Cigna Medical Coverage Policy

Subject **Genetic Testing for Alzheimer's Disease**

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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. About 25% of all AD is familial (i.e., ≥2 persons in a family have AD) of which approximately 95% is late-onset, age >60-65 years, and 5% is early-onset, age <65 years (Bird, 2013). 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).

Genetic testing has been proposed as a means to diagnose or predict susceptibility to early- and late-onset AD; however, neuropathologic findings of beta-amyloid plaques and intraneuronal neurofibrillary tangles on autopsy examination remain the gold standard for diagnosis of AD (Bird, 2013). Clinical diagnosis prior to autopsy confirmation is made by use of diagnostic testing, including the Diagnostic and Statistical Manual of Mental Disorders, fourth edition. Previous recommendations by the National Institute of Neurological and Communicative Diseases and Stroke and the Alzheimer's Disease and Related Disorders Association ([NINCDS-ADRDA]) criteria were recently updated by McKhann et al. (2011), on behalf of the National Institute on Aging and the Alzheimer's Association. These criteria correctly diagnose the disease 80%-90% of the time. Treatment for AD is necessarily supportive with each symptom managed on an individual basis (Bird, 2013). 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). At this time there are no proven pharmacologic or lifestyle choices that can reduce the risk of developing AD or stop its progression (National Society of Genetic Counselors [NSGC]/American College of Medical Genetics [ACMG], 2010).

Early- Onset Familial Alzheimer's Disease (EOFAD): About 60% of early onset Alzheimer's disease (AD) is familial type with 13% appearing to be inherited in an autosomal dominant manner (Bird, 2012). EOFAD characterizes families in whom multiple cases of 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, generally age 40-50 (Bird, 2013). However, the distinction between EOFAD and LOFAD is somewhat arbitrary. Early-onset cases can occur in families with generally late-onset disease (Bird, 2013). The dementia phenotype is similar to that of late-onset AD (Bird, 2013). EOFAD cannot be clinically distinguished from other types of AD except on the basis of family history and age of onset. Treatment is the same regardless of the type of AD.

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); type 3 (AD3) (i.e., PSEN1 gene which encodes the protein presenilin-1; 30%–70% of EOFAD), and type 4 (AD4) (i.e., PSEN2 gene which encodes the protein presenilin-2; <5% of EOFAD) (Bird, 2012). The presence of APP has been associated with an estimated sensitivity of 88.6% for patients with mild AD and 85.7% for patients with very mild AD, with a specificity of 88% for controls (Padovani, 2002). Data are limited regarding sensitivity, specificity, and PPV of genetic testing for PSEN1 and PSEN2. 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, 2013; Cruts, 1998).

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, genetic testing is not helpful in predicting age of onset, severity, type of symptoms, or rate of progression in asymptomatic individuals. At this time genotyping for PSEN1, PSEN2, and APP mutations does not reduce the risk of developing Alzheimer's disease, change the clinical treatment, or substantially modify disease progression in individuals with EOFAD.

Summary for Early-Onset Familial Alzheimer's Disease: There is insufficient evidence to demonstrate the clinical utility of genetic testing to diagnose or manage EOFAD in at-risk individuals or as a screening tool in the general population. The role of genetic testing for this indication has not yet been established.

Late Onset Alzheimer's Disease (LOAD): LOAD is a slowly progressive dementia associated with diffuse cerebral atrophy on neuroimaging studies and is the most common form of AD. Clinical investigations have supported the concept that LOAD is a complex disorder that may involve multiple susceptibility genes (Bird, 2013; Kamboh, 2004; Bertram, 2004). As with EOFAD, establishing the diagnosis of LOAD relies on clinical neuropathological assessment. The gold standard for diagnosis of this condition remains neuropathology found on autopsy.

The role of apolipoprotein-E epsilon (APOE epsilon) in LOAD is a topic of research interest. At least three different alleles of APOE epsilon have been identified: APOE epsilon-2 (APOE e2), APOE epsilon-3 (APOE e3) and APOE epsilon-4 (APOE e4). APOE is a susceptibility polymorphism; the presence of one or two e4 alleles increases the risk but does not guarantee that someone will develop AD (Bird, 2013). A large proportion of individuals with epsilon-4 alleles who are demented have been found to have neuropathologic confirmation of AD at autopsy (Relkin, 1996; Mayeux, 1998).

Genetic Testing for Late-Onset Alzheimer's Disease: Genotyping for the APOE e4 mutation is clinically available and results in specificity estimates ranging from 75% to 81% (Bird, 2012; 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 Alzheimer's disease (AD) do not have an apolipoprotein-E (APOE) epsilon-4 allele. The absence of this allele does not rule out the diagnosis of Alzheimer's disease, however (Mayeux, 1998). The influence of the APOE genotype on AD risk may be also modulated by cholesterol level, alpha-1 -antichymotrypsin genotype, and very low-density lipoprotein receptor gene (ACMG, 1995). According to Bird (2012a) "The association of the APOE e4 allele with AD is significant; however, APOE genotyping is neither fully specific nor sensitive. While APOE genotyping may have an adjunct role in the diagnosis of AD in

symptomatic individuals, it appears to have little role at this time in predictive testing of asymptomatic individuals."

Additional genes and loci under investigation include SORL-1, A2M, GST01 and GST02, GAB2, CALHM1,TOMM40, Clusterin, CR1, and PICALM (Bird, 2013; Blacker, 2002). At this time genotyping for LOFAD mutations does not reduce the risk of developing Alzheimer's disease, change the clinical treatment, or substantially modify disease progression in individuals with LOFAD.

Literature Review
The Agency for Healthcare Research and Quality ([AHRQ], 2010) identified 15 cohort studies involving 8509 subjects that examined the association between APOE and the risk of cognitive decline. Various studies reported that APOE epsilon-4 (e4) was associated with greater decline on some, but not all, cognitive measures. Presence of an APOEe4 allele was not, however, significantly different in those who maintained cognitive performance compared to those with minor declines.

Tsuang et al. (1999) prospectively evaluated APOE testing for 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 94%. In those patients with a clinical diagnosis of non-Alzheimer's dementia the absence of an APOE e4 allele increased the negative predictive value from 64% to 72% (Waldemar, 2007).

Summary for Late Onset Alzheimer's Disease (LOAD): The presence of an APOE e4 allele or alleles is neither necessary nor sufficient to establish a diagnosis. As such, the clinical utility of genetic testing for LOAD 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, nor would it change treatment, as treatment is supportive. 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, 2012). Estimates of risk are not generally considered clinically useful. The usefulness of APOE genotyping in clinical diagnosis and risk assessment remains unclear (Bird, 2013).

Non-Familial Alzheimer's Disease (AD): Non-familial AD is considered to be sporadic; individuals with non-familial AD meet the diagnostic criteria for AD but have a negative family history. Onset can be anytime in adulthood. Although cause is unknown it is thought that non-familial AD is multifactoral and results from a combination of aging, genetic disposition and environmental factors (Bird, 2012). The gold standard for the diagnosis of non-familial AD remains neuropathological assessment on autopsy. At this time no therapeutic intervention has been identified that can cure the disease or modify progression.

Genetic Testing for Non-Familial AD: According to Bird (2013), "Genetic counseling for people with non-familial AD and their family members must be empiric and relatively nonspecific. AD is common and the overall lifetime risk to any individual of developing dementia is approximately 10%-12%."

Summary for Non-Familial AD: There is insufficient evidence regarding the clinical utility of genetic testing for non-familial AD. The role of genetic testing for this indication has not yet been established.

Professional Societies/Organizations
Alzheimer's Association: The Alzheimer's Association notes "Genetic tests are available for both apolipoprotein-E (APOE e4) and the rare genes that directly cause Alzheimer's. However, health professionals do not currently recommend routine genetic testing for Alzheimer's disease. Testing for APOE e4 is sometimes included as a part of research studies."

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 Psychiatric Association: Practice Guidelines for the treatment of patients with Alzheimer's disease and other dementias note that a definitive diagnosis of AD 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 disease conforms to the pathological diagnosis 70%–90% of the time (2006).

National Institute on Aging (NIA, 2011): In a fact sheet published by the NIA, the following was noted, "Although a blood test can identify which APOE alleles a person has, it cannot predict who will or will not develop Alzheimer's disease. It is unlikely that genetic testing will ever be able to predict the disease with 100% accuracy because too many other factors may influence its development and progression. At present, APOE testing is used in research settings to identify study participants who may have an increased risk of developing Alzheimer's."

National Institute on Aging (NIH)/Alzheimer's Association ([AA]; 2011): The NIA/AA issued consensus recommendations regarding the diagnosis of Alzheimer's disease (AD) which noted for probable AD dementia in a carrier of a causative genetic mutation, "In persons who meet the core clinical criteria for probable AD dementia, evidence of a causative genetic mutation (in APP, PSEN1, or PSEN2), increases the certainty that the condition is caused by AD pathology." The workgroup also noted that carriage of the 3/4 allele of the apolipoprotein E gene was not sufficiently specific to be considered in this category.

National Society of Genetic Counselors (NSGC)/American College of Medical Genetics (ACMG): On behalf of the NSGC/ASGC, Goldman et al. (2011) published consensus practice guidelines for genetic counseling and testing for AD. The Guidelines recommend "Pediatric testing for AD should not occur and that direct-to-consumer APOE testing is not advised."

The Guidelines note "A risk assessment should be performed by pedigree analysis to determine whether the family history is consistent with early-onset Alzheimer's disease (EOAD) or late-onset Alzheimer's disease (LOAD) and with autosomal dominant (with or without complete penetrance), familial, or sporadic inheritance. Patients should be informed that currently there are no proven pharmacologic or lifestyle choices that reduce the risk of developing AD or stop its progression." The Guidelines also note:

For families in which an autosomal dominant AD gene mutation is a possibility:

- Testing for genes associated with early- onset autosomal dominant AD should be offered in the following situations:
    - A symptomatic individual with EOAD in the setting of a family history of dementia or in the setting of an unknown family history (e.g., adoption).
    - Autosomal dominant family history of dementia with one or more cases of EOAD.
    - A relative with a mutation consistent with EOAD (currently PSEN1/2 or APP).
    - Ideally, an affected family member should be tested first. If no affected family member is available for testing and an asymptomatic individual remains interested in testing despite counseling about the low likelihood of an informative result (a positive result for a pathogenic mutation), he/she should be counseled according to the recommended protocol. If the affected relative, or their next of kin, is uninterested in pursuing tested, the option of DNA banking should be discussed.

For families in which autosomal dominant AD is unlikely:

- Genetic testing for susceptibility loci (e.g., apolipoprotein-E [APOE]) is not clinically recommended due to limited clinical utility and poor predictive value."

Use Outside of the US

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.

European Federation of Neurological Societies (EFNS): On behalf of the EFNS Hort et al. (2007) published guidelines for the diagnosis and management of Alzheimer's disease. The Guideline notes "Screening for known pathogenic mutations can be undertaken in patients with appropriate phenotype or a family history of an autosomal dominant dementia. Routine apolipoprotein E (Apo E) genotyping is not recommended."

Summary
Neuropathological testing remains the gold standard for diagnosis of Alzheimer disease Genetic testing has been proposed for the diagnosis and management of early- and late-onset familial Alzheimer's disease (EOFAD; LOFAD) and as a means to predict susceptibility to the disease. Published, peer-reviewed data are primarily limited to association studies. While genetic testing for a number of genes thought to be associated with Alzheimer disease is available, knowledge of the mutations does not reduce the risk of developing EOFAD, change the clinical treatment, or modify disease progression. At present there is insufficient evidence to support the clinical utility of genetic testing for APP, PSEN1, PSEN2 or any gene for individuals with EOFAD.

Likewise, genotyping for apolipoprotein-E (APOE) is clinically available; however the presence of APO-E is not fully specific or sensitive to diagnose or predict susceptibility to LOFAD. Further, knowledge of the mutation does not change the clinical treatment or modify disease progression in individuals with LOFAD. There is insufficient evidence to support the clinical utility of genetic testing for LOFAD, including for APO-E mutation.

Additionally, data are lacking to support genetic testing for Alzheimer's disease in the general population, including testing for APP, PSEN1, PSEN2, and APO-E. At present, the role of genetic testing for AD has not been established.

Coding/Billing Information

Note: 1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Experimental/Investigational/Unproven/Not Covered when used to report genetic testing for the screening, diagnosis or management of Alzheimer's Disease:

CPT®* Codes	**Description**
81401	Molecular pathology procedure, Level 2 (eg, 2-10 SNPs, 1 methylated variant, or 1 somatic variant [typically using nonsequencing target variant analysis], or detection of a dynamic mutation disorder/triplet repeat) • APOE (apolipoprotein E) (eg, hyperlipoproteinemia type III, cardiovascular disease, Alzheimer disease), common variants (eg, *2, *3, *4)

81405	Molecular pathology procedure, level 6 (eg, analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons) • PSEN1 (presenilin 1) (eg, Alzheimer disease), full gene sequence
81406	Molecular pathology procedure, level 7 (eg, analysis of 11-25 exons by DNA sequence anylysis, mutation scanning or duplication/deletion variants of 26-50 exons, cytogenomic array analysis for neoplasia) • APP (amyloid beta [A4] precursor protein) (eg, Alzheimer disease), full gene sequence • PSEN2 (presenilin 2 [Alzheimer disease 4]) (eg, Alzheimer disease), full gene sequence
83890	Molecular diagnosticsmolecular isolation or extraction. Each nucleic acid type (i.e., DNA or RNA) (Code deleted 12/31/2012)
83891	Molecular diagnostics; molecular isolation or extraction; isolation or extraction of highly purified nucleic acid (Code deleted 12/31/2012)
83892	Molecular diagnostics; enzymatic digestion, each enzyme treatment (Code deleted 12/31/2012)
83893	Molecular diagnostics;dot/slot blot production; each nucleic acid preparation (Code deleted 12/31/2012)
83894	Molecular diagnostics; separation by gel electrophoresis (eg, agarose, polycrylamide), each nucleic acid preparation (Code deleted 12/31/2012)
83896	Molecular diagnostics; nucleic acid probe, each (Code deleted 12/31/2012)
	Molecular diagnostics; nucleic acid transfer (e.g., Southern, Northern), each nucleic acid preparation (Code deleted 12/31/2012)
83898	Molecular diagnostics; amplification, target, each nucleic acid sequence (Code deleted 12/31/2012)
83900	Molecular diagnostics; amplification, target, multiplex, first 2 nucleic acid sequences (Code deleted 12/31/2012)
83901	Molecular diagnostics; amplification, target, multiplex, each additional nucleic acid sequence beyond 2 (List separately in addition to code for primary procedure) (Code deleted 12/31/2012)
83902	Molecular diagnostics; reverse transcription (Code deleted 12/31/2012)
83903	Molecular diagnostic; mutation scanning, by physical properties (eg single strand conformational polymorphisms [SSCP], heteroduplex, denaturing gradient gel electrophoresis[DGGE], RNA'ase A), single segment, each (Code deleted 12/31/2012)
83904	Molecular diagnostics; mutation identification by sequencing, single segment, each segment (Code deleted 12/31/2012)
83905	Molecular diagnostics; mutation identification by allele specific transcription, single segment, each segment (Code deleted 12/31/2012)
83906	Molecular diagnostics; mutation identification by allele specific translation, single segment, each segment (Code deleted 12/31/2012)
83907	Molecular diagnostics; lysis of cells prior to nucleic acid extraction (eg, stool specimens, paraffin embedded tissue), each specimen (Code deleted 12/31/2012)
83908	Molecular diagnostics; amplification, signal, each nucleic acid sequence (Code deleted 12/31/2012)
83909	Molecular diagnostics; separation and identification by high resolution technique (eg, capillary electrophoresis), each nucleic acid preparation (Code deleted 12/31/2012)
83912	Molecular diagnostics; interpretation and report (Code deleted 2/31/2012)
83913	Molecular diagnostics; RNA stabilization (Code deleted 12/31/2012)
83914	Mutation identification by enzymatic ligation or primer extension, single segment, each segment (oligonucleotide ligation assay [OLA], single base chain extension [SBCE], or allele-specific primer extension [ASPE] (Code deleted 12/31/2012)

88384	Array-based evaluation of multiple molecular probes; 11 through 50 probes (Code deleted 12/31/2012)
88385	Array-based evaluation of multiple molecular probes; 51 through 250 (Code deleted 12/31/2012)
88386	Array-based evaluation of multiple molecular probes; 251 through 500 (Code deleted 12/31/2012)

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

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