Genetic Testing for CADASIL Syndrome

Effective: June 1, 2019

Next Review: April 2020
Last Review: May 2019

Important Reminder

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

Description

Variants in the NOTCH3 gene have been causally associated with CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy). Genetic testing is available to determine if pathogenic variants exist in the NOTCH3 gene for patients with suspected CADASIL and their family members.

Medical Policy Criteria

I. Genetic testing of NOTCH3 for the diagnosis of CADASIL may be considered medically necessary when one or more of the following criteria are met:
   A. Clinical signs and symptoms are consistent with CADASIL (subcortical ischemic events, cognitive impairment, migraine with aura, mood disturbances, and/or apathy); or
   B. In adults when there is a first- or second-degree family member with a diagnosis of CADASIL syndrome.

II. Genetic testing for CADASIL syndrome for all other situations, including but not limited to testing in children, is considered investigational.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.
POLICY GUIDELINES

CLINICAL SIGNS AND SYMPTOMS

The clinical presentation of CADASIL varies among and within families. The disease is characterized by five main symptoms: subcortical ischemic events, cognitive impairment, migraine with aura, mood disturbances, and apathy.

FAMILY MEMBERS

- First-degree relatives are parents, siblings, and children of an individual; and
- Second-degree relatives are grandparents, aunts, uncles, nieces, nephews, grandchildren, and half-siblings (siblings with one shared biological parent) of an individual.

LIST OF INFORMATION NEEDED FOR REVIEW

In order to determine the clinical utility of gene test(s), all of the following information must be submitted for review:

1. Name of the genetic test(s) or panel test
2. Name of the performing laboratory and/or genetic testing organization (more than one may be listed)
3. The exact gene(s) and/or mutations being tested
4. Relevant billing codes
5. Brief description of how the genetic test results will guide clinical decisions that would not otherwise be made in the absence of testing. Medical records related to this genetic test, if available:
   - History and physical exam
   - Conventional testing and outcomes
   - Conservative treatment provided

CROSS REFERENCES

1. Genetic and Molecular Diagnostic Testing

BACKGROUND

CADASIL is an uncommon, autosomal dominant disease, although it is the most common cause of hereditary stroke and hereditary vascular dementia in adults. The CADASIL syndrome is an adult-onset, disabling systemic condition, characterized by migraine with aura, recurrent lacunar strokes, progressive cognitive impairment, and psychiatric disorders. The overall prevalence of the disease is unknown in the general population.

The clinical presentation of CADASIL is variable and may be confused with multiple sclerosis, Alzheimer dementia, andBinswanger disease. The specific clinical signs and symptoms, along with family history and brain magnetic resonance imaging (MRI) findings, are important in determining the diagnosis of CADASIL. The clinical features and mode of inheritance (autosomal dominant versus autosomal recessive) help to distinguish other inherited disorders in the differential diagnosis from CADASIL.

When the differential diagnosis includes CADASIL, various other tests are available for
diagnosis:

- Immunohistochemistry assay of a skin biopsy sample, using a monoclonal antibody with reactivity against the extracellular domain of the NOTCH3 receptor. Positive immunostaining reveals the accumulation of NOTCH3 protein in the walls of small blood vessels.[1] Lesnick Oberstein (2003) estimated sensitivity and specificity at 85-90% and 95-100%, respectively, for two observers of the test results in a population of patients and controls correlated with clinical, genetic and MRI parameters.[2]

- Detection of granular osmiophilic material (GOM) in the same skin biopsy sample by electron microscopy. The major component of GOM is the ectodomain of the NOTCH3 gene product.[3] GOM accumulates directly in vascular smooth muscle cells and, when present, is considered a hallmark of the disease.[4] However, GOM may not be present in all biopsy samples. Sensitivity has been reported as low as 45% and 57%, but specificity is generally near or at 100%.[5-7]

- Genetic testing by direct sequencing of selected exons or of exons 2-24 of the NOTCH3 gene (see Scientific Evidence section below)

- Examination of brain tissue for the presence of GOM. GOM was originally described as limited to brain vessels.[8] Examination of brain biopsy or autopsy after death was an early gold standard for diagnosis. In some cases, peripheral staining for GOM has been absent even though positive results were seen in brain vessels.

**NOTCH3 VARIANTS**

Variants in NOTCH3 have been identified as the underlying cause of CADASIL. In almost all cases, the variants lead to loss or gain of a cysteine residue that could lead to increased reactivity of the NOTCH3 protein, resulting in ligand-binding and toxic effects.[9]

The NOTCH3 gene is found on chromosome 19p13.2-p13.1 and encodes the third discovered human homologue of the Drosophila melanogaster type I membrane protein NOTCH. The NOTCH3 protein consists of 2,321 amino acids primarily expressed in vascular smooth muscle cells and plays an important role in the control of vascular transduction. It has an extracellular ligand-binding domain of 34 epidermal growth factor-like repeats, traverses the membrane once, and has an intracellular domain required for signal transduction.[10]

Variants in the NOTCH3 gene have been differentiated into those that are causative of the CADASIL syndrome (pathogenic variants) and those that are of uncertain significance. Pathogenic variants affect conserved cysteine residues within 34 epidermal growth factor (EGF)-like repeat domains in the extracellular portion of the NOTCH3 protein.[10, 11] More than 150 pathogenic variants have been reported in at least 500 pedigrees. NOTCH3 has 33 exons, but all CADASIL variants reported to date have been found in exons 2–24, which encode the 34 EGF-like repeats, with strong clustering in exons 3 and 4, which encode EGFR 2–5 (>40% of variants in >70% of families occur in these exons).[12]

**REGULATORY STATUS**

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA). NOTCH3 genetic testing is available under the auspices of CLIA. Laboratories that offer LDTs must be licensed by CLIA for high-complexity
testing. To date, the U.S. Food and Drug Administration has not chosen to require any regulatory review of this test.

**EVIDENCE SUMMARY**

Human Genome Variation Society (HGVS) nomenclature\[^{[13]}\] is used to describe variants found in DNA and serves as an international standard. It is being implemented for genetic testing medical evidence review updates starting in 2017. According to this nomenclature, the term “variant” is used to describe a change in a DNA or protein sequence, replacing previously-used terms, such as “mutation.” Pathogenic variants are variants associated with disease, while benign variants are not. The majority of genetic changes have unknown effects on human health, and these are referred to as variants of uncertain significance.

Validation of the clinical use of any genetic test focuses on three main principles:

1. The analytic validity of the test, which refers to the technical accuracy of the test in detecting a variant that is present or in excluding a variant that is absent;
2. The clinical validity of the test, which refers to the diagnostic performance of the test (sensitivity, specificity, positive and negative predictive values) in detecting clinical disease; and
3. The clinical utility of the test, which refers to how the results of the diagnostic test will be used to change management of the patient, and whether these changes in management lead to clinically important improvements in health outcomes.

**ANALYTICAL VALIDITY**

There is limited data on analytic validity of NOTCH3 testing were identified. The test is generally done by gene sequencing analysis, which is expected to have high analytic validity when performed under optimal conditions.

Fernandez described the development of a next-generation sequencing (NGS) protocol for NOTCH3 and HTRA1 genes in 70 patients referred for clinical suspicion of CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy), all of whom had previously undergone Sanger sequencing of exons 3 and 4 of the NOTCH3 gene.\[^{[14]}\] NOTCH3 variants were detected in six patients on NGS, including two variants previously detected with Sanger sequencing and four variants in exons 6, 11, and 19.

**CLINICAL VALIDITY**

Several retrospective and prospective studies have examined the association between NOTCH3 genes and cerebral autosomal dominant arteriopathy with CADASIL, as shown in Table 1. These studies have been divided into two categories:

- Part 1, diagnostic studies, in which the patients enrolled were suspected, but not confirmed to have CADASIL; and
- Part 2, clinical validity studies, in which the patients had already been diagnosed with the disease by some method other than genetic testing. The diagnostic studies are more likely to represent the target population in which the test would be used.
Table 1. Studies of the association of NOTCH3 with CADASIL

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients Evaluated</th>
<th>NOTCH3 Exons Evaluated</th>
<th>Results</th>
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<tbody>
<tr>
<td><strong>Part 1 Diagnostic Studies</strong></td>
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<tr>
<td>Choi 2011[8]</td>
<td>Patients: 151 consecutive Korean patients with acute ischemic stroke.</td>
<td>Bidirectional sequencing of exons 3, 4, 6, 11 and 18.</td>
<td>Patients: six patients (4%) were found with the identical NOTCH3 variant (R544C; exon 11). Of these, all had pre-existing lacunar infarction, five (83.3%) had grade 2-3 white-matter hyperintensity lesions, and a history of hypertension; a history of stroke and dementia was higher in patients with variants.</td>
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<tr>
<td>Patient Selection: History of acute ischemic stroke, neurologic exam, cranial computed tomography or MRI.</td>
<td></td>
<td>Family Members: No data for additional family members</td>
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<tr>
<td>Patient Selection: History of premature strokes; migraine with aura; vascular dementia; suggestive MRI findings; a consistent family history; or a combination of the above criteria.</td>
<td></td>
<td>Family Members: Analysis of 15 additional family members identified 11 of the same causative variants.</td>
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<tr>
<td>Patient Selection: Suggestive MRI findings and at least one of the following: young age at onset, cognitive decline, psychiatric disorders, or consistent family history.</td>
<td></td>
<td>Family members: No data for additional family members</td>
<td></td>
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<tr>
<td>Markus 2002[7]</td>
<td>Patients: 83 patients with suspected CADASIL (UK). Patients were younger than 60 years of age with recurrent lacunar stroke with leukoaraiosis on neuroimaging. Migraine, psychiatric disorders, or dementia could occur but were not essential.</td>
<td>Direct sequencing of exons 3-4; SSCP of exons 2, 5-23.</td>
<td>Patients: 15 different single nucleotide variants identified in 48 families with a total of 116 symptomatic patients, 73% in exon 4, 8% in exon 3, and 6% in exons 5 and 6.</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Family Members: No data for additional family members</td>
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<tr>
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<td>Patients Evaluated</td>
<td>NOTCH3 Exons Evaluated</td>
<td>Results</td>
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<td>Yin 2015[16]</td>
<td>Patients: 47 subjects from 34 families (Chinese) diagnosed with suspected CADASIL. Patient diagnosis/selection: MRI abnormalities and the presence of more than one typical symptom (e.g., migraine, stroke, cognitive deficits, psychiatric symptoms) or the presence of atypical symptoms with a positive family history.</td>
<td>Testing method: exons 3 and 4 screened first; if no variants detected, remaining exons analyzed.</td>
<td>Patients: six known variants were identified in eight families and two novel variants were identified in two families (exons 3 and 4), and one VUS was identified in one family (exon 2). Overall NOTCH3 variant prevalence: 29.4%</td>
</tr>
<tr>
<td>Maksemous 2016[17]</td>
<td>Patients: 44 patients with suspected CADASIL previously screened for standard sequencing exons (3 and 4, and/or 2, 11, 18, 19) by Sanger sequencing and classified as negative for known pathogenic variants.</td>
<td>Custom NGS panel</td>
<td>Patients: six typical CADASIL variants were identified in 7/44 patients.</td>
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</table>

### Part 2 Clinical Validity Studies

<table>
<thead>
<tr>
<th>Sensitivity</th>
<th>Specificity</th>
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<tbody>
<tr>
<td>Choi 2013[18]</td>
<td>Bidirectional sequencing of R544C (exon 11).</td>
</tr>
<tr>
<td>Tikka 2009[19]</td>
<td>Direct sequencing of exons 2-24.</td>
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</table>
The results of the clinical validity studies demonstrate that a NOTCH3 variant is found in a high percentage of patients with a clinical diagnosis of CADASIL, with studies reporting a clinical sensitivity of 90-100%. Limited data on specificity is from testing small numbers of healthy controls, and no false positive NOTCH3 variants have been reported in these populations. The diagnostic yield studies report a variable diagnostic yield, ranging from 10-54%. These lower numbers likely reflect testing in heterogeneous populations that include patients with other disorders.

CLINICAL UTILITY

Genetic testing may have clinical utility in several situations. The clinical situations addressed in herein are:

- confirmation of a clinical diagnosis of CADASIL in an individual with signs and symptoms of the disease; and
- Informing the reproductive decision-making process in preimplantation testing, prenatal (in utero) testing or altering reproductive planning decisions when a NOTCH3 pathogenic variant is present in a parent.

Confirmation of a CADASIL Diagnosis

The clinical specificity of genetic testing for CADASIL is high, and false-positive results have not been reported in studies of clinical validity. Therefore, a positive genetic test in a patient with clinical signs and symptoms of CADASIL is sufficient to confirm the diagnosis with a high degree of certainty. The clinical sensitivity is also relatively high, in the range of 90% to 100%.
for patients with a clinical diagnosis of CADASIL. This indicates that a negative test reduces the likelihood that CADASIL is present. However, because false-negative tests do occur, a negative test is less definitive in ruling out CADASIL. Whether a negative test is sufficient to rule out CADASIL depends on the pretest likelihood that CADASIL is present.

Pescini (2012) published a study that attempted to identify clinical factors that increase the likelihood of a pathogenic variant being present and therefore might be helpful in selecting patients for testing.\cite{23} The authors first performed a systematic review to determine the frequency with which clinical and radiologic factors are associated with a positive genetic test. Evidence was identified from 15 clinical series of patients with CADASIL. Table 2 summarizes the pooled frequency of clinical and radiologic features.

**Table 2. Clinical and Radiological Features in Patients with NOTCH3 Variants**

<table>
<thead>
<tr>
<th>Features</th>
<th>No. With NOTCH3 Variant</th>
<th>Percent With NOTCH3 Variant, %</th>
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<tbody>
<tr>
<td><strong>Clinical features</strong></td>
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<tr>
<td>Migraine</td>
<td>239/463</td>
<td>52%</td>
</tr>
<tr>
<td>Migraine with aura</td>
<td>65/85</td>
<td>76%</td>
</tr>
<tr>
<td>Transient ischemic attack/stroke</td>
<td>380/526</td>
<td>72%</td>
</tr>
<tr>
<td>Psychiatric disturbance</td>
<td>106/380</td>
<td>28%</td>
</tr>
<tr>
<td>Cognitive decline</td>
<td>188/434</td>
<td>43%</td>
</tr>
<tr>
<td><strong>Radiologic features</strong></td>
<td></td>
<td></td>
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<tr>
<td>LE (leukoencephalopathy)</td>
<td>277/277</td>
<td>100%</td>
</tr>
<tr>
<td>LE extended to temporal pole</td>
<td>174/235</td>
<td>74%</td>
</tr>
<tr>
<td>LE extended to external capsule</td>
<td>228/303</td>
<td>75%</td>
</tr>
<tr>
<td>Subcortical infarcts</td>
<td>210/254</td>
<td>83%</td>
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</table>

Using these frequencies, a preliminary scoring system was developed and tested in 61 patients with NOTCH3 variants, and in 54 patients with phenotypic features of CADASIL who were NOTCH3-negative. With the addition of family history and age at onset of transient ischemic attack (TIA)/stroke, a scoring system was developed with the following point values: migraine (1); migraine with aura (3); TIA/stroke (1); TIA/stroke 50 years old or younger (2); psychiatric disturbance (1); cognitive decline (3); leukoencephalopathy (3); leukoencephalopathy extended to temporal pole (1); leukoencephalopathy extended to external capsule (5); subcortical infarcts (2); family history, one generation (1); and family history, two generations or more (2). The authors recommended that a total score of 14 be used to select patients for testing, because this score resulted in a high sensitivity (96.7%) and a moderately high specificity (74.2%).

A 2017 study reported by Mizuta analyzed clinical features of Japanese patients suspected for CADASIL to determine new diagnostic criteria for CADASIL.\cite{24} Criteria were developed and validated with two separate groups of genetically diagnosed CADASIL patients, with 37 patients in the first group and 65 in the second. Controls groups were young stroke patients (n = 67) and CADASIL-like patients without NOTCH3 variants (n = 53). Clinical criteria were as follows:

1. Age at onset less than or equal to 55 years
2. At least two of the following clinical findings:
   a. Either subcortical dementia, long tract signs, or pseudobulbar palsy.
   b. Stroke-like episode with a focal neurological deficit.
   c. Mood disorder.
d. Migraine.

3. Autosomal dominant inheritance.
4. White matter lesions involving the anterior temporal pole by MRI or CT.
5. Exclusion of leukodystrophy

Genetic and pathological criteria were:

- **NOTCH3** variants localized in exons 2–24 and result in the gain or loss of cysteine residues in the epidermal growth factor-like repeat domain. Cysteine-sparing variants should be carefully evaluated by skin biopsy and segregation studies.
- The pathological hallmark of CADASIL is granular osmiophilic material (GOM) detected by electron microscopy. Immunostaining of NOTCH3 extracellular domain is also useful.

CADASIL diagnosis was considered definite when white matter lesions were detected by MRI or CT, clinical criteria #5 was met, and genetic or pathological criteria were met. Diagnosis was considered probable when the subject met all five clinical criteria and possible when the subject had abnormal white matter lesions and either was less than or equal to 55 years old or had at least one of the symptoms in clinical criteria number two. The sensitivity and specificity of the new criteria were 97.1% and 7.5%, respectively, when calculated using both control groups. Sensitivity and specificity of the scale proposed by Pescini (above) using this cohort was also calculated. Sensitivity and specificity were 52.1% and 64.1%, respectively.

Currently, no specific clinical treatment for CADASIL has established efficacy. Supportive care in the form of practical help, emotional support, and counseling are appropriate for affected individuals and their families.[3] Four studies were found that addressed the efficacy of potential treatments for CADASIL.

A double-blind, placebo-controlled trial evaluating the efficacy and safety of donepezil hydrochloride (HCl) in individuals with CADASIL was conducted. The study showed donepezil HCl had no effect on the primary cognitive endpoint, the Cognitive subscale of the Vascular AD Assessment Scale score in patients with CADASIL and cognitive impairment.[25]

Another study evaluated the efficacy and tolerance of a 24-week treatment with acetazolamide 250 mg/d to improve cerebral hemodynamics in CADASIL patients (n=16). Treatment with acetazolamide resulted in a significant increase of mean blood flow velocity (MFV) in the middle cerebral artery (MCA) compared with MFV in the MCA at rest before treatment (57.68±12.7 cm/s vs 67.12±9.4 cm/s; p=0.001). During the treatment period, none of the subjects developed new neurologic symptoms, and the original symptoms in these patients (e.g., headaches, dizziness) were relieved.[26]

A third study evaluated the use of 3-hydroxy-3-methylglutaryl-coenzyme A-reductase inhibitors (statins) in 24 CADASIL subjects treated with atorvastatin for eight weeks. Treatment was started at 40 mg, followed by a dosage increase to 80 mg after four weeks. Transcranial Doppler sonography measuring MFV in the MCA was performed at baseline and at the end of treatment. There was no significant treatment effect on MFV (p=0.5) or cerebral vasoreactivity, as assessed by hypercapnia (p=0.5) or intravenous L-arginine (p=0.4) in the overall cohort. However, an inverse correlation was found between vasoreactivity at baseline and changes of both CO2- and L-arginine–induced vasomotor response (both p<0.05). Short-term treatment with atorvastatin resulted in no significant improvement of hemodynamic parameters in the overall cohort of CADASIL subjects.[27]
De Maria reported the results of a randomized, double-blinded trial comparing sapropterin with placebo for adults with CADASIL.[28] Sapropterin is a synthetic analog of tetrahydrobiopterin, which is an essential cofactor in nitric oxide synthesis in endothelial cells. Given nitric oxide’s role in cerebrovascular function, the authors hypothesized that sapropterin supplementation would improve cerebral endothelium-dependent vasodilation in CADASIL patients. Endothelial dysfunction was assessed using the reactive hyperemia peripheral arterial tonometry (RH-PAT) response, which has been shown to be impaired in patients with CADASIL syndrome. Peripheral arterial tonometry (PAT) is a noninvasive, quantitative test that measures changes in digital pulse volume during reactive hyperemia (RH) and evaluates the endothelial function of resistance arteries and nitric oxide–mediated changes in microvascular response. The study randomized 61 subjects from 38 families, 32 to sapropterin and 29 to placebo. In intention-to-treat analysis, there was no significant difference in change in RH-PAT response (mean difference in RH-PAT change, 0.19: 95% confidence interval, -0.18 to 0.56). Both groups demonstrated improvements in RH-PAT values over the course of the study, but, after results were adjusted for age, sex, and clinical characteristics, the improvement was not associated with treatment.

**Genetic Testing of NOTCH3 in Relatives of Patients with CADASIL**

For individuals that have family members with CADASIL syndrome who receive genetic testing, the evidence is limited. Relevant outcomes are overall survival, test accuracy and validity, changes in reproductive decision making, change in disease status, and morbid events. For family members of an individual with known CADASIL, knowledge of the presence of a familial variant may lead to changes in lifestyle decisions for the affected individual (eg, reproduction, employment). However, the impact of these lifestyle decisions on health outcomes is uncertain, and there are no interventions for asymptomatic individuals that are known to delay or prevent the onset of disease. A chain of evidence can be constructed to demonstrate that identification of a NOTCH3 familial variant predicts future development of CADASIL in asymptomatic individuals, eliminates the need for additional diagnostic testing, allows for earlier monitoring for development of systems, aids in reproductive planning and helps determine the likelihood of an affected offspring.

It has been suggested that asymptomatic family members follow the guidelines for presymptomatic testing for Huntington disease. Genetic counseling is recommended to discuss the impact of positive or negative test results, followed by molecular testing if desired.[4] For an asymptomatic individual, knowledge of variant status will generally not lead to any management changes that can prevent or delay the onset of the disorder. Avoiding tobacco use may be one factor that delays onset of disease, but this is a general recommendation that is not altered by genetic testing.

**PRACTICE GUIDELINE SUMMARY**

**EUROPEAN FEDERATION OF NEUROLOGICAL SOCIETIES (EFNS)**

The ENFS guidelines[29] state that among patients with suspected genetic disorders, “direct sequencing of exons 3 and 4 in the Notch3 gene is suggested as a first step if clinical suspicion for CADASIL is high (Level B).” According to guideline authors, a Level B rating is defined as “probably useful/predictive or not useful/predictive” and requires “at least one convincing class II study or overwhelming class III evidence.” The methods used to formulate these recommendations are based upon expert consensus.
SUMMARY

There is enough research to show that testing for NOTCH3 variants can help diagnose CADASIL in patients with signs and symptoms consistent with CADASIL. Therefore, genetic testing to confirm the diagnosis of CADASIL syndrome may be considered medically necessary when the policy criteria are met.

There is enough evidence to show that testing for NOTCH3 variants associated with CADASIL in individuals who have a family member with the disease can help patients make reproductive planning decisions and avoid unnecessary diagnostic testing. Therefore, genetic testing for NOTCH3 variants in adults that have a first- or second-degree family member with a diagnosis of CADASIL syndrome may be considered medically necessary.

There is not enough research to show that genetic testing for CADASIL improves health outcomes or decision-making in patients that do not meet the policy criteria. Therefore, genetic testing for CADASIL syndrome in all other situations, including but not limited to testing in children, is considered investigational.

REFERENCES


### CODES

<table>
<thead>
<tr>
<th>Codes</th>
<th>Number</th>
<th>Description</th>
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<tbody>
<tr>
<td>CPT</td>
<td>81406</td>
<td>Molecular pathology procedure, Level 7</td>
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<tr>
<td>HCPCS</td>
<td>None</td>
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*Date of Origin: April 2013*