



CIGNA MEDICAL COVERAGE POLICY

The following Coverage Policy applies to all plans administered by CIGNA Companies including plans administered by Great-West Healthcare, which is now a part of CIGNA.

Subject Genetic Testing to Diagnose and Predict Susceptibility to Alzheimer’s Disease

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Hyperlink to Related Coverage Policies

- Genetic Counseling
- Genetic Testing of Heritable Disorders
- Preimplantation Genetic Diagnosis

INSTRUCTIONS FOR USE

Coverage Policies are intended to provide guidance in interpreting certain **standard** CIGNA HealthCare benefit plans as well as benefit plans formerly administered by Great-West Healthcare. Please note, the terms of a participant’s particular benefit plan document [Group Service Agreement (GSA), Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a participant’s benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a participant’s benefit plan document **always supercedes** the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable group benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. Proprietary information of CIGNA. Copyright ©2010 CIGNA

Coverage Policy

CIGNA does not cover genetic testing for the screening, diagnosis or management of Alzheimer’s disease, including but not limited to genetic testing for APP, PSEN1, PSEN2, or apolipoprotein-E (APOE), because it is considered experimental, investigational or unproven.

General Background

Alzheimer’s disease (AD), also known as dementia of the Alzheimer type, is the most common cause of dementia and is characterized by either late onset AD or early onset familial AD (EOFAD). It is a progressive, fatal neurodegenerative condition characterized by deterioration in cognition and memory, progressive impairment in the ability to carry out activities of daily living, and a number of neuropsychiatric and behavioral symptoms (Jalbert, 2008).

Definitive diagnosis of AD is based on neuropathological findings of beta-amyloid plaques and intraneuronal neurofibrillary tangles in brain tissue on autopsy. Clinical diagnosis prior to autopsy confirmation is made by use of the Diagnostic and Statistical Manual of Mental Disorders, fourth edition, and the National Institute of Neurological and Communicative Diseases and Stroke and the Alzheimer’s Disease and Related Disorders Association ([NINCDS-ADRDA]) criteria, which correctly diagnoses the disease 80%-90% of the time (Bird, 2008). Differential diagnosis of AD includes other causes of dementia, especially treatable forms of cognitive decline.

The mainstay of treatment for AD is necessarily supportive, and each symptom is managed on an individual basis. Medications (e.g., cholinesterase inhibitors, n-methyl d-aspartate [NMDA] antagonists) have been shown to produce a modest but useful behavioral or cognitive benefit in a minority of patients. Although progress is being made in developing new therapies for AD, no therapeutic interventions to cure or substantially modify disease progression currently exist (Jalbert, 2008). No accurate clinical diagnostic test for Alzheimer's disease (AD) exists. Neuropathologic findings on autopsy examination remain the gold standard for diagnosis of AD. Genetic testing has been proposed as a means to diagnose or predict susceptibility to early onset familial and late onset AD.

Early Onset Familial Alzheimer's Disease (EOFAD): EOFAD characterizes families in which multiple cases of Alzheimer's disease (AD) occur (e.g., usually multiple affected persons in more than one generation) in which the age of onset is consistently before age 60 to 65 and often before age 55. About 1%-6% of all AD is early onset; about 60% of early-onset AD is familial type with 13% appearing to be inherited in an autosomal dominant manner (Bird, 2008). Autosomal dominant inheritance is characterized by affected individuals in three generations. The risk of inheriting EOFAD is 50% for each child of an affected person. This type of AD cannot be clinically distinguished from nonfamilial AD except on the basis of family history and age of onset. The dementia phenotype is similar to that of late onset AD (Bird, 2009).

By use of genome-wide association studies gene mutations have been associated with three subtypes of EOFAD: Alzheimer's disease type 1 (AD1) (i.e., APP gene which encodes the amyloid precursor protein; 10%–15% of EOFAD); Alzheimer's disease type 3 (AD3) (i.e., PSEN1 gene which encodes the protein presenilin-1; 30%–70% of EOFAD), and Alzheimer's disease type 4 (AD4) (i.e., PSEN2 gene which encodes the protein presenilin-2; <5% of EOFAD) (Bird, 2009). It is likely that other genes will be identified as kindreds with autosomal dominant familial AD with no known mutations in PSEN1, PSEN2, or APP have been described (Bird, 2009; Cruts, 1998). At present, no other phenotypes have been associated with mutations in PSEN1 and PSEN2.

Genetic Testing for Early Onset Familial Alzheimer's Disease: Genetic testing of at-risk asymptomatic adults for EOFAD is clinically available for PSEN1, PSEN2 and APP mutations; prenatal diagnosis for pregnancies at increased risk for PSEN1 mutations is also possible. However, it is not helpful in predicting age of onset, severity, type of symptoms, or rate of progression in asymptomatic individuals. At this time there is insufficient evidence to demonstrate the clinical utility of genetic testing to diagnose or manage early onset familial AD in at risk individuals or as a screening tool in the general population. The clinical utility of genetic testing for this indication has not yet been established.

Late Onset Alzheimer's Disease (AD): Late onset AD is a nonfamilial, slowly progressive dementia associated with diffuse cerebral atrophy on neuroimaging studies. It is the most common form of AD. Investigations have supported the concept that late onset AD is a complex disorder that may involve multiple susceptibility genes (Bird, 2008; Kamboh, 2004; Bertram, 2004). Establishing the diagnosis of Alzheimer's disease relies on clinical-neuropathologic assessment. Individuals must meet diagnostic clinical criteria for AD and have a negative family history. The gold standard for diagnosis of AD is neuropathology found on autopsy.

At least three different alleles of apolipoprotein-E (APOE) have been identified: APOE epsilon-2, APOE epsilon3, and APOE epsilon-4. APOE epsilon-4 is considered significant for late onset AD. By unknown mechanisms this allele appears to affect the age of onset by shifting the onset curve toward an earlier age. It is thought that the presence of this allele contributes to the susceptibility of AD; conversely, the presence of APOE epsilon-2 may offer protection against the development of AD. The influence of APOE genotype on AD risk may also be modulated by cholesterol level, alpha-1 -antichymotrypsin genotype, and very low-density lipoprotein receptor gene (ACMG, 1995). Several other potential genes and loci are under investigation (Blacker, et al., 2002).

Genetic Testing for Late Onset Alzheimer's Disease (AD): APOE genotyping is neither fully specific nor sensitive for AD, with moderate specificity estimates ranging from 75% to 81% (Bird, 2010; American College of Medical Genetics [ACMG], 1995; Corder, 1993). This genotype is found in many elderly persons without dementia and about 42% of persons with late-onset AD do not have an APOE epsilon-4 allele; however, the absence of this allele does not rule out the diagnosis of AD (Mayeux, et al., 1998). Although the presence of an APOE epsilon-4 allele or alleles is neither necessary nor sufficient to establish a diagnosis, it has been suggested that APOE genotyping may have an adjunct role in the diagnosis of AD because a large proportion of

individuals with epsilon-4 alleles who are demented have been found to have neuropathologic confirmation of AD at autopsy (Relkin, et al., 1996; Mayeux, et al., 1998). Determination of the APOE genotype is not recommended for diagnostic use at this time (Friedman, 2007).

Tsuang et al. (1999) prospectively evaluated APOE testing for Alzheimer's disease (AD) in a community-based case series of 970 persons with no previous diagnosis of dementia. Clinical diagnosis yielded a sensitivity of 84%, specificity of 50%, and positive and negative predictive values of 81% and 56%, respectively. Neuropathologic AD was confirmed in 94 of 132 patients, with a prevalence of 71%. The presence of an APOE epsilon-4 allele was associated with an estimated sensitivity of 59%, specificity of 71%, and positive and negative predictive values of 83% and 41%, respectively. The authors noted that findings do not support the use of APOE genotyping alone in the diagnosis of AD in the general medical community.

In a neuropathologically confirmed series, the addition of APOE testing increased the positive predictive value of a diagnosis of AD from 90% to only 94%. In those patients with a clinical diagnosis of non-Alzheimer dementia the absence of an APOE epsilon-4 allele increased the negative predictive value from 64% to 72% (Waldemar, 2007).

The clinical utility of genetic testing has not been established; results in the form of APOE genotyping would not modify the recommended diagnostic work-up to rule-out other causes of dementia. Although genetic tests for prenatal, and preimplantation genetic diagnosis may be clinically available, requests for testing of adult onset diagnoses are uncommon. APOE genotyping appears to have little role in predictive testing of asymptomatic individuals (Bird, 2010). Estimates of risk are not generally considered clinically useful.

Biochemical Testing for AD: In addition to genetic testing, biochemical testing for AD has been proposed as a method of diagnosis and monitoring disease progression and response to therapy. Potential biochemical markers include cerebral spinal fluid (CSF) A beta₄₂, CSF hyperphosphorylated tau (P-tau), and CSF-total tau protein (T-tau), among others. In a recent report by Mattsson et al. (2009) involving individuals with mild cognitive impairment (n=750), Alzheimer's disease (n=529) and healthy controls (n=303), A beta₄₂ peptide had a sensitivity of 79% and a specificity of 65% in predicting incipient AD in individuals with mild cognitive impairment, while P-tau had a sensitivity of 84% and a specificity of 47%, and T-tau had a sensitivity of 86% and a specificity of 56%. The predictive value of the biomarkers combined was greater than the predictive value of any individual biomarker. In comparing patients with MCI and incipient AD with healthy controls, the sensitivity achieved was 83% with a specificity of 88%. Evidence is currently insufficient to support or direct the use of biomarkers in usual clinical practice for dementia diagnosis or disease management purposes (Mattsson, 2009; Jalbert, 2008). The clinical utility of biochemical markers in the screening, diagnosis and management of AD is unknown at this time.

Professional Societies/Organizations

American Academy of Neurology (AAN): The Quality Standards Subcommittee of the AAN updated an earlier practice parameter for the diagnosis of dementia in the elderly. Regarding AD, this evidence-based review concluded that there are no laboratory tests, including APOE genotyping or other genetic markers or biomarkers, which are appropriate for routine use in the clinical evaluation of patients with suspected AD. However, genotyping and biomarkers, as well as imaging, are promising avenues that are being pursued (Knopman, et al., 2001; reaffirmed 2004).

American College of Medical Genetics (ACMG)/American Society of Human Genetics (ASHG): A consensus statement was published by the ACMG/ASHG Working Group on APOE and Alzheimer Disease (1995) that notes, "There is general consensus that APOE epsilon-4 is strongly associated with AD and that when present may represent an important risk factor for the disease. However, at the present time it is not recommended for use in routine clinical diagnosis nor should it be used for predictive testing. Studies to date indicate that the APOE genotype alone does not provide sufficient sensitivity or specificity to allow genotyping to be used as a diagnostic test. Because AD develops in the absence of APOE epsilon-4 and because many with APOE epsilon-4 seem to escape disease, genotyping is also not recommended for use as a predictive genetic test."

American Psychiatric Association: Practice Guidelines for the treatment of patients with Alzheimer's disease and other dementias note that a definitive diagnosis of Alzheimer's disease requires both the clinical syndrome and microscopic examination of the brain at autopsy, at which time the characteristic plaques and neurofibrillary

tangles widely distributed in the cerebral cortex will be seen. A careful clinical diagnosis of Alzheimer's disease conforms to the pathological diagnosis 70%–90% of the time (2006).

National Human Genome Research Institute (NHGRI): A multidisciplinary National Study Group, supported by the NHGRI of the National Institutes of Health (NIH), convened to review emerging information on AD genetic testing and presented their findings in 1997. Their statement concluded that: (1) except for autosomal dominant EOFAD families, genetic testing in asymptomatic individuals is unwarranted; (2) use of APOE genetic testing as a diagnostic adjunct in patients already presenting with dementia may prove useful but remains under investigation; and (3) the premature introduction of genetic testing and possible adverse consequences are to be avoided (Post, et al., 1997).

National Institute on Aging (NIA)/Alzheimer's Association: In 1996, the NIA/Alzheimer's Association Working Group issued a consensus statement on APOE testing, which concluded the following (Relkin et al., 1996):

- APOE testing should not be used as the sole diagnostic test for AD, since genotyping cannot provide certainty about the presence or absence of AD.
- APOE testing may have a role as an adjunct to other diagnostic tests in persons with dementia, since patients with AD are more likely to have an APOE epsilon-4 allele than are patients with other forms of dementia or individuals without dementia.
- The use of APOE genotyping to predict future risk of AD in asymptomatic individuals is not recommended at this time.
- Physicians and patients should be aware that genotype disclosure can have adverse effects on insurability, employability, and the psychosocial status of patients and family members.
- Clinical and research applications of APOE genotyping must include adequate pretest and post-test counseling, education, and psychosocial support.
- The consensus statement leaves to the physician's discretion the diagnostic use of APOE genotype testing as an adjunct to established diagnostic tests (Relkin et al., 1996).

National Institute on Aging and the Alzheimer's Association (NIA/AA): In 1998, the NIA/AA Working Group on Molecular and Biochemical Markers of AD issued a consensus report. The report concluded that: (1) for suspected EOFAD, it is appropriate to search for mutations in the PS-1, PS-2, and APP genes; (2) in late-onset and sporadic AD, these measures are not useful, but detecting an APOE epsilon-4 allele can add confidence to the clinical diagnosis when the test is used as an adjunct test in the diagnostic workup; and (3) among the other proposed molecular and biochemical markers for sporadic AD, cerebrospinal fluid (CSF) assays showing low levels of A β ₄₂ and high levels of microtubule-associated protein as combined indices come closest to fulfilling criteria for a useful biomarker.

Canadian Medical Association: Recommendations for risk assessment and prevention of Alzheimer's disease, based on the Third Canadian Consensus Conference on the Diagnosis and Treatment of Dementia held in March 2006, were reported by Patterson and colleagues (2008). The recommendations for genetic risk factors included:

- Predictive genetic testing may be offered to the following at-risk individuals with an apparent autosomal dominant inheritance when a family specific mutation has been identified:
 - first-degree relatives (e.g., children and siblings) of an affected person with the mutation
 - first cousins of an affected person if the common ancestors (parents who were siblings) died before the average age of onset of dementia in the family
 - nieces and nephews of an affected person whose parent (sibling of the affected person) died before the average age of onset of dementia in the family
 - minors are not usually referred for predictive genetic testing
- Genetic screening for the APOE genotype in asymptomatic individuals in the general population is not recommended because of low sensitivity and specificity (Patterson, 2008).

Summary

There is insufficient evidence in the published, peer-reviewed scientific literature to demonstrate the clinical utility of genetic testing including APP, PSEN1, PSEN2, or apolipoprotein-E (APOE) genotyping to diagnose or

manage AD in at risk patients or as a screening tool in the general population. The role of genetic testing in both early and late onset Alzheimer's disease has not yet been established.

Coding/Billing Information

Note: This list of codes may not be all-inclusive.

Experimental/Investigational/Unproven/Not Covered:

| CPT ^{®*} Codes | Description |
|----------------------------|---|
| 83891 [†] | Molecular diagnostics; molecular isolation or extraction; isolation or extraction of highly purified nucleic acid |
| 83892 [†] | Molecular diagnostics; enzymatic digestion, each enzyme treatment |
| 83894 [†] | Molecular diagnostics; separation by gel electrophoresis (eg, agarose, polyacrylamide), each nucleic acid preparation |
| 83898 [†] | Molecular diagnostics; amplification, target, each nucleic acid sequence |
| 83902 [†] | Molecular diagnostics; reverse transcription |
| 83904 [†] | Molecular diagnostics; mutation identification by sequencing, single segment, each segment |
| | Multiple/varied |

[†]**Note:** Experimental, investigational, unproven and not covered when used to report genetic testing for the screening, diagnosis or management of Alzheimer's Disease.

| HCPCS Codes | Description |
|----------------|--|
| S3852 | DNA analysis for apoe epsilon 4 allele for susceptibility to Alzheimer's disease |
| S3855 | Genetic testing for detection of mutations in the presenilin -1 gene |

| ICD-9-CM Diagnosis Codes | Description |
|--------------------------------|---------------------|
| 331.0 | Alzheimer's disease |

*Current Procedural Terminology (CPT[®]) © 2010 American Medical Association: Chicago, IL.

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Policy History

| <u>Pre-Merger Organizations</u> | <u>Last Review Date</u> | <u>Policy Number</u> | <u>Title</u> |
|---------------------------------|-------------------------|----------------------|---|
| CIGNA HealthCare | 8/15/2008 | 0392 | Genetic Testing to Diagnose and Predict Susceptibility to Alzheimer's Disease |
| Great-West Healthcare | 2/20/2007 | 05.272.02 | Genetic Testing for Susceptibility to Alzheimer Disease |

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