Corporate Medical Policy

Genetic Testing for Familial Alzheimer's Disease AHS – M2038

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Description of Procedure or Service

Alzheimer's disease (AD) is a neurodegenerative disease defined by a gradual decline in memory, cognitive functions, gross atrophy of the brain, and accumulation of extracellular amyloid plaques and intracellular neurofibrillary tangles (Karch, Cruchaga, & Goate, 2014).

Familial Alzheimer's disease (FAD) is a rare, inherited form of Alzheimer's disease. FAD has a much earlier onset than other forms of Alzheimer's with symptoms developing in individuals in their thirties or forties.

Related Policies

General Genetic Testing, Germline Disorders AHS – M2145
General Genetic Testing, Somatic Disorders AHS – M2146

******Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.***

Policy

BCBSNC will provide coverage for genetic testing for familial Alzheimer's disease when it is determined the medical criteria or reimbursement guidelines below are met.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When Genetic Testing for Familial Alzheimer's Disease is covered

Reimbursement is allowed for genetic counseling for familial Alzheimer's disease genetic testing.

Genetic testing for APP, PSEN1 and PSEN2 genes associated with familial Alzheimer's disease (i.e., autosomal-dominant, early-onset dementia not attributable to other factors) is considered medically necessary

- when the results of the testing will inform reproductive decision making AND
- the individual is in one of the following situations
    - Individuals with a family history of autosomal dominant dementia with one or more instances of early-onset AD, OR

- Individuals with a first degree biological relative with a known mutation in the PSEN1, PSEN2, or APP genes, OR
- Symptomatic individuals with suspected early-onset AD when there is an unknown family history (adoption)

When Genetic Testing for Familial Alzheimer's Disease is not covered

Genetic testing for Alzheimer's disease is considered investigational in the following situations:

- Testing to confirm a diagnosis of Alzheimer's disease (any type)
- Testing for familial Alzheimer's disease in children
- Testing for late-onset Alzheimer's disease (age >65 years)
- Testing for other purposes than reproductive decision making
- Testing of *APOE* gene and/or any other genes not listed above
- Testing for purposes of Alzheimer's disease risk assessment
- Screening asymptomatic individuals
- Testing in all other situations not described above

Policy Guidelines

Alzheimer's disease (AD) is a devastating neurodegenerative disease with a strong genetic component, and the predominant form of dementia (50–75%) (Van Cauwenberghe, Van Broeckhoven, & Sleegers, 2016). In 2015, over 46 million people lived with dementia worldwide, and this number is estimated to increase to 131.5 million by 2050 (Prince, 2016). The average lifetime risk of developing Alzheimer disease is 10–12%. This risk at least doubles with the presence of a first-degree relative with the disorder (Goldman et al., 2011). The genetic predisposition of AD, even for late-onset AD patients, is estimated to be 60–80% (Gatz et al., 2006).

Most patients develop clinical symptoms at after the age of 65 (spontaneous or late-onset AD), however up to 10% of patients have an earlier onset of disease (early-onset AD) (Kumar, 2018). AD is characterized by severe neuronal loss, aggregation of extracellular amyloid β plaques, and intraneuronal tau protein tangles resulting in progressive deterioration of memory and cognitive functions (Keene, 2018). Enormous burden on public health is due to the high costs associated with care and treatment. Aside from drugs that temporarily relieve symptoms, no treatment currently exists for AD (Van Cauwenberghe et al., 2016).

Autosomal dominant AD is very rare (<1%), but the discovery of fully penetrant pathogenic mutations of *Amyloid precursor protein (APP) (*Goate et al., 1991; St George-Hyslop et al., 1987), *Presenilin 1 (PSEN1)* (Sherrington et al., 1995; Van Broeckhoven et al., 1992), and *Presenilin 2 (PSEN2) (*Sherrington et al., 1996) inherited in an autosomal dominant fashion, has identified molecular mechanisms and pathways involved in AD pathogenesis and valuable targets currently used in diagnosis and drug development (Schneider et al., 2014; Van Cauwenberghe et al., 2016).

One of the primary features of AD is the buildup of amyloid-β protein in the brain. This protein is poisonous to neurons and is normally cleaved by secretases. However, certain genetic mutations may cause these clearing mechanisms to weaken or an overall increase in amyloid-β production. As amyloid-β starts to aggregate in the brain, it creates fibrils that ultimately cause neurological damage, such as the characteristic dementia (Keene, 2018).

APP is proteolytically processed in the constitutive pathway by α- and γ-secretases resulting in nonpathogenic fragments. However, in the amyloidogenic pathway, subsequent proteolysis of APP by β-secretase and γ-secretase gives rise to a mixture of Aβ peptides with different lengths, of which $A\beta_{1–42}$ are more aggregation-prone and are predominantly present in amyloid plaques in brains of AD patients. 39 *APP* mutations have been described, all of which affect proteolysis of APP in favor of $A\beta_{1–42}$ (Cruts, Theuns, & Van Broeckhoven, 2012).

PSEN1 and *PSEN2* are highly homologous genes. Both proteins encoded by these genes are essential components of the γ-secretase complex, which catalyzes the cleavage of membrane proteins, including APP. Mutations in *PSEN1* and *PSEN2* impair the γ-secretase mediated cleavage of APP resulting in an increased proportion of $A\beta_{1-42}$ (Cruts & Van Broeckhoven, 1998). PSEN1 is located on chromosome 14 whereas PSEN2 is located on chromosome 1. However, PSEN1 is generally associated with a worse prognosis; it has full penetrance compared to 95% penetrance for PSEN2, and age of onset was over 10 years earlier for PSEN1 mutations compared to PSEN2 (Ryman et al., 2014; Sherva & Kowall, 2018)

Late-onset AD is considered to be multifactorial with a strong but complex genetic predisposition (Gatz et al., 2006) involving gene mutations and polymorphisms that may interact with each other or with environmental factors. The ε4 allele of *APOE* was the only major gene known to increase disease risk for both early-onset and late-onset AD. More recently, genome-wide association studies (GWAS) and massive parallel resequencing (MPS) efforts have identified of at least 21 additional genetic risk loci. These loci, shown in the table below from Van Cauwenberghe et al. (2016), are estimated to explain about 28% of the heritability of liability, 30% of familial risk, and over 50% of sibling recurrence risk of developing AD (Van Cauwenberghe et al., 2016). Researchers have recently identified a rare missense variant in the *CASP7* gene that may be associated with familial late-onset AD (Zhang et al., 2019), as well as a T allele of the CD33 rs3865444 polymorphism also associated with late-onset AD (Mehdizadeh et al., 2019).

The *APOE* gene has several alleles, with the ε4 allele contributing to an increased risk of late-onset AD and the ε2 allele contributing to a decreased risk of late-onset AD compared to the common *APOE* ε3 allele (Yamazaki, Zhao, Caulfield, Liu, & Bu, 2019). Researchers now report that *APOE* influences tau pathology as well as neurodegeneration mediated by tau and microglial responses to AD pathologies; further, *APOE* ε4 is "either pathogenic or shows reduced efficiency in multiple brain homeostatic pathways, including lipid transport, synaptic integrity and plasticity, glucose metabolism and cerebrovascular function (Yamazaki et al., 2019)."

Gene	Genes in locus	Possible candidate genes	Function	Pathway	Effect on APP or tau
MS4A4A/MS4A6E locus (chr11:59,268,00-60,480,00)	17 genes	*MS4A2, MS4A3, MS4A4A, MS4A4E, MS4A6A, MS4A6E*	Signal transduction	Immune response	—
HLA-DRB5/HLA-DRB1 locus (chr6:3,609,009-4,535,100)	17 genes	Not defined due to the complex genetic organization of the locus	Immunocompetence and histocompatibility	Immune response	—
ZCWPW1 locus (chr7:99,905, 955-100,093,149)	10 genes	*ZCWPW1*; *NYAP1*: affecting brain size, neurite elongation, neuronal morphogenesis	Epistatic regulation (*ZCWPW1*); brain and neural development (*NYAP1*)	Neural development	—
SLC24A4/RIN3 locus (chr14:92,789,411-93,176,224)	2 genes	*SLC24A4*: brain expression; *RIN3*: known interactor of *BIN1* gene product	Neural development and regulation of blood pressure and hypertension	Neural development and synapse function	—
NME8 locus (chr7:37,779, 803-37,992,860)	4 genes	*NME8*: association signal adjacent to the gene	Ciliary functions	Cytoskeletal function and axonal transport	—
CELF1 locus (chr11:47,291, 161-47,666,021)	10 genes	*CELF1; MADD*: long-term neuronal viability in AD	RNA splicing, editing, and translation (*CELF1*); long-term neuronal viability (*MADD*)	Cytoskeletal function and axonal transport	Tau toxicity

For each locus, the number of genes in each locus is shown with the possible candidate genes. The pathway, function, and effect on APP or tau pathway are reported for each locus.

APP, amyloid precursor protein; GWAS, genome-wide association studies.

Chung et al. (2018) conducted genome-wide pleiotropy analyses using these association summary statistics. Significant findings were further examined by expression quantitative trait locus and differentially expressed gene analyses in AD vs. control brains using gene expression data. The authors state that pleiotropy analysis is a useful approach to identifying novel genetic associations with complex diseases and their endophenotypes. However, functional studies are needed to determine whether *ECRG4* or *HDAC9* is plausible as a therapeutic target.

Clinical Validity and Utility

Early Onset AD

Comprehensive genetic counseling protocols are available for AD diagnostic and predictive testing to provide a framework for clinicians and geneticists to evaluate which patients may benefit from genetic testing. Available genetic diagnostic and predictive screening for causal mutations of early-onset AD in *APP*, *PSEN1*, and *PSEN2* are only responsible for a small portion of AD patients' risk. They account for approximately 60%-70% of familial autosomal dominant AD, but less than 10 percent of early-onset AD and less than one percent of AD overall (Sherva & Kowall, 2018). For a significant number of patients for whom genetic diagnostic screening is requested, the tests will be negative without excluding a genetic cause of disease (Van Cauwenberghe et al., 2016). Furthermore, the identification of a mutation is not a certain predictor of disease or onset age, given that these mutations can vary in terms of penetrance and gene expression. Nevertheless, the ability to identify an explanation for the clustering of AD in a family and the ability to use this toward predictive testing in subsequent generations provide an important step toward autonomy of patients and at-risk individuals (Van Cauwenberghe et al., 2016). Testing for these highly penetrant mutations often carries significant personal and familial utility which the ACMG (American College of Medical Genetics) has recently supported as important clinical utilities (ACMG, 2015a). New mutations in the *APP*, *PSEN1*, and *PSEN2* genes are constantly being identified. For example, two probable pathogenic variants, *PSEN2* p.A415S and p.M174I, were recently identified by Wong, Seelaar, Melhem, Rozemuller, and van Swieten (2020).

Janssen et al. (2003) aimed to determine the proportion of patients with early-onset AD with a positive family history that had mutations in the amyloid precursor protein (APP), presenilin 1 (*PSEN1*), and presenilin 2 (*PSEN2*) genes. A mutational analysis was performed in 31 probands with probable or definite AD from UK families (age at onset <61 years). A total of 23 patients fulfilled criteria for autosomal dominant inheritance. In 17 (55%) probands the authors identified eight novel *PSEN1* sequence variants and eight recognized pathogenic mutations. In four (13%) probands the authors identified one novel *APP* sequence variant (H677R) and two recognized mutations. Further, 21 of 31 (68%) probands were associated with a sequence variant in *APP* or *PSEN1*. Nine of the 11 (82%) probands with neuropathologically confirmed AD who additionally fulfilled recognized criteria for autosomal dominant inheritance were associated with a sequence variant in *APP* or *PSEN1*. The 10 patients in whom the authors were unable to identify a mutation in *APP*, *PSEN1*, or *PSEN2* were older than the probands with sequence variants (55.4 vs 44.7 years, respectively). The authors concluded that sequence variants in *APP* and *PSEN1* accounted for the majority of neuropathologically confirmed autosomal dominant early-onset AD.

Shea et al. (2016) conducted a study to assess the differences in clinical presentations of different genotypes of FAD. A total of 658 pedigrees were evaluated. The authors found that patients with *PSEN1* mutations tended to have earlier age of onset than either *PSEN2* or *APP* mutations. Patients with *PSEN1* were also more commonly affected by symptoms such as seizures or myoclonus, whereas patients with *PSEN2* mutations were more commonly affected by disorientation. Patients with *APP* mutations were more likely to present with aggression or apraxia (Shea et al., 2016).

Lanoiselee et al. (2017) completed a large genetic screening study of familial and sporadic cases of *APP*, *PSEN1*, and *PSEN2* mutations in early-onset AD. Data was taken from 23 French hospitals from 1993 onward; the total number of families identified with mutations was 170 (these families were required to have two first-degree relatives with early-onset AD with an age of onset ≤65 years). One hundred and twenty-nine sporadic cases were also screened with an age of onset ≤51 years. The authors not that "*APP*, *PSEN1*, or *PSEN2* mutations were identified in 53 novel AD-EOAD [early-onset AD] families. Of the 129 sporadic cases screened, 17 carried a *PSEN1* mutation and 1 carried an *APP* duplication (13%); this led to the conclusion that a portion of *PSEN1* mutations occur de novo (Lanoiselee et al., 2017).

Several companies have developed hereditary AD panels. The Invitae Hereditary Alzheimer Disease (AD) Panel tests for three genes associated with early-onset hereditary AD: *APP*, *PSEN1* and *PSEN2* (Invitae, 2020). This test may utilize a blood, DNA or saliva sample and has a 10-21-day turnaround time. The ADmark® Early Onset Alzheimer's Evaluation also tests for the three known early-onset hereditary AD genes: *APP*, *PSEN1* and *PSEN2* (Athena, 2020b). This test detects sequence variants in these genes, as well as duplications in the *APP* gene. A whole blood sample is required, and a turnaround time of 21-28 days can be expected.

Another panel by Fulgent, termed the Parkinson-Alzheimer-Dementia NGS panel, tests for 35 genes that are associated with developing Parkinson disease, Alzheimer disease and dementia (Fulgent, 2019). Some of the genes tested in this panel include *APOE*, *APP*, *PSEN1* and *PSEN2*. This test also requires a blood sample or buccal swab and has a three-week turnaround time.

Late-Onset AD

The primary gene associated with late-onset AD is the apolipoprotein E (*APOE*) gene on chromosome 19, particularly its epsilon (ε) allele. This apolipoprotein is thought to play a role in cholesterol homeostasis and aid in removal of the amyloid- β protein that is at the core of AD. There are three isoforms of this allele: ε2, ε3, and ε4. The ε4 allele binds much more rapidly to the amyloid protein; however, it is less efficient than the other two alleles in protein transfer. These characteristics combined have made the ε4 allele a potential genetic risk factor of AD (Sherva & Kowall, 2018).

The role of genetics in diagnosis and risk prediction in late-onset AD is much less straightforward. *APOE* ε4 is associated with changes in lipid metabolomics in AD patients, and is likely a factor in even the early stages of AD development (Pena-Bautista et al., 2020). Further, it has been suggested that *APOE* ε4 is a selective risk factor, affecting memory-related AD manifestations of the disease more than language-related implications (Weintraub et al., 2020). Despite the established evidence of *APOE* ε4 as a risk factor for AD, its value in disease prediction in a clinical setting is limited, and the relevance of clinical testing for common genetic variations identified in GWAS is even more limited. Combining multiple susceptibility loci into a global genetic risk score (GRS) might improve the prediction of individuals at risk. However, the most comprehensive risk prediction model developed to date only achieved a sensitivity of 55% and a specificity of 78%, impeding use in clinical practice (de Calignon et al., 2012; Van Cauwenberghe et al., 2016).

Neu et al. (2017) performed a global meta-analysis of 27 observational studies in more than 58,000 adults and found that those with only one copy of *APOE* ε4 did not see any difference in risk of developing Alzheimer's disease from ages 55-85. However, the authors did find that women from 65-75 with one copy of *APOE* ε4 were at higher risk than men of the same age (odds ratio of 4.37 for women, 3.14 for men). Both genders were found to have higher risk of mild cognitive impairment with any additional copies of the ε4 allele compared to ε2 or ε3 (Neu et al., 2017).

Naj et al. (2014) assessed the effect of *APOE* alleles on average age of onset in AD patients. Fourteen studies containing 9,162 patients were examined, and the *APOE* allele was found to contribute 3.9% of the variation of age of onset. Each copy of the ε4 was found to reduce the age of onset by 2.45 years (Naj et al., 2014).

Cohn-Hokke et al. (2017) examined the social and personal effects of testing for hereditary neurodegenerative diseases from 74 patient survey responds. The authors concluded that "the result of predictive testing on adult-onset neurodegenerative diseases does not have a large negative effect on social and personal life, although these observations should be interpreted with caution because of the small number of participants and low response rate (Cohn-Hokke et al., 2017)."

The ancestral *APOE* ε4 risk of AD has been studied across Puerto Rican and African American populations. A total of 1,986 participants with late-onset AD (1,766 African Americans and 220

Puerto Ricans) and 3,899 healthy controls older than 65 years of age (3,730 African Americans and 169 Puerto Ricans) participated in this study. The authors note that "*APOE* ε4 alleles on an African background conferred a lower risk than those with a European ancestral background, regardless of population (Rajabli et al., 2018)." This study shows that the risk conferred by the *APOE* ε4 allele differs across populations; the cause of this risk is unknown but may be due to genetic variation, environmental factors, or cultural factors associated with ancestry.

Athena diagnostics developed the ADmark® ApoE Genotype Analysis and Interpretation test which detects *APOE* ε2, ε3, ε4 alleles (Athena, 2020a). Athena will not perform this test on individuals younger than 18 years of age and recommends pre and post-test genetic counseling; a whole blood sample is required and a turnaround time of 7-14 days can be expected.

Applicable Federal Regulations

On April 6, 2017 the FDA approved the 23andMe PGS Genetic Health Risk Report for Late-onset Alzheimer's Disease, indicated for reporting of the ε4 variant in the APOE gene. The report describes if a person's genetic result is associated with an increased risk of developing Late-onset Alzheimer's Disease, but it does not describe a person's overall risk of developing Alzheimer's Disease. The ε4 variant included in this report is found and has been studied in many ethnicities. Detailed risk estimates have been studied the most in people of European descent (FDA, 2017a).

Other tests for Alzheimer's genes are considered laboratory developed tests (LDT); developed, validated and performed by individual laboratories. LDTs are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA'88). As an LDT, the U. S. Food and Drug Administration has not approved or cleared these tests; however, FDA clearance or approval is not currently required for clinical use.

Guidelines and Recommendations

American College of Medical Genetics and Genomics (ACMG) and National Society of Genetic Counselors (NSGC) (Goldman et al., 2011, 2019)

The American College of Medical Genetics and Genomics (ACMG) and the National Society of Genetic Counselors (NSGC) issued joint practice guidelines related to the genetic assessment of AD. These guidelines include the following recommendations (Goldman et al, 2011):

- "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 videoconference) and support by someone with expertise in this area. Symptomatic patients: Genetic counseling for symptomatic patients should be performed in the presence of the individual's legal guardian or family member."
- "DTC (direct to consumer) APOE testing is not advised."
- "A risk assessment should be performed by pedigree analysis to determine whether the family history is consistent with EOAD [early-onset AD] or LOAD (late-onset AD) and with autosomal dominant (with or without complete penetrance), familial or sporadic inheritance."

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 an autosomal dominant AD is unlikely:

- "Discuss that both sporadic and familial cases can be due to a genetic susceptibility. Risk estimates are only available for first-degree relatives of an affected individual in sporadic or familial cases."
- "Genetic testing for susceptibility loci (e.g., APOE) is not clinically recommended due to limited clinical utility and poor predictive value. If a patient wishes to pursue testing despite genetic counseling and recommendations to the contrary, testing may be considered at the clinician's discretion."

Finally, the authors comment that "in general, clear genotype-phenotype correlations cannot typically be made for the three causative genes, and age of onset can vary more than 20 years within the same family" (Goldman et al., 2011).

In 2019, an addendum was published for the aforementioned guidelines. The ACMB board of directors reaffirmed these guidelines with two changes:

- "To use the phrase "pathogenic variant" rather than the word "mutation" in discussing pathogenic variants related to autosomal dominant early-onset Alzheimer disease. This would be consistent with current ACMG/AMP Guidelines for Variant Interpretation and Reporting.
- Because this document no longer meets the criteria for an evidence-based practice guideline by either the American College of Medical Genetics and Genomics (ACMG) or National Society of Genetic Counselors (NSGC), NSGC reclassified this document as a Practice Resource in 2016, and ACMG is also classifying it as a Practice Resource as of this reaffirmation (Goldman et al., 2019)."

American College of Medical Genetics and Genomics (ACMG)

In the Choosing Wisely Initiative, the ACMG recommended "Don't order *APOE* genetic testing as a predictive test for Alzheimer's disease." The rationale for the recommendation is that "*APOE* is a susceptibility gene for later-onset Alzheimer disease (AD), the most common cause of dementia. The presence of an ε4 allele is neither necessary nor sufficient to cause AD. The relative risk conferred by the ε4 allele is confounded by the presence of other risk alleles, gender, environment and possibly ethnicity. *APOE* genotyping for AD risk prediction has limited clinical utility and poor predictive value (ACMG, 2015b)."

American Association of Neurology (AAN)

In 2001 (reaffirmed in 2004), AAN made the following recommendation on the use of genetic testing for Alzheimer's disease:

- Routine use of APOE genotyping in patients with suspected AD is not recommended at this time (Guideline).
- There are no other genetic markers recommended for routine use in the diagnosis of AD (Guideline).

National Institute on Aging (NIH) (Jack et al., 2018; NIH, 2011)

In 2011, Alzheimer's Disease diagnostic guidelines were revised including latest research results and better scientific understanding of the disease. The development of the new guidelines was led by the National Institute of Health and the Alzheimer's Association. Diagnostic criteria for Alzheimer's disease were re-defined. In respect to genetic testing, NIH issued following guidance and recommendations: "A rare type of familial Alzheimer's disease, called Early-Onset Alzheimer's Disease (EOAD), is caused by mutations in the amyloid precursor protein, presenilin 1, or presenilin 2 genes. A person who inherits any of these mutations from a parent will almost surely develop Alzheimer's dementia before age 65. Genetic testing for the disease is common in families with a history of EOAD"; "The major genetic risk factor for the more common, sporadic form of the disease, or Late-Onset Alzheimer's disease (LOAD), is the ε4 allele of the APOE gene. But carrying this allele by itself does not mean a person has or will develop Alzheimer's dementia, so genetic testing for APOE ε4 is not recommended outside of a research setting (NIH, 2011)."

The NIH and Alzheimer's Association released a joint research framework in 2018. In that framework, they state that "Genetics is not formally included in the research framework because our concept of disease rests on neuropathologic change (that can be detected by biomarkers). In contrast, gene variants do not measure pathologic change but rather indicate an individual's risk for developing pathologic change (Jack et al., 2018)."

The Alzheimer's Association Medical and Scientific Advisory Council (AA, 2017)

The Alzheimer's Association Medical and Scientific Advisory Council published a genetic testing statement in 2017. This document states that "For individuals from families in which dementia is of the late-onset type, or in which there is only one additional affected individual, screening for the deterministic genes is not recommended (AA, 2017)." Further, the AA "strongly recommends that people receive genetic counseling before a test is ordered and when the results are obtained (AA, 2017)."

Canadian Consensus Conference on Diagnosis and Treatment of Dementia (Moore, Patterson, Lee, Vedel, & Bergman, 2014)

Fourth Canadian Consensus Conference (Moore et al., 2014)

Expert committee members helped to revise guidelines for the fourth consensus committee on the diagnosis and treatment of dementia. These guidelines note that "All patients with early-onset dementia should be referred to a memory clinic, preferably one with access to genetic counseling and testing when available" (Moore et al., 2014).

European Federation of Neurological Societies (EFNS) and European Neurological Society (ENS) (Sorbi et al., 2012)

The EFNS and ENS have developed guidelines for the diagnosis and management of disorders associated with dementia. Regarding genetic testing, these guidelines state that "No studies have addressed the value of genetic counselling for patients with dementia or their families when autosomal-dominant disease is suspected. Because the genetics of dementing illnesses is a very young field, expertise in genetic counselling for the dementias of the elderly is likely to be found only in specialized dementia research centres (Good Practice Point). Screening for known pathogenic mutations can be undertaken in patients with appropriate phenotype or a family history of an autosomal-dominant dementia. This should only be undertaken in specialist centres with appropriate counselling of the patient and family caregivers, and with consent (Good Practice Point). Pre-symptomatic testing may be performed in adults where there is a clear family history, and when there is a known mutation in an affected individual to ensure that a negative result is clinically significant. (Good Practice Point) (Sorbi et al., 2012)."

European Federation of Neurological Sciences (EFNS) (Hort et al., 2010)

In 2010, EFNS published revised recommendations on the diagnosis and management of Alzheimer disease. It stated that "the ApoE 4 allele is the only genetic factor consistently implicated in late-onset AD, but it is neither necessary nor sufficient for development of the disease. Hence, there is no evidence to suggest ApoE testing is useful in a diagnostic setting." The EFNS recommended that "screening for known pathogenic mutations can be undertaken in patients with appropriate phenotype or a family history of an autosomal dominant dementia. Routine Apo E genotyping is not recommended (Hort et al., 2010)."

United States Preventive Services Task Force (USPSTF) (Owens et al., 2020)

The USPSTF has concluded that "the current evidence is insufficient to assess the balance of benefits and harms of screening for cognitive impairment in older adults (Owens et al., 2020)."

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable codes: 81401, 81405, 81406, 96040, S0265, S3852

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources

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Policy Implementation/Update Information

1/1/19	New policy developed. BCBSNC will provide coverage for genetic testing for familial alzheimer's disease when it is determined to be medically necessary because the medical criteria and guidelines are met. Medical Director review 1/1/2019. Policy noticed 1/1/2019 for effective date 4/1/2019. (sk)
8/27/19	Reviewed by Avalon 2nd Quarter 2019 CAB. Added "Related Policies" section. Policy Guidelines updated. References updated. Coding table removed from the Billing/Coding section of the policy. Medical Director review 8/2019. (sk)
9/10/19	Added codes 81401, 81405, 81406, 81407, 96040, S0265, and S3852 back to policy. Codes were removed erroneously on 8/27/19. (sk)
10/29/19	Wording in the Policy, When Covered, and/or Not Covered section(s) changed from Medical Necessity to Reimbursement language, where needed.
11/26/19	Specialty Matched Consultant Advisory Panel review 10/16/2019. (sk)
7/28/20	Reviewed by Avalon 2nd Quarter 2020 CAB. Policy Guidelines updated. Literature review updated. References updated. Code 81407 removed from the Billing/Coding section. Medical Director review 7/2020. (bb)
11/10/20	Specialty Matched Consultant Advisory Panel review 10/21/2020. (sk)