective Date: 07/01/12  
Next Review Date: 03/13

| Preauthorization* | Yes | Review Dates: 07/07, 07/08, 05/09, 03/10, 03/11, 03/12 |

The following Protocol contains medical necessity criteria that apply for this service. It is applicable to Medicare Advantage products unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. **Preauthorization is required if, despite this protocol position, you feel this service is medically necessary; supporting documentation must be submitted to Use Management by the requesting/ordering physician.**

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.

### Description

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. (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 three alleles—epsilon 2, 3, and 4—with the epsilon 3 allele being the most common. Individuals carry two APOE alleles. The presence of at least one 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. 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 three genes have been identified in affected families: amyloid-beta precursor protein gene (APP), presenilin 1 (PSEN1) gene, and presenilin 2 (PSEN2) gene. These mutations have nearly 100% penetrance absent death from other causes, although rare cases of nonpenetration in elderly individuals have been reported. 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.

Currently, the clinical diagnosis of AD is established by the presence of a consistent history, and 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. (2) 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. The diagnostic categories are defined as follows:

**Possible Alzheimer’s Disease**

Clinical diagnosis of possible AD:
1. May be made on the basis of the dementia syndrome in the absence of other neurological, psychiatric, or systemic disorders sufficient to cause dementia, and in the presence of variations in the onset, the presentation, or the clinical course
2. May be made in the presence of a second systemic or brain disorder sufficient to produce dementia, which is not considered to be the cause of the dementia
3. Should be used in research studies when a single gradually progressive severe cognitive deficit is identified in the absence of other identifiable cause.

**Probable Alzheimer’s Disease**

The criteria for the clinical diagnosis of probable AD include all of the following:
1. Dementia, established by clinical examination and documented by the Mini-Mental State Examination, the Blessed Dementia Scale, or some similar examination and confirmed by neuropsychological tests
2. Deficits in two or more areas of cognition
3. Progressive worsening of memory and other cognitive functions
4. No disturbance of consciousness
5. Onset between ages 40 and 90, most often after the age of 65
6. Absence of systemic disorders or other brain diseases that in and of themselves could account for the progressive deficits in memory and cognition.

The diagnosis of probable AD is supported by:
1. Progressive deterioration of specific cognitive functions such as language (aphasia), motor skills (apraxia), and perception (agnosia)
2. Impaired activities of daily living and altered patterns of behavior
3. Family history of similar disorders, particularly if confirmed neuropathologically
4. Laboratory results: normal lumbar puncture as evaluated by standard techniques, normal pattern or nonspecific changes in the electroencephalogram (EEG), and evidence of cerebral atrophy on computed tomography (CT) scanning with progression documented by serial observation.

Other clinical features consistent with the diagnosis of probable AD, after exclusion of causes of dementia other than AD, include
1. Plateaus in the course of progression of the illness;
2. Associated symptoms of depression, insomnia, incontinence, delusions, illusions, hallucinations, sexual disorders, weight loss, and catastrophic verbal, emotional, or physical outbursts;
3. Other neurologic abnormalities in some patients, especially with more advanced disease and including motor signs such as increased muscle tone, myoclonus, or gait disorder;
4. Seizures in advanced disease CT normal for age.

Features that make the diagnosis of probable AD uncertain or unlikely include:
1. Sudden apoplectic onset
2. Focal neurological findings such as hemiparesis, sensory loss, visual field deficits, and incoordination early in the course of the illness
3. Seizures or gait disturbances at the onset or very early in the course of the illness.

**Definite Alzheimer’s Disease**

Criteria for diagnosis of definite AD are:
1. Clinical criteria for probable Alzheimer’s disease AND
2. Histopathologic evidence obtained from a biopsy or autopsy.

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

**Corporate Medical Guideline**

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.

**Policy Guideline**

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). Refer also to Protocol Genetic Testing for Inherited Disorders.

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.

3. 1999 TEC Assessments; Tab 7.


