Genetic testing for Alzheimer's disease

Clinical Policy ID: CCP.1233

Recent review date: 2/2024

Next review date: 6/2025

Policy contains: Alzheimer's disease; apolipoprotein genetic testing; mutation.

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Coverage policy

Genetic testing for Alzheimer's disease is investigational/not clinically proven and, therefore, not medically necessary.

Limitations

No limitations were identified during the writing of this policy.

Alternative covered services

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

Background

Alzheimer's disease is the most common dementia in the United States (National Institute on Aging, 2019a). Most people with Alzheimer's disease have the late-onset form, in which symptoms become apparent in their mid-60s. Early-onset Alzheimer's disease is rare, representing less than 10% of all people with the disease. The inheritability is estimated between 60% and 80%, which provides an important opportunity to define newer biological and prognosticating factors related to this disease via genetic risk factors (Bellenguez, 2022).

Neuropathologic findings of beta-amyloid plaques and intraneuronal neurofibrillary tangles on autopsy examination remain the gold standard for definitive diagnosis of Alzheimer's disease (National Institute on Aging, 2019a). Medical history and clinical testing (diagnostic, cognitive, and laboratory) are used for a clinical diagnosis. A genetic characterization of Alzheimer's and other dementia types, helps to provide insight into the pathophysiological processes taking place before death (Bellenguez, 2022). Genetic testing has been proposed as a means to diagnose or predict susceptibility to early- and late-onset Alzheimer's disease. It may also offer a cost-effective way to identify and track change in individuals at high risk for progressing to mild cognitive impairment and dementia stages of Alzheimer's disease and to facilitate future prevention of the disease.

While the causes of Alzheimer's disease are not fully understood, researchers have identified genetic variants associated with increased risk of developing the disease (National Institute on Aging, 2019a). The three confirmed single-gene variants, which result in the production of abnormal proteins associated with early-onset disease, are (Goldman, 2011; National Institute on Aging, 2019b; Alzheimer Association, 2022):

- Amyloid precursor protein on chromosome 21.
- Presenilin 1 on chromosome 14.
- Presenilin 2 on chromosome 1.

According to Alzheimer's association (2022) genes with these specific abnormal changes termed mutations are considered to be deterministic . That means inheriting one of the genes would determine that an individual would develop Alzheimer's. In this situation symptoms tend to develop prior to age 65 and possibly as early as 30, while the majority of those to develop latent disease would begin at age 65 or older. For those rare families with a known genetic mutation for Alzheimers, genetic testing may be helpful to identify the carrier.

Another gene called the apolipoprotein E gene provides the basis of a protein that is a cholesterol transporter in the blood. This is inherited from both parents as apolipoprotein gene type e2, e3, or e4. The e3 version is most common and most inherit that one from both parents in about 60% of the population in the United States. A 20-30% of the population inherits one to two copies of the e4 form, and 10-20% inherit one or two copies of the e2 form. Having the e3 is believed to neither increase or decrease your chances of developing Alzheimer's. Having the e2 form is believed to decrease your chances and e4 to increase your risk of developing Alzheimers and at an earlier age. But unlike a deterministic gene, the e4 doesn't guarantee your development of the disease but is considered a risk gene for it (Alzheimer's Association, 2022).

An extra copy of chromosome 21 places persons with Down syndrome at higher risk for developing early-onset Alzheimer's disease (National Institute on Aging, 2019b).

Late-onset Alzheimer's disease arises from a complex series of brain changes from a combination of genetic, environmental, and lifestyle factors that occur over decades (National Institute on Aging, 2019b). A number of regions of interest in the genome may increase or decrease a person's risk for late-onset disease to varying degrees. The apolipoprotein E gene is a confirmed susceptibility gene associated with Alzheimer's disease. Of its three allelic forms — ε2, ε3, and ε4 — apolipoprotein E ε4 is associated with increased risk of developing late-onset disease. However, carrying the apolipoprotein E ε4 allele does not mean that a person will definitely develop the disease, and some without the allele may, in fact, develop the disease. Thus, presence of apolipoprotein E ε4 is neither sufficient nor necessary for developing Alzheimer's disease.

Findings

A key component of testing for Alzheimer's disease 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 Alzheimer's disease as an integral part of the testing protocol. However, there is a dearth of medical evidence available at the present time to support the clinical use of genetic testing for Alzheimer's disease.

Practice guidelines (Goldman, 2011) of the American College of Medical Genetics and the National Society of Genetic Counselors outline a number of potential interventions and practices appropriate for identifying individuals who may benefit from genetic counseling and testing for Alzheimer's disease, including:

- Family history.
- Risk assessment by pedigree analysis.
- Obtaining informed consent for genetic testing.
- Pediatric testing for Alzheimer's disease.
- Neurological examination.
- Psychological assessment and referral.
- Genetic testing for Alzheimer's disease in adults.
- Testing for susceptibility loci (apolipoprotein E).
- Direct-to-consumer genetic testing.
- Genetic testing for presenilin 1, presenilin 2, amyloid precursor protein, and other known familial mutations.
- Deoxyribonucleic acid banking.
- Post-test results counseling and follow-up.

Among the recommendations made by the group are:

- Pediatric testing for Alzheimer's disease should not occur.
- Prenatal testing for Alzheimer's disease is not advised if the patient intends to continue a pregnancy with a mutation.
- Genetic testing for Alzheimer's disease 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 Alzheimer's disease from the National Institute on Aging and the Alzheimer's Association (McKahnn, 2011) do not advocate for the routine diagnostic use of biomarkers for Alzheimer's disease, calling for more research on the matter. The authors do go on to add, though, that "the use of biomarkers to enhance certainty of Alzheimer's disease 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 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.

A two-stage genome-wide study using 111,326 clinically diagnosed Alzheimer's disease cases with a control group of 677,663. They found 42 new risk loci in the 75 seen at time of analysis and confirmed the involvement of the amyloid/tau pathways with microgaglia. The gene prioritization uncovered 31 genes, including the tumor necrosis factor alpha strongly suggestively associated with the processes (Bellenguez, 2022).

In 2017, we updated the policy references with no changes to the policy.

In 2018, we updated the policy references with no changes to the policy.

In 2019, we updated the policy references with no changes to the policy. The policy ID was changed from 02.01.20 to CCP.1233.

In 2020, we updated the policy references with no changes to the policy.

In 2021, we deleted four references and added six systematic reviews and meta-analyses to the policy (Andrews, 2020; Marshe, 2019; Piscopo, 2019; Swarbrick, 2019; Zeng, 2019; Zhu, 2019). These new recent research findings reflect the attempt to identify non-invasive biomarkers to improve diagnosis. The most prominently studied sampling methods are cerebrospinal fluid and peripheral blood, which have potential implications for population screening and disease monitoring. Knowledge of the influence of small non-coding micro-ribonucleic acid sequences and polymorphisms on Alzheimer's disease risk continues to expand, but further confirmation of their clinical significance is warranted.

In 2022, the Alzheimer's association does not recommend genetic testing for Alzheimer's disease in the general population.

In 2023, the Alzheimer's association's position remains the same, viewing genes as only one element that contributes as a risk factor and cautions against genetic screening (Alzheimer's association, 2022).

Recent larger genome-wide association studies and meta-analyses have identified new susceptibility loci (Bellenguez, 2022; Andrews, 2020; Zhu, 2019). However large overlapping study populations and variation in methods and conclusions limit interpretation of these analyses. The results do not establish a causal relationship between the genetic variants and the disease, nor do they equate to the discovery of Alzheimer's disease genes. To do that, functional genomics studies that combine results of variant, gene expression, and gene-based or pathway-based analyses are needed. No policy changes are warranted.

In 2024, the medical and scientific advisory groups at the Alzheimer's Association issued a guideline that recommended against genetic testing for Alzheimer's disease risk in healthy individuals. It emphasized the importance of genetic counseling to help individuals understand the implications of such testing, including the potential social and economic impact. The guideline points out that genetic factors, such as the presence of the APOE-Ɛ4 allele, can influence the risk of Alzheimer's disease, but they are just one part of a complex picture that includes many other factors. Genetic testing for Alzheimer's risk is of primary value in research settings or clinical trials (Alzheimer's Association, 2023).

We found one systematic review and meta-analysis related to predictive genetic testing for the detection of Alzheimer's. That study reviewed 53 clinical practice guidelines covering various countries and regions and found that recommendations for screening and diagnosing Alzheimer's disease have remained largely consistent over the past 20 years (Hashemi, 2023). A sub-analysis of 15 guidelines published between 2018 - 2022 found screening was not recommended for asymptomatic populations, and biomarker testing was not advocated for routine diagnosis. Brief cognitive assessments and excluding other causes were suggested for testing. The Traditional Chinese Medicine guidelines were the only ones identified that recommended genetic testing for those with a family history of Alzheimer's disease. However, this recommendation was based on expert consensus rather than robust evidence (Hashemi, 2023).

References

On November 29, 2023, we searched PubMed and the databases of the Cochrane Library, the U.K. National Health Services Centre for Reviews and Dissemination, the Agency for Healthcare Research and Quality, and the Centers for Medicare & Medicaid Services. Search terms were "gene expression" (MeSH), "Alzheimer's disease" (MeSH), and "genetic testing for Alzheimer's disease, apolipoprotein, neurocognitive testing neuropsychological testing." We included the best available evidence according to established evidence

hierarchies (typically systematic reviews, meta-analyses, and full economic analyses, where available) and professional guidelines based on such evidence and clinical expertise.

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Policy updates

5/2016: initial review date and clinical policy effective date: 7/2016

4/2017: Policy references updated.

2/2018: Policy references updated.

3/2019: Policy references updated. Policy ID changed.

2/2020: Policy references updated.

2/2021: Policy references updated.

2/2022: Policy references updated

2/2023: Policy references updated.

2/2024: Policy references updated.