Clinical Policy Title: Genetic testing for Alzheimer’s disease

Clinical Policy Number: 02.01.20

Effective Date: July 1, 2016
Initial Review Date: May 18, 2016
Most Recent Review Date: May 18, 2016
Next Review Date: May 2017

Policy contains:
- Genetic testing.
- Mutation.
- Alzheimer’s disease.

Related policies:

CP# 02.01.09 Genetic testing, rare diseases
CP# 17.02.00 Genomic tests in neurology

ABOUT THIS POLICY: Prestige Health Choice has developed clinical policies to assist with making coverage determinations. Prestige Health Choice’s clinical policies are based on guidelines from established industry sources, such as the Centers for Medicare & Medicaid Services (CMS), state regulatory agencies, the American Medical Association (AMA), medical specialty professional societies, and peer-reviewed professional literature. These clinical policies along with other sources, such as plan benefits and state and federal laws and regulatory requirements, including any state- or plan-specific definition of “medically necessary,” and the specific facts of the particular situation are considered by Prestige Health Choice when making coverage determinations. In the event of conflict between this clinical policy and plan benefits and/or state or federal laws and/or regulatory requirements, the plan benefits and/or state and federal laws and/or regulatory requirements shall control. Prestige Health Choice’s clinical policies are for informational purposes only and not intended as medical advice or to direct treatment. Physicians and other health care providers are solely responsible for the treatment decisions for their patients. Prestige Health Choice’s clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, Prestige Health Choice will update its clinical policies as necessary. Prestige Health Choice’s clinical policies are not guarantees of payment.

Coverage policy

Prestige Health Choice considers the use of genetic testing for Alzheimer’s disease (AD) to be investigational, and therefore, not medically necessary.

Limitations:

Coverage determinations are subject to benefit limitations and exclusions as delineated by the state Medicaid authority. The Florida Medicaid website can be accessed at http://ahca.myflorida.com/Medicaid/.

Alternative covered services:
A primary care physician or a neurologic, medical geneticist or other qualified specialist may evaluate a patient for AD with alternative covered services, including routine office consultation and clinical investigation (i.e., laboratory, imaging, functional testing and diagnostic procedures, specifically brain biopsy.

**Background**

The merits of genetic testing for AD are several, but its primary purpose is to provide clinicians with a framework for assessing their patients' genetic risk for purposes of early diagnosis, prevention and amelioration of progression, and counseling of the patient’s family and caretaker regarding their personal risk and challenges in caring for someone with AD.

The lifetime risk of AD in the general population is approximately 10 % to 12 % in a 75- to 80-year lifespan. AD is the most common dementia in the United States and up to 80 % is believed to have some genetic etiology. However, only 1 % to 5 % of the disease follows an autosomal dominant inheritance pattern. The presenilin 1 and 2 (PSEN1, PSEN2) and the amyloid-β precursor protein (APP) genes account for about 80 % of these cases of early-onset familial AD (EOFAD). Although most autosomal dominant cases have onset under the age of 65, late-onset cases are also found in these families.

Mutations in PSEN1 on chromosome 14 account for at least 50 % of EOFAD. Mutations in APP on chromosome 21 account for another 10 % to 15 %, and mutations in PSEN2 on chromosome 1 are very rare except in families of Volga German origin. In addition to single-base changes, duplications in APP and a deletion in PSEN 2 have been reported. Inter- and intra-familial phenotypic variations are common for all these genes, including age of onset (29–88 years) and symptomatology. Seizures are more common in these autosomal dominant cases and disease duration is usually shorter. All three genes are highly penetrant, although several carriers of PSEN2 mutations have lived into their 80s without symptoms and died of other causes.

In addition to mutations in these three genes, mutations in genes responsible for autosomal dominant frontotemporal degeneration (MAPT, PGRN, C2orf72) and familial prion disease (PRNP) have been found in families that were clinically diagnosed with AD. When genetic testing of the autosomal dominant AD genes does not reveal a mutation, testing for MAPT, PGRN, C9orf72 and PRNP should be considered.

A much larger %age of AD is due to risk factor or susceptibility genes. The apolipoprotein E gene (APOE) is associated with the greatest risk of developing the disease, accounting for 20 % to 29 % of late-onset AD risk. APOE has three different allelic forms, e2, e3, and e4, which lead to six possible genotypes, APOE 2ε / e2, ε2/ ε3, ε2/ ε4, ε3/ ε3, ε3/ ε4, ε4/ ε4. Individuals with the APOE 3/4 genotype have approximately a two- to three-fold lifetime risk of developing AD over the background risk which is about 10.4 %, whereas those with APOE ε4/ ε4 have up to a 15-fold risk. Risk is higher in women than in men. Research indicates that APOE 4 lowers the age of onset and increases the rate of decline.
Approximately 41% of individuals with AD have an APOE 3/4 as compared to about 21% of normal controls, and about 13% of AD cases have APOE 4/4 compared to less than 1% of normal controls. Additionally, up to 50% of people with a single APOE ε4 never develop AD. Thus, although APOE ε4 increases the risk of AD, it is neither sufficient nor necessary for developing AD. Many guidelines have been written concerning the use of APOE genetic testing. None of these encourage APOE genetic testing for either diagnostic or predictive testing. Importantly, with or without knowing APOE status, having a parent with AD confers a lifetime risk of about 2.5 times that of not having a parent with the disease. Having more relatives with AD may further increase the risk.

Finally, APP-β interacts with reelin, a protein implicated in a number of brain disorders, including AD.

A key component of testing for AD centers on identifying which individuals may benefit from genetic testing, as well as the ethical requirement to provide the key elements of genetic counseling for AD as an integral part of the testing protocol. Genetic testing for AD may also offer a cost-effective way to identify and track change in individuals at high risk for progressing to mild cognitive impairment (MCI) and dementia stages of AD and facilitate future prevention of the disease.

**Searches**

Prestige Health Choice searched PubMed and the databases of:

- UK National Health Services Center for Reviews and Dissemination.
- Agency for Healthcare Research and Quality’s National Guideline Clearinghouse and other evidence-based practice centers.
- The Centers for Medicare & Medicaid Services (CMS).

We conducted searches on April 5, 2016. Search terms were: "gene expression (MeSH)," "Alzheimer’s disease (MeSH)" and "genetic testing for Alzheimer’s disease."

We included:

- **Systematic reviews**, which pool results from multiple studies to achieve larger sample sizes and greater precision of effect estimation than in smaller primary studies. Systematic reviews use predetermined transparent methods to minimize bias, effectively treating the review as a scientific endeavor, and are thus rated highest in evidence-grading hierarchies.
- **Guidelines based on systematic reviews.**
- **Economic analyses**, such as cost-effectiveness, and benefit or utility studies (but not simple cost studies), reporting both costs and outcomes — sometimes referred to as efficiency studies — which also rank near the top of evidence hierarchies.

**Findings**

There is a dearth of medical evidence available at the present time regarding genetic testing for Alzheimer’s disease.
Practice guidelines (2011) of the American College of Medical Genetics (ACMC) and the National Society of Genetic Counselors (NSGC) outline a number of interventions and practices appropriate for identifying individuals who may benefit from genetic counseling and testing for AD.

Among the interventions and practices cited by the group are:

- Family history.
- Risk assessment by pedigree analysis.
- Obtaining informed consent for genetic testing.
- Pediatric testing for AD.
- Neurological examination.
- Psychological assessment and referral.
- Genetic testing for AD in adults.
- Testing for susceptibility loci (APOE).
- Direct-to-consumer genetic testing.
- Genetic testing for PSEN1, PSEN2, APP and other known familial mutations.
- Deoxyribonucleic acid (DNA) banking.
- Post-test results counseling and follow-up.

Among the recommendations made by the group are:

- Pediatric testing for AD should not occur.
- Prenatal testing for AD is not advised if the patient intends to continue a pregnancy with a mutation.
- Genetic testing for AD should only occur in the context of genetic counseling (in-person or through video conference) and support by someone with expertise in this area.
- Genetic counseling for symptomatic patients should be performed in the presence of the individual's legal guardian or family member.

Revised diagnostic guidelines for AD from the National Institute on Aging (NIA) and the Alzheimer's Association (AA) (McKahn 2011) do not advocate for the routine diagnostic use of biomarkers for AD, calling for more research on the matter. The authors do go on to add, though, that "the use of biomarkers to enhance certainty of AD pathophysiological process may be useful in three circumstances: 1) investigational studies, 2) clinical trials and 3) as optional clinical tools for use where available and when deemed appropriate by the clinician."

A protocol for asymptomatic screening for AD is based on the recommendations of the International Huntington Association (IHA) and World Federation of Neurology (WFN) Research Group on Huntington's chorea. Their guidelines recommend that a ≥3-generation family history should be obtained in patients screened for AD, with specific attention to the age of onset of any neurologic and/or psychiatric symptoms, type of dementia (if present) and method of diagnosis, current ages or ages at death (especially unaffected relatives), and causes of death. A risk assessment should be
performed by pedigree analysis to determine whether the family history is consistent with early onset AD (EOAD) or late onset AD (LOAD) and with autosomal dominant (with or without complete penetrance), familial or sporadic inheritance.

In the event genetic testing is chosen, the following is recommended:

- Through neurologic examination, assess for signs of dementia in asymptomatic patients and establish a baseline.
- Assess the patient's and any accompanying family member's psychological state of mind. In the case of asymptomatic testing, a consultation with a psychologist/psychiatrist may be recommended for the patient.
- If the patient seems to suffer from, or is potentially at risk for, significant psychological/psychiatric problems, consider a psychotherapy referral before testing.
- If the psychological assessment suggests testing is not in the person's current best interest (e.g., untreated depression or recent death), share these reservations openly, and agree to revisit testing once the underlying condition and/or stressors have diminished. A referral for psychotherapy may also be appropriate.

A narrative review (Goldman 2012) opined that epigenetic and environmental factors are yet to be revealed that may play a role, along with genetic make-up, in risk and progression to AD and other neurodegenerative disease (including frontotemporal depression [FTD]). The authors noted that genetic testing of the AD autosomal dominant genes can predict whether one will develop AD or FTD, but not when or how symptoms will present. The authors conclude that as technologies change, genetic testing will become more accessible but harder to interpret. Thus, genetic counseling, which is essential, now before and after testing, will become even more essential in the future.

A systematic review (SR) of 2,186 confirmed AD cases and 2,507 healthy controls examined the genomic association of PSEN2 polymorphisms, rs8383 and 5’indel, with the risk of sporadic AD (Chen 2012). The analysis suggested a significant association between single nucleotide polymorphism (SNP) rs8383 and AD risk with no evidence of between-study heterogeneity or publication bias. The authors did not find any evidence supporting the association between the 5’indel SNP and the risk of AD. The stratified analyses of apolipoprotein ε4 status or ethnicity also failed to reveal a statistically significant association between the 5’indel SNP of PSEN2 and AD risk. The authors concluded that PSEN2 rs8383 SNP is associated with an increased risk of sporadic AD. The authors also acknowledged that larger-scale studies are needed to confirm these findings and to define potential gene-gene interactions.

**Personal impact of testing for AD**

A small study (Hooper 2013) on the impact on patients undergoing genetic testing cited 34 preclinical Latinos (n = 26) and non-Latinos (n=8) unaware of their genetic status and considered at-risk for familial Alzheimer’s disease (FAD), who were administered a questionnaire exploring their interest in undergoing revealing genetic testing at baseline and in the context of eligibility for four prevention trials.
of increasing invasiveness. Forty-four % of subjects expressed a baseline interest in undergoing revealing testing, which increased to 85 % in order to be eligible for a study of an oral drug “felt to be very safe.” If there were a 50 % chance of receiving placebo, this number dropped to 62 % (p = 0.02). For those not interested in a study involving a 50 % chance of receiving placebo, a range of 5 % to 40 % chance of receiving placebo was given as acceptable. For more invasive studies, living in the United States (as opposed to Mexico) positively influenced the likelihood of participating. The authors conclude that there is data to suggest that clinical trial designs in which persons must confront their genetic status prior to enrollment are feasible. They also believe study designs to minimize the likelihood of being placed on placebo or provide the eventual administration of the drug through open-label extensions should be considered.

A narrative review (Paulsen 2013) summarized 41 studies examining health-related outcomes following predictive genetic testing for neurodegenerative disease. The authors concluded that 1) extreme or catastrophic outcomes are rare; 2) consequences commonly include transiently increased anxiety and/or depression; 3) most participants report no regret; 4) many persons report extensive benefits to receiving genetic information; and 5) stigmatization and discrimination for genetic diseases are poorly understood and policy and laws need review in this regard. The authors conclude that caution is appropriate for earlier identification of neurodegenerative diseases but findings suggest further progress is safe, feasible and likely to advance clinical care.

Policy updates:

None.

Summary of clinical evidence:

<table>
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<tr>
<th>Citation</th>
<th>Content, Methods, Recommendations</th>
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<tbody>
<tr>
<td>Goldman (2011)</td>
<td>Genetic counseling and testing for Alzheimer disease: joint practice guidelines of the ACMC and NSGC</td>
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</table>

Key points:

- Practice guidelines identify a number of interventions and practices appropriate for screening for AD:
  - Family history.
  - Risk assessment by pedigree analysis.
  - Obtaining informed consent for genetic testing.
  - Pediatric testing for AD.
  - Neurological examination.
  - Psychological assessment and referral.
  - Genetic testing for AD in adults.
  - Testing for susceptibility loci (APOE).
  - Direct-to-consumer genetic testing.
  - Genetic testing for PSEN1, PSEN2, APP and other known familial mutations.
  - DNA banking.
  - Post-test results counseling and follow-up.
- Practice recommendations include and exclude the following:
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Key points:  
- Guidelines for AD do not advocate for the routine diagnostic use of biomarkers for AD, calling for more research on the matter.  
- However, the guidelines go on to say, "the use of biomarkers to enhance certainty of AD pathophysiological process may be useful in three circumstances: 1) investigational studies, 2) clinical trials and 3) as optional clinical tools for use where available and when deemed appropriate by the clinician." |
| IHA/WFN Research Group on Huntington’s Chorea (1994) | Guidelines for the molecular genetics predictive test in Huntington’s disease  

Key points:  
- IHA/WFN guideline recommendations:  
  - ≥3-generation family history with specific attention to:  
    - Age of onset of any neurologic and/or psychiatric symptoms,  
    - Type of dementia (if present) and method of diagnosis,  
    - Current ages, or ages at death (especially unaffected relatives), and  
    - Causes of death.  
- A risk assessment should be performed looking for:  
  - EOAD.  
  - LOAD.  
- Asymptomatic patients should receive a neurologic examination to assess for signs of dementia and to establish a baseline.  
- Assessment of patient's and any accompanying family member's psychological state of mind.  
- If the patient seems to suffer from, or is potentially at risk for, significant psychological/psychiatric problems, consider a psychotherapy referral before testing. |
| Goldman (2012)                   | New Approaches to Genetic Counseling and Testing for Alzheimer’s Disease and Frontotemporal Degeneration  

Key points:  
- A narrative review concluded that risk and progression to AD and other neurodegenerative disease (e.g., FTD) is multifactorial.  
- The authors noted that genetic testing of the AD autosomal dominant genes can predict whether one will develop AD or FTD, but not when or how symptoms will present. |
### Citation, Methods, Recommendations

<table>
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<tr>
<td>Chen (2012)</td>
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<td>Presenilin-2 polymorphisms and risk of sporadic AD: evidence from a meta-analysis</td>
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<td></td>
<td>• SR with meta-analysis to evaluate the association of the two most extensively studied PSEN2 polymorphisms, rs8383 and 5'indel, with the risk of sporadic AD.</td>
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<td>• Included 2,186 confirmed AD cases and 2,507 healthy controls in total.</td>
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<td>• Established an association between SNP rs8383 and AD.</td>
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### Personal impact of testing for AD

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<td>Hooper (2013)</td>
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<td>The Impact of the Availability of Prevention Studies on the Desire to Undergo Predictive Testing in Persons at-risk for Autosomal Dominant Alzheimer’s Disease</td>
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<td>• Thirty-four preclinical Latinos (n = 26) and non-Latinos at-risk for FAD were administered a questionnaire exploring their interest in undergoing revealing genetic testing:</td>
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<td>– 44% expressed a baseline interest in undergoing revealing testing which increased to 85% in order to be eligible for a study of an oral drug “felt to be very safe.”</td>
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<td>– If there were a 50% chance of receiving placebo, this number dropped to 62% (p = 0.02).</td>
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<td>– Stigmatization and discrimination for genetic diseases are poorly understood and policy and laws are needed.</td>
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### Glossary
Alzheimer’s disease (AD) — AD is the most common dementia in the United States. It is associated with advancing age and is characterized by profound memory loss and neurologic dysfunction. It is thought to be heritably acquired, and genetic testing has been proposed as a useful means of early detection and monitoring of individuals at risk for progression of preclinical AD to frank neurocognitive disability.

Genetic testing (also known as gene expression assay and gene expression profiling) — A type of test that is used to determine the presence or absence of a specific gene or set of genes to help diagnose a disease, screen for specific health conditions, and for other purposes.

Mutation — A change in DNA sequence that may occur spontaneously or as a result of carcinogens and co-factors introduced to human cells. These mutations may in some cases be hereditary and affect multiple members of a family.

References

Professional society guidelines/other:


Peer-reviewed references:


**Clinical trials:**

Searched clinicaltrials.gov on April 5, 2016, using terms “genetic testing for Alzheimer’s disease” | Open Studies. 10 studies found, 1 relevant.


**CMS National Coverage Determination (NCDs):**

No NCDs identified as of the writing of this policy.

**Local Coverage Determinations (LCDs):**

No LCDs identified as of the writing of this policy.

**Commonly submitted codes**

Below are the most commonly submitted codes for the service(s)/item(s) subject to this policy. This is not an exhaustive list of codes. Providers are expected to consult the appropriate coding manuals and bill accordingly.
<table>
<thead>
<tr>
<th>CPT Code</th>
<th>Description</th>
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<tr>
<td>81401</td>
<td>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)</td>
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<tr>
<td>81405</td>
<td>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, regionally targeted cytogenomic array analysis)</td>
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<tr>
<td>81406</td>
<td>Molecular pathology procedure, Level 7 (eg, analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons, cytogenomic array analysis for neoplasia)</td>
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<tr>
<td>83520</td>
<td>Immunoassay for analyte other than infectious agent antibody or infectious agent antigen; quantitative, not otherwise specified</td>
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<th>ICD-10 Code</th>
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<tr>
<td>F03.90</td>
<td>Unspecified dementia without behavioral disturbance</td>
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<tr>
<td>F03.91</td>
<td>Unspecified dementia with behavioral disturbance</td>
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<tr>
<td>G30.0</td>
<td>Alzheimer's disease with early onset</td>
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<tr>
<td>G30.1</td>
<td>Alzheimer's disease with late onset</td>
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<tr>
<td>G30.8</td>
<td>Other Alzheimer's disease</td>
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<tr>
<td>G30.9</td>
<td>Alzheimer's disease, unspecified</td>
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<tr>
<td>G31.1</td>
<td>Senile degeneration of brain, not elsewhere classified</td>
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<td>R41.0</td>
<td>Disorientation, unspecified</td>
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<td>R41.3</td>
<td>Other amnesia</td>
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<td>R41.81</td>
<td>Age-related cognitive decline</td>
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<th>Description</th>
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<tr>
<td>S3852</td>
<td>DNA analysis for APOE epsilon 4 allele for susceptibility to Alzheimer's disease</td>
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