Genetic Testing for CADASIL Syndrome

Effective: June 1, 2026

Next Review: April 2027
Last Review: April 2026

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 individuals with suspected CADASIL and their family members.

MEDICAL POLICY CRITERIA

Note: Clinical documentation to support criteria is required (See Required Documentation)

Medically Necessary

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**.**

Investigational

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.

REQUIRED DOCUMENTATION

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:
   - o History and physical exam
   - o Conventional testing and outcomes
   - o Conservative treatment provided

CROSS REFERENCES

1. Genetic and Molecular Diagnostic Testing, Genetic Testing, Policy No. 20

BACKGROUND

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (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, and Binswanger 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:

- Genetic testing by direct sequencing of selected exons or of exons 2-24 of the *NOTCH3* gene (see Scientific Evidence section below). Identification of a *NOTCH3* pathogenic variant definitively establishes a diagnosis of CADASIL without the need for additional testing (eg, skin biopsy).
- 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]
- 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 was implemented for genetic testing medical evidence review updates 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

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 (2015) 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

Study	Patients Evaluated	*NOTCH3* Exons Evaluated	Results	
Part 1 Diagnostic Studies			**Diagnostic Yield**	**Specificity**
Maksemous 2016[15]	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	Custom NGS panel	Patients: six typical CADASIL variants were identified in 7/44 patients.	NR
Yin 2015[16]	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 (eg, migraine, stroke, cognitive deficits, psychiatric symptoms) or the presence of atypical symptoms with a positive family history	Testing method: exons 3 and 4 screened first; if no variants detected, remaining exons analyzed	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%	NR
Choi 2011[8]	Patients: 151 consecutive Korean patients with acute ischemic stroke. Patient Selection: History of acute ischemic stroke, neurologic exam, cranial computed tomography or MRI.	Bidirectional sequencing of exons 3, 4, 6, 11 and 18.	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. Family Members: No data for additional family members	NR
Mosca 2011[9]	Patients: 140 patients with clinical suspicion of CADASIL (Italian and Chinese).	Direct sequencing of exons 2-8, 10, 14, 19, 20, and 22.	Patients: 14 patients with causative variants located in 10 different exons. 126 patients free of pathogenic variants.	NR

Study	Patients Evaluated	*NOTCH3* Exons Evaluated	Results	
	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.		Family Members: Analysis of 15 additional family members identified 11 of the same causative variants.	
Lee 2009[17]	Patients: 39 patients with suspected CADASIL (China). 100 healthy elderly controls 80 years or older. Patient Selection: Suggestive MRI findings and at least one of the following: young age at onset, cognitive decline, psychiatric disorders, or consistent family history.	Direct sequencing of exons 2-23.	Patients: nine different single nucleotide variants identified in 21/39 patients. Family members: No data for additional family members	100% No variants found in 100 healthy elderly controls.
Markus 2002[7]	Patients: 83 patients with suspected CADASIL (UK). Patient Selection: 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.	Direct sequencing of exons 3-4; SSCP of exons 2, 5-23.	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. Family Members: No data for additional family members	NR
Part 2 Clinical Validity Studies			**Sensitivity**	**Specificity**
Choi 2013[18]	Patients: 73 unrelated patients diagnosed with CADASIL between 2004-2009. Patient Diagnosis/Selection: Patients were diagnosed via clinical and MRI, and stroke history.	Bidirectional sequencing of R544C (exon 11).	Patients: 65 of 73 Patients (90.3%) had the same R544C genotype.	NR
Tikka 2009[19]	Patients: 131 patients from 28 families diagnosed with CADASIL (Finnish, Swedish, and French). Patient Diagnosis/Selection: EM examination of skin biopsy was performed; 26	Direct sequencing of exons 2-24.	Sensitivity: 100% Patients: 131 CADASIL patients were variant positive. Family Members: No data for additional family patients. No variant reporting per family or per unrelated individual.	100% No variants were found in the 26 negative controls.

Study	Patients Evaluated	*NOTCH3* Exons Evaluated	Results	
	asymptomatic controls from CADASIL families.			
Dotti et al. 2005[20]	Patients: 28 unrelated, consecutively diagnosed patients with CADASIL (Italian). Patient Diagnosis/Selection: Patients were diagnosed via clinical and MRI.	DHPLC, followed by confirmatory sequencing of identified variants.	Sensitivity: 100%. Patients: All 28 patients had variants.	NR
Peters 2005[21]	Patients: 125 unrelated patients diagnosed with CADASIL. Patient Diagnosis/Selection: Skin biopsy-proven CADASIL pts referred between 1994 and 2003 (German).	Bidirectional sequencing of all exons.	Sensitivity: 96% Patients: 54 distinct variants in 120 (96.0%) of the 125 patients. In five patients (4.0%), no variant was identified. Family Members: No data for additional family patients	NR
Joutel 1997[22]	Patients: 50 unrelated patients with a clinical suspicion of CADASIL and 100 healthy controls. Patient Diagnosis/Selection: History of recurrent strokes, migraine with aura, vascular dementia, or a combination; brain MRI with suggestive findings; and a consistent familial history.	SSCP or heteroduplex analysis of all exons, followed by confirmatory sequencing of identified variants.	Sensitivity: 90% Patients: 45 of 50 CADASIL patients had variants.	100% No variants were found in 100 healthy controls.

Key: MRI, magnetic resonance imaging; SSCP, single-stranded conformational polymorphism; EM, electron microscope; DHPLC, denaturing high-performance liquid chromatography

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 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.

Hack (2023) published a three-tiered risk stratification system for individualized *NOTCH3*-small vessel disease prediction based on *NOTCH3* genotype.[23] The frequency of cysteine-altering missense variants in each EGF repeat domain was assessed in the CADASIL literature, cohorts, and population databases among 2,574 CADASIL patients and 1,657 individuals from population databases. EGF repeat domains were classified as either low, medium, or high risk. The three risk categories were validated with comparisons to small vessel disease imaging markers and clinical outcomes using a genotype-phenotype dataset of 434 CADASIL patients and 1,003 individuals with *NOTCH3* cysteine-altering variants. CADASIL patients and individuals with *NOTCH3* cysteine-altering variants had 379 unique *NOTCH3* cysteine-altering variants. Nine EGF repeat domains were classified as high risk, 10 were classified as medium risk, and 11 were classified as low risk. In the population genotype-phenotype dataset, individuals with high risk EGF repeat variants had the highest risk of stroke (odds ratio [OR]=10.81, 95% confidence interval [CI]: 5.46 to 21.37) followed by medium risk individuals (OR=1.81, 95% CI: 0.84 to 3.88), and low risk individuals (OR=1). In the CADASIL genotype-phenotype group, patients with high risk EGF repeat domain variants had a significantly higher risk of stroke (p=0.002) and disability (p=0.041).

Chen (2021) published a study in 45 patients with young-onset cognitive impairment with leukodystrophy in which a custom panel of 200 neurodegeneration-associated genes was performed.[24] The frequency of gene variants was evaluated along with study participants' brain magnetic resonance imaging (MRI) findings to inform the diagnostic utility of combining the two approaches. In more than half (19/37, 51.4%) of patients with MRI changes consistent with vascular cognitive impairment secondary to small vessel disease (VCI-SVD), a pathogenic variant was identified, including all patients with pathogenic NOTCH3 (17/19, 89.5%) and HTRA1 variants (2/19, 11.5%). Anterior temporal white matter involvement was specific to patients with pathogenic NOTCH3 variants (6/17, 35.3%) in this cohort. No pathogenic variant was identified in 26/45 (57.8%) patients evaluated. The impact of genetic testing on health care decision making or on clinical outcomes was not evaluated in this study.

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.[25] 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

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

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%).

Mizuta (2017) analyzed clinical features of Japanese patients suspected for CADASIL to determine new diagnostic criteria for CADASIL.[26] 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. Control 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 to 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] Studies that addressed the efficacy of potential treatments for CADASIL are summarized below.

De Maria (2014) reported the results of a randomized, double-blinded trial comparing sapropterin with placebo for adults with CADASIL.[27] 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.

Another study published by Huang (2010) evaluated the efficacy and tolerance of a 24-week treatment with acetazolamide 250 mg/d to improve cerebral hemodynamics in CADASIL patients (n=16).[28] 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. A double-blind, placebo-controlled trial evaluating the efficacy and safety of donepezil hydrochloride (HCl) in individuals with CADASIL was published in 2008 by Dichgans.[29] 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.

Peters (2007) evaluated the use of 3-hydroxy-3-methylglutaryl-coenzyme A-reductase inhibitors (statins) in 24 CADASIL subjects treated with atorvastatin for eight weeks.[30] 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.

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

In a 2023 scientific statement, the American Heart Association reviewed the current clinical, genetic, and imaging aspects of CADASIL to provide prevention, management, and therapeutic considerations to support future treatment recommendations.[31] In consideration of when to test for *NOTCH3* mutations, the statement recommends to "consider gene testing in patients with small vessel stroke before 55 years of age with a paucity of vascular risk factors (eg, normotensive, nondiabetic, nonsmoker) or positive family history of CADASIL."

SUMMARY

Medically Necessary

There is enough research to show that testing for *NOTCH3* variants can help diagnose CADASIL in individuals 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 individuals 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.

Investigational

There is not enough research to show that genetic testing for CADASIL improves health outcomes or decision-making in individuals 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

1. Joutel A, Favrole P, Labauge P, et al. Skin biopsy immunostaining with a Notch3 monoclonal antibody for CADASIL diagnosis. *Lancet.* 2001;358(9298):2049-51. PMID: 11755616
2. Lesnik Oberstein SA, van Duinen SG, van den Boom R, et al. Evaluation of diagnostic NOTCH3 immunostaining in CADASIL. *Acta neuropathologica.* 2003;106(2):107-11. PMID: 12756589
3. Muqtadar H, Testai FD. Single gene disorders associated with stroke: a review and update on treatment options. *Current treatment options in cardiovascular medicine.* 2012;14(3):288-97. PMID: 22528196
4. del Rio-Espinola A, Mendioroz M, Domingues-Montanari S, et al. CADASIL management or what to do when there is little one can do. *Expert review of neurotherapeutics.* 2009;9(2):197-210. PMID: 19210195
5. Malandrini A, Gaudiano C, Gambelli S, et al. Diagnostic value of ultrastructural skin biopsy studies in CADASIL. *Neurology.* 2007;68(17):1430-2. PMID: 17452591
6. Brulin P, Godfraind C, Leteurtre E, et al. Morphometric analysis of ultrastructural vascular changes in CADASIL: analysis of 50 skin biopsy specimens and pathogenic implications. *Acta neuropathologica.* 2002;104(3):241-8. PMID: 12172909
7. Markus HS, Martin RJ, Simpson MA, et al. Diagnostic strategies in CADASIL. *Neurology.* 2002;59(8):1134-8. PMID: 12395806
8. Choi JC, Lee KH, Song SK, et al. Screening for NOTCH3 Gene Mutations Among 151 Consecutive Korean Patients With Acute Ischemic Stroke. *Journal of stroke and cerebrovascular diseases : the official journal of National Stroke Association.* 2011. PMID: 22133740
9. Mosca L, Marazzi R, Ciccone A, et al. NOTCH3 gene mutations in subjects clinically suspected of CADASIL. *Journal of the neurological sciences.* 2011;307(1-2):144-8. PMID: 21616505
10. Lesnik Oberstein SAJ, Boon EMJ, Terwindt GM. Cadasil. 1993. PMID: 20301673
11. Donahue CP, Kosik KS. Distribution pattern of Notch3 mutations suggests a gain-of-function mechanism for CADASIL. *Genomics.* 2004;83(1):59-65. PMID: 14667809
12. Chabriat H, Joutel A, Dichgans M, et al. Cadasil. *Lancet neurology.* 2009;8(7):643-53. PMID: 19539236
13. den Dunnen JT, Dalgleish R, Maglott DR, et al. HGVS Recommendations for the Description of Sequence Variants: 2016 Update. *Human mutation.* 2016;37(6):564-9. PMID: 26931183
14. Fernandez A, Gomez J, Alonso B, et al. A Next-Generation Sequencing of the NOTCH3 and HTRA1 Genes in CADASIL Patients. *Journal of molecular neuroscience : MN.* 2015;56(3):613-6. PMID: 25929831

15. Maksemous N, Smith RA, Haupt LM, et al. Targeted next generation sequencing identifies novel NOTCH3 gene mutations in CADASIL diagnostics patients. *Human genomics.* 2016;10(1):38. PMID: 27881154
16. Yin X, Wu D, Wan J, et al. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy: Phenotypic and mutational spectrum in patients from mainland China. *The International journal of neuroscience.* 2015;125(8):585-92. PMID: 25105908
17. Lee YC, Liu CS, Chang MH, et al. Population-specific spectrum of NOTCH3 mutations, MRI features and founder effect of CADASIL in Chinese. *Journal of neurology.* 2009;256(2):249-55. PMID: 19242647
18. Choi JC, Song SK, Lee JS, et al. Diversity of stroke presentation in CADASIL: study from patients harboring the predominant NOTCH3 mutation R544C. *Journal of stroke and cerebrovascular diseases : the official journal of National Stroke Association.* 2013;22(2):126-31. PMID: 21852154
19. Tikka S, Mykkanen K, Ruchoux MM, et al. Congruence between NOTCH3 mutations and GOM in 131 CADASIL patients. *Brain : a journal of neurology.* 2009;132(Pt 4):933-9. PMID: 19174371
20. Dotti MT, Federico A, Mazzei R, et al. The spectrum of Notch3 mutations in 28 Italian CADASIL families. *Journal of neurology, neurosurgery, and psychiatry.* 2005;76(5):736-8. PMID: 15834039
21. Peters N, Opherk C, Bergmann T, et al. Spectrum of mutations in biopsy-proven CADASIL: implications for diagnostic strategies. *Archives of neurology.* 2005;62(7):1091-4. PMID: 16009764
22. Joutel A, Vahedi K, Corpechot C, et al. Strong clustering and stereotyped nature of Notch3 mutations in CADASIL patients. *Lancet.* 1997;350(9090):1511-5. PMID: 9388399
23. Hack RJ, Gravesteijn G, Cerfontaine MN, et al. Three-tiered EGFr domain risk stratification for individualized NOTCH3-small vessel disease prediction. *Brain : a journal of neurology.* 2023;146(7):2913-27. PMID: 36535904
24. Chen Z, Tan YJ, Lian MM, et al. High Diagnostic Utility Incorporating a Targeted Neurodegeneration Gene Panel With MRI Brain Diagnostic Algorithms in Patients With Young-Onset Cognitive Impairment With Leukodystrophy. *Front Neurol.* 2021;12:631407. PMID: 33597917
25. Pescini F, Nannucci, S., Bertaccini B, et al. . The Cerebral Autosomal-Dominsant Arteriopathy With Subrotical Infarcts and Leukoencephalopathy (CADASIL) Scale: a screening tool to select patients for NOTCH3 gene analysis. *Stroke.* 2015;56(3):613-16. PMID:
26. Mizuta I, Watanabe-Hosomi A, Koizumi T, et al. New diagnostic criteria for cerebral autosomal dominant arteriopathy with subcortical infarcts and leukocencephalopathy in Japan. *Journal of the neurological sciences.* 2017;381:62-67. PMID: 28991717
27. De Maria R, Campolo J, Frontali M, et al. Effects of sapropterin on endothelium-dependent vasodilation in patients with CADASIL: a randomized controlled trial. *Stroke.* 2014;45(10):2959-66. PMID: 25184356
28. Huang L, Yang Q, Zhang L, et al. Acetazolamide improves cerebral hemodynamics in CADASIL. *Journal of the neurological sciences.* 2010;292(1-2):77-80. PMID: 20227091
29. Dichgans M, Markus HS, Salloway S, et al. Donepezil in patients with subcortical vascular cognitive impairment: a randomised double-blind trial in CADASIL. *Lancet neurology.* 2008;7(4):310-8. PMID: 18296124

30. Peters N, Freilinger T, Opherk C, et al. Effects of short term atorvastatin treatment on cerebral hemodynamics in CADASIL. *Journal of the neurological sciences.* 2007;260(1-2):100-5. PMID: 17531269
31. Meschia JF, Worrall BB, Elahi FM, et al. Management of Inherited CNS Small Vessel Diseases: The CADASIL Example: A Scientific Statement From the American Heart Association. *Stroke.* 2023;54(10):e452-e64. PMID: 37602377

CODES

Codes	Number	Description
CPT	81406	Molecular pathology procedure, Level 7
HCPCS	None	

Date of Origin: *April 2013*