2.04.75	Genetic Testing of CADASIL Syndrome		
Original Policy Date:	September 27, 2013	**Effective Date:**	June 1, 2023
Section:		**Page:**	Page 1 of 20

Policy Statement

I. Genetic testing for a NOTCH3 variant to confirm the diagnosis of cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) syndrome in an individual may be considered **medically necessary** under the following conditions:
   A. Clinical signs, symptoms, and imaging results are consistent with CADASIL, indicating that the pretest probability of CADASIL is at least in the moderate-to-high range (see the Policy Guidelines section); and
   B. The diagnosis of CADASIL is inconclusive following alternative methods of testing, including magnetic resonance imaging.

For individuals who are asymptomatic with a family member with a diagnosis of CADASIL syndrome:

II. If there is a family member (first- and second-degree relative) with a known variant, targeted genetic testing of the known *NOTCH3* familial variant may be considered **medically necessary**.

III. If the family member's genetic status is unknown, genetic testing of *NOTCH3* (see Policy Guidelines section) may be considered **medically necessary**.

IV. Genetic testing for a *NOTCH3* variant to confirm the diagnosis of CADASIL syndrome in all other situations is considered **investigational**.

NOTE: Refer to Appendix A to see the policy statement changes (if any) from the previous version.

Policy Guidelines

Genetic testing for NOTCH3 comprises targeted sequencing of specific exons (e.g., exon 4 only, exons 2-6), general sequencing of NOTCH3 exons (e.g., exons 2-24 or all 33 exons), or targeted testing for known NOTCH3 pathogenic variants.

The probability that CADASIL is present in an individualized assessment depends on numerous factors such as family history, symptoms, imaging results, and other specialized testing such as skin biopsy.

First degree relatives are defined as a blood relative with whom the individual shares approximately 50% of his/her genes, including parents, full-siblings, and children on both maternal and paternal sides.

Second degree relatives are defined as a blood relative with whom an individual shares approximately 25% of his/her genes, including grandparents, grandchildren, uncles, aunts, nieces, nephews, and half-siblings.

Pescini et al (2012) attempted to identify clinical factors that increase the likelihood of a pathogenic variant being present. Table PG1 summarizes the pooled frequency of clinical and radiologic features, and the points assigned for each finding. 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%).

Table PG1. Pooled Frequency of Clinical and Radiologic Features

Features	No. With *NOTCH3* Variant	Percent With *NOTCH3* Variant	Points
Clinical			
Migraine	239/463	52%	1
Migraine with aura	65/85	76%	3
Transient ischemic attack/stroke	380/526	72%	1 (2 if <50 y)
Psychiatric disturbance	106/380	28%	1
Cognitive decline	188/434	43%	3
Radiologic			
LE	277/277	100%	3
LE extended to temporal pole	174/235	74%	1
LE extended to external capsule	228/303	75%	5
Subcortical infarcts	210/254	83%	2

Adapted from Pescini et al (2012).
LE: leukoencephalopathy.

Genetics Nomenclature Update

The Human Genome Variation Society (HGVS) nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. It is being implemented for genetic testing medical evidence review updates starting in 2017 (see Table PG2). HGVS nomenclature is recommended by the Human Variome Project, the HUman Genome Organization (HUGO), and by the Human Genome Variation Society itself.

The American College of Medical Genetics and Genomics (ACMG) and the Association for Molecular Pathology (AMP) standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations, in addition to the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table PG3 shows the recommended standard terminology—"pathogenic," "likely pathogenic," "uncertain significance," "likely benign," and "benign"—to describe variants identified that cause Mendelian disorders.

Table PG2. Nomenclature to Report on Variants Found in DNA

Previous	Updated	Definition
Mutation	Disease-associated variant	Disease-associated change in the DNA sequence
	Variant	Change in the DNA sequence
	Familial variant	Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives

Table PG3. ACMG-AMP Standards and Guidelines for Variant Classification

Variant Classification	Definition
Pathogenic	Disease-causing change in the DNA sequence
Likely pathogenic	Likely disease-causing change in the DNA sequence
Variant of uncertain significance	Change in DNA sequence with uncertain effects on disease
Likely benign	Likely benign change in the DNA sequence
Benign	Benign change in the DNA sequence

ACMG: American College of Medical Genetics and Genomics; AMP: Association for Molecular Pathology.

Genetic Counseling

Experts recommend formal genetic counseling for patients who are at risk for inherited disorders and who wish to undergo genetic testing. Interpreting the results of genetic tests and understanding risk factors can be difficult for some patients; genetic counseling helps individuals understand the impact of genetic testing, including the possible effects the test results could have on the individual or their

family members. It should be noted that genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing; further, genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

Coding
There is CPT coding to report *NOTCH3* genetic testing. Code **81406** includes:
NOTCH3 (notch 3) (e.g., cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy [CADASIL]), targeted sequence analysis (e.g., exons 1-23).

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.

Related Policies

- Preimplantation Genetic Testing

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

Regulatory Status

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

Rationale

Background
CADASIL
Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is an uncommon, autosomal dominant disease, though it is the most common cause of hereditary stroke and hereditary vascular dementia in adults. CADASIL syndrome is an adult-onset, disabling systemic condition, characterized by a migraine with aura, recurrent lacunar strokes,

progressive cognitive impairment, and psychiatric disorders. The overall prevalence of the disease is unknown in the general population.

Diagnosis

The differential diagnosis of CADASIL includes the following conditions (see Table 1).

Table 1. Differential Diagnosis of CADASIL

Acquired Disorders	Inherited Disorders
• **Sporadic SVD with or without hypertension as the main risk factor** • **Multiple sclerosis** • **Primary angiitis of the central nervous system**	• Fabry disease • Cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy • Familial SVD caused by heterozygous variants in the *HTRA1* gene • Some forms of leukodystrophy

SVD: small vessel disease.

Since the clinical presentation of CADASIL varies, the condition 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 findings, are extremely important in diagnosing CADASIL. The clinical features and mode of inheritance (autosomal dominant vs autosomal recessive) help to distinguish CADASIL from other inherited disorders in a differential diagnosis.

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

- Genetic testing, by direct sequencing of select exons or of exons 2 through 24 of the *NOTCH3* gene (see the Rationale section). Identification of a *NOTCH3* pathogenic variant definitively establishes a diagnosis of CADASIL without the need for additional diagnostic testing (e.g., 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 the NOTCH3 protein in the walls of small blood vessels.[1,] Lesnick Oberstein et al (2003) estimated the sensitivity and specificity at 85% to 90% and 95% to 100%, respectively, for 2 observers of the test results in a population of patients and controls correlated with clinical, genetic, and magnetic resonance imaging 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%.[5,6,7,]
- Examination of brain tissue for the presence of GOM was originally described as limited to brain blood vessels.[8,] Examination of brain biopsy or autopsy after death was an early criterion standard for diagnosis. In some cases, peripheral staining for GOM has been absent even though positive results were seen in brain blood vessels

NOTCH3 Variants

Variants in *NOTCH3* have been identified as the underlying cause of CADASIL. In almost all cases, the pathogenic variants lead to loss or gain of a cysteine residue that can 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 2321 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 (EGF)-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 causative of the CADASIL syndrome (pathogenic variants) and those of uncertain significance. Pathogenic variants affect conserved cysteine residues within 34 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 occurred in exons 2 to 24, which encode the 34 EGF-like repeats, with strong clustering in exons 3 and 4, which encode EGF receptors 2 to 5 (>40% of variants in >70% of families occur in these exons).[12,] Some studies have indicated that the clinical variability in CADASIL presentation, particularly about the development of white-matter hyperintensities on magnetic resonance imaging, may be related to genetic modifiers outside the *NOTCH3* locus but the specific role of these modifiers is not well-delineated.[13,]

The probability that CADASIL is present in an individualized assessment depends on numerous factors such as family history, symptoms, imaging results, and other specialized testing (e.g., skin biopsy). Pescini et al (2012) attempted to identify clinical factors that increase the likelihood of a pathogenic variant being present, with increasing likelihood with the presence of one or several factors, including a migraine, migraine with aura, transient ischemic attack/stroke, psychiatric disturbance, cognitive decline, leukoencephalopathy (with greater risk for leukoencephalopathy extending to the temporal pole or external capsule), and subcortical infarcts.[14,]

Literature Review

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

Promotion of greater diversity and inclusion in clinical research of historically marginalized groups (e.g., People of Color [African-American, Asian, Black, Latino and Native American]; LGBTQIA (Lesbian, Gay, Bisexual, Transgender, Queer, Intersex, Asexual); Women; and People with Disabilities [Physical and Invisible]) allows policy populations to be more reflective of and findings more applicable to our diverse members. While we also strive to use inclusive language related to these groups in our policies, use of gender-specific nouns (e.g., women, men, sisters, etc.) will continue when reflective of language used in publications describing study populations.

Testing Individuals with Suspected CADASIL Syndrome

Clinical Context and Test Purpose

The purposes of genetic testing of symptomatic individuals with suspected cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) syndrome are to establish the diagnosis of CADASIL without skin biopsy or other invasive testing and to aid in reproductive planning when the diagnosis cannot be made clinically.

The questions addressed in this evidence review are: Does the use of genetic testing in individuals with suspected CADASIL improve net health outcomes?

The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest is individuals with suspected CADASIL.

Interventions
The test being considered is genetic testing for *NOTCH3* variants. Genetic testing is used to confirm a diagnosis of CADASIL. Referral for genetic counseling is important for the explanation of genetic disease, heritability, genetic risk, test performance, and possible outcomes.

Comparators
The following practice is currently being used: standard clinical management without genetic testing.

Outcomes
The potential beneficial outcome of primary interest would be changes in management associated with improved outcomes initiated based on confirming a genetic diagnosis of CADASIL. Reductions in skin biopsies or other invasive tests to confirm the diagnosis of CADASIL are also potentially beneficial outcomes.

Potential harmful outcomes are those resulting from a false-positive or false-negative test result. False-positive test results can lead to the inappropriate initiation of treatments or psychological harm after receiving positive test results. False-negative test results can lead to lack of medical or neurologic treatments or surveillance.

The time frame for outcome measures varies from the short-term development of symptoms to long-term changes in disease status and outcomes.

Study Selection Criteria
For the evaluation of clinical validity of the tests, studies that met the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores)
- Included a suitable reference standard
- Patient/sample clinical characteristics were described
- Patient/sample selection criteria were described
- Included a validation cohort separate from development cohort

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Several retrospective and prospective studies have examined the association between *NOTCH3* variants and CADASIL, as shown in Table 2. Studies have been divided into 2 categories: Part 1: Diagnostic studies, in which 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.

The results of the clinical validity studies demonstrated that a *NOTCH3* pathogenic variant is found in a high percentage of patients with a clinical diagnosis of CADASIL, with studies reporting a clinical sensitivity ranging from 90% to 100%. Limited data on specificity derive from testing small numbers of healthy controls, and no false-positive *NOTCH3* variants have been reported in these populations. The diagnostic yield studies have reported a variable yield (range, 10%-54%). These lower numbers likely reflect testing in heterogeneous populations that include individuals with other disorders.

Testing Strategy

Identification of a *NOTCH3* pathogenic variant establishes a diagnosis of CADASIL. For individuals suspected of CADASIL:

- Perform targeted sequencing and analysis of specific *NOTCH3* exons (e.g., exon 4 only, exons 2-6) OR
- Perform general testing of *NOTCH3* exons (e.g., exons 2-24 or all 33 exons).
- If no *NOTCH3* pathogenic variant is identified, a skin biopsy is warranted for immunohistochemical staining for *NOTCH3* protein and/or electron microscopy for granular osmiophilic material.

Table 2. Association Between *NOTCH3* and CADASIL Diagnosis: Results From Studies Supporting *NOTCH3* Genotyping Test Claims

Study	Patients Evaluated	*NOTCH3* Exons Sequenced	Results	
Part 1: Diagnostic studies			*Diagnostic Yield*	*Specificity*
Mosca et al (2011)[9,]	**Patients:** 140 with clinical suspicion of CADASIL (Italian, Chinese) **Selection:** History of premature strokes; migraine with aura; vascular dementia; suggestive MRI findings; consistent family history; or combination of previous criteria	Direct sequencing of exons 2-8, 10, 14, 19-20, 22	**Patients:** 14 with pathogenic variants located in 10 exons. 126 patients free of pathogenic variants **Family members:** Analysis of 15 additional family members identified 11 of the same pathogenic variants	NR
Lee et al (2009)[15,]	**Patients:** 39 with suspected CADASIL (Chinese); 100 healthy elderly controls ≥80 y **Selection:** Suggestive MRI findings and at least 1 of the following: young age at onset, cognitive decline, psychiatric disorders, or consistent family history	Direct sequencing of exons 2-23	**Patients:** 9 different SNVs identified in 21/39 patients **Family members:** No data	100% No variants in 100 healthy elderly controls
Markus et al (2002)[7,]	**Patients:** 83 with suspected CADASIL (U.K.) **Selection:** Patients were <60 y 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 SNVs identified in 48 families with 116 symptomatic patients, 73% in exon 4, 8% in exon 3, 6% in exons 5 and 6 **Family members:** No data	NR
Choi et al (2013)[8,]	**Patients:** 151 consecutive patients (Korean) **Selection:** History of acute ischemic stroke, neurologic exam, cranial computed tomography, or MRI	Bidirectional sequencing of exons 3, 4, 6, 11, 18	**Patients:** 6 (4%) found with identical *NOTCH3* variant (R544C; exon 11). Of these, all had preexisting lacunar infarction, 5 (83.3%) had grade 2-3 white-matter hyperintensity lesions, and a history of hypertension; history of stroke and dementia higher in patients with variants **Family members:** No data	NR
Yin et al (2015)[16,]	**Patients:** 47 subjects from 34 families (Chinese) diagnosed with suspected CADASIL **Diagnosis/selection:** MRI abnormalities and presence of >1 typical symptom (e.g., migraine, stroke, cognitive deficits,	Testing method per Joutel et al (1997)[17,]: exons 3 and 4 screened first; if no variants detected,	**Patients:** 6 known familial variants identified in 8 families and 2 novel pathogenic variants identified in 2 families (exons 3 and 4), and 1 VUS identified in 1 family (exon 2).	NR

Study	Patients Evaluated	*NOTCH3* Exons Sequenced	Results	
	psychiatric symptoms) or presence of atypical symptoms with a positive family history	remaining exons analyzed	Overall *NOTCH3* pathogenic variant prevalence: 29.4%.	
Abramycheva et al (2015)[18,]	**Patients:** 30 unrelated patients with suspected CADASIL	Direct sequencing of exons 2-23 via PCR	**Patients:** 16 SNVs identified in 18 unrelated patients, 12 of which had been previously described and 4 were novel (*C194G*, *V252M*, *C338F*, *C484G*)	NR
Maksemous et al (2016)[19,]	**Patients:** 44 with suspected clinical diagnosis of CADASIL previously screened for standard Sanger sequencing exons (3, 4) and/or (2, 11, 18, 19) and classified as negative for known pathogenic variants	Custom NGS panel	**Patients:** 6 typical CADASIL pathogenic variants identified in 7/44 patients	NR
Part 2: Clinical validity studies			*Sensitivity*	*Specificity*
Peters et al (2005)[20,]	**Patients:** 125 unrelated patients diagnosed with CADASIL **Diagnosis/selection:** Skin biopsy-proven CADASIL patients	Bidirectional sequencing of all exons	**Sensitivity:** 96% **Patients:** 54 distinct variants in 120 (96.0%) of 125 patients. In 5 (4.0%) patients, no variants identified. **Family members:** No data	NR
Tikka et al (2009)[21,]	**Patients:** 131 patients from 28 families diagnosed with CADASIL (Finnish, Swedish, French) **Diagnosis/selection:** EM examination of skin biopsy was performed; 26 asymptomatic controls from CADASIL families	Direct sequencing of exons 2-24	**Sensitivity:** 100% **Patients:** 131 CADASIL patients were pathogenic variant-positive **Family members:** No data; no pathogenic variant reported per family or per unrelated individual	100% No pathogenic variants in 26 negative controls
Dotti et al (2005)[22,]	**Patients:** 28 unrelated, consecutively diagnosed patients with CADASIL (Italian) **Diagnosis/selection:** Patients diagnosed via clinical and MRI criteria	DHPLC, followed by confirmatory sequencing of identified pathogenic variants	**Sensitivity:** 100% **Patients:** All 28 had pathogenic variants	NR
Joutel et al (1997)[17,]	**Patients:** 50 unrelated patients with a clinical suspicion of CADASIL and 100 healthy controls **Diagnosis/selection:** History of recurrent strokes, migraine with aura, vascular dementia, or a combination; brain MRI with suggestive findings; and consistent familial history	SSCP or heteroduplex analysis of all exons, followed by confirmatory sequencing of identified variants	**Sensitivity:** 90% **Patients:** 45/50 CADASIL patients had variants	100% No variants in 100 healthy controls

CADASIL: cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; DHPLC: denaturing high-performance liquid chromatography; EM: electron microscope; MRI: magnetic resonance imaging; NGS: next-generation sequencing; NR: not reported; PCR: polymerase chain reaction; SNV: single nucleotide variant; SSCP: single-stranded conformational polymorphism; VUS: variant of uncertain significance.

Section Summary: Clinically Valid

The clinical sensitivity of genetic testing is high given that *NOTCH3* is the only gene for which pathogenic variants are known to cause CADASIL. In clinical situations where the diagnosis of CADASIL cannot be confirmed by other methods (clinical presentation, MRI findings), identification of a pathogenic variant in *NOTCH3* establishes a diagnosis of CADASIL.

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if individuals receive correct therapy, more effective therapy, or avoid unnecessary therapy or testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for individuals managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials (RCTs).

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 an individual 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 individuals 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 et al (2012) attempted to identify clinical factors that increase the likelihood of a pathogenic variant being present and therefore might be helpful in selecting individuals for testing.[14,] 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 individuals with CADASIL. Table 3 summarizes the pooled frequency of clinical and radiologic features.

Table 3. Clinical and Radiologic Features in Patients With *NOTCH3* Variants

Features	No. With *NOTCH3* Variant	Percent With NOTCH3 Variant	Points
Clinical			
Migraine	239/463	52	1
Migraine with aura	65/85	76	3
Transient ischemic attack/stroke	380/526	72	1 (2 if <50 y)
Psychiatric disturbance	106/380	28	1
Cognitive decline	188/434	43	3
Radiologic			
LE	277/277	100	3
LE extended to temporal pole	174/235	74	1
LE extended to external capsule	228/303	75	5
Subcortical infarcts	210/254	83	2

Adapted from Pescini et al (2012).[14,]
LE: leukoencephalopathy.

Using these frequencies, a preliminary scoring system was developed and tested in 61 patients with *NOTCH3* pathogenic variants, and in 54 individualswith phenotypic features of CADASIL who were *NOTCH3*-negative. With the addition of family history and age at onset of transient ischemic attack or stroke, a scoring system was developed, as provided in Table 3. The authors recommended that a total score of 14 be used to select individuals for testing because this score resulted in a high sensitivity (96.7%) and moderately high specificity (74.2%).

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.[3,10,] Four studies were found that addressed the efficacy of potential treatments for CADASIL.

A double-blind, placebo-controlled trial by Dichgans et al (2008) evaluated the efficacy and safety of donepezil hydrochloride in individuals with CADASIL.[23,] The trial showed donepezil hydrochloride 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.

Another study, by Huang et al (2010), assessed the efficacy and tolerance of a 24-week therapy with acetazolamide 250 mg/day to improve cerebral hemodynamics in CADASIL patients (N =16).[24,] Treatment with acetazolamide resulted in a significant increase of blood mean flow velocity in the middle cerebral artery (57.68 cm/s) compared with mean flow velocity in the middle cerebral artery at rest before treatment (67.12 cm/s; p=0.001). During the treatment period, none of the subjects developed new neurologic symptoms, and the original symptoms in these individuals (eg, headaches, dizziness) were relieved.

A third study, by Peters et al (2007), evaluated the use of 3-hydroxy-3-methylglutaryl-coenzyme A-reductase inhibitors (statins) in 24 CADASIL subjects treated with atorvastatin for 8 weeks.25, Treatment was started at 40 mg, followed by a dosage increase to 80 mg after 4 weeks. Transcranial Doppler sonography measuring mean flow velocity in the middle cerebral artery was performed at baseline and the end of treatment. There was no significant treatment effect on mean flow velocity (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 CO_2- 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.

De Maria et al (2014) reported on the results of a randomized, double-blinded trial comparing sapropterin with placebo for adults with CADASIL.[26,] Sapropterin is a synthetic analogue 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 response, which has been shown to be impaired in patients with CADASIL syndrome. Peripheral arterial tonometry is a noninvasive, quantitative test that measures changes in digital pulse volume during reactive hyperemia and evaluates the endothelial function of resistance arteries and nitric oxide-mediated changes in microvascular response. The trial randomized 61 subjects from 38 families, 32 to sapropterin and 29 to placebo. In the intention-to-treat analysis, there was no significant difference in change in reactive hyperemia peripheral arterial tonometry response (mean difference, 0.19: 95% confidence interval, -0.18 to 0.56). Both groups demonstrated improvements in reactive hyperemia peripheral arterial tonometry levels during the study, but, after results were adjusted for age, sex, and clinical characteristics, the improvement was not associated with treatment.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.
Genetic testing of individuals with suspected CADASIL may have clinical utility by:

- Establishing a diagnosis of CADASIL in an individual with signs and symptoms of the disease, particularly when other disorders are being considered, without the need for a skin biopsy.
- 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. Preimplantation testing is addressed elsewhere (evidence review 4.02.05).

Section Summary: Clinically Useful

Direct evidence for the clinical utility of genetic testing of individuals with suspected CADASIL is lacking. No specific clinical treatment for CADASIL has established efficacy. However, a chain of evidence for the clinical validity of *NOTCH3* pathogenic variants in establishing a diagnosis of CADASIL leading to initiation of supportive care in the form of practical help, emotional support, and counseling may provide a chain of evidence for potential clinical utility.

Targeted Familial Variant Testing in Asymptomatic Patients With Relatives Who Have CADASIL Syndrome

Clinical Context and Test Purpose

The purposes of targeted familial variant testing of asymptomatic individuals with family members who have CADASIL are to screen at-risk individuals and predict the development of disease, to determine the need for surveillance, and to aid in reproductive planning.

The questions addressed in this evidence review are: Does the use of genetic testing in an asymptomatic patient with relatives who have CADASIL syndrome improve net health outcomes? The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is asymptomatic individuals with relatives who have CADASIL syndrome.

Interventions

The following test is currently being used: targeted familial variant testing of *NOTCH3*. Asymptomatic individuals with family members with CADASIL may be referred to a medical geneticist for investigation of genetic status for carrying a known familial variant. Referral for genetic counseling is important for the explanation of genetic disease, heritability, genetic risk, test performance, and possible outcomes.

Comparators

The following practice is currently being used: standard clinical management without genetic testing.

Outcomes

The potential beneficial outcomes of primary interest would be confirming or excluding the need for surveillance or changes in reproductive decision making. A negative genetic test result would eliminate the need for surveillance to detect the development of symptoms and disease. A positive genetic test result would confirm a need for active surveillance and inform the reproductive decision process.

Potential harmful outcomes are those resulting from a false-positive or false-negative test result. False-positive test results can lead to unnecessary medical or neurologic surveillance of asymptomatic individuals. False-negative test results can lead to lack of medical or neurologic surveillance.

The time frame for outcome measures varies from short-term surveillance of asymptomatic individuals for the development of signs or symptoms of CADASIL to long-term development of the disease.

Study Selection Criteria

For the evaluation of clinical validity of the tests, studies that met the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores)
- Included a suitable reference standard

- Patient/sample clinical characteristics were described
- Patient/sample selection criteria were described
- Included a validation cohort separate from development cohort

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

See the clinical validity discussion in the *Testing Individuals With Suspected CADASIL Syndrome* section.

Testing Strategy

Identification of a *NOTCH3* pathogenic variant establishes a diagnosis of CADASIL in both symptomatic and asymptomatic individuals. For testing in asymptomatic individuals with family members who have CADASIL:

- When the proband's *NOTCH3* pathogenic variant is known, conduct targeted familial variant testing to determine genetic status.

The testing strategy described is a general approach for targeted genetic testing for a known pathogenic variant previously identified in a family member (familial variant) with CADASIL.

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, more effective therapy, or avoid unnecessary therapy or testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for individuals managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

No randomized trials were identified addressing outcomes managed with CADASIL testing.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.
Genetic testing of asymptomatic individuals with family members who have CADASIL may have clinical utility by:

- Confirming or excluding the need for surveillance based on the presence or absence of a known familial variant.
- Informing the reproductive decision-making process in preimplantation testing, prenatal (in utero) testing, or altering reproductive planning decisions when a known *NOTCH3* familial variant is present in a parent. Preimplantation testing is addressed elsewhere (evidence review 4.02.05).

Genetic counseling is recommended to discuss the impact of positive or negative test results, followed by molecular testing if desired.[4,] At present, for an asymptomatic individual, knowledge of familial variant status will generally not lead to any management changes that can prevent or delay the onset of the disorder. Avoiding tobacco use can be a factor that delays the onset of disease, but this is a general recommendation that is not altered by genetic testing. However, a negative test may preclude the need for surveillance for complications. Genetic testing may also assist reproductive decision making.

A chain of evidence can be constructed to demonstrate that identification of a *NOTCH3* pathogenic variant predicts future development of CADASIL in an asymptomatic individual, 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.

Section Summary: Clinically Useful

Direct evidence for the clinical utility of genetic testing of asymptomatic relatives of individuals with CADASIL is lacking. No specific clinical treatment for CADASIL has established efficacy. However, a chain of evidence can be developed for potential clinical utility, particularly for reproductive decision-making process for preimplantation and/or prenatal testing.

Genetic Testing of *NOTCH3* in Asymptomatic Patients with Relatives who have CADASIL and Unknown Genetic Status

Clinical Context and Test Purpose

The purposes of genetic testing of *NOTCH3* in asymptomatic individuals with family members with CADASIL whose genetic status is unknown are to screen at-risk individuals and to predict the development of disease, determine the need for surveillance, and aid in reproductive planning.
The questions addressed in this evidence review are: Does the use of NOTCH3 genetic testing in an asymptomatic patient with relatives who have CADASIL and whose genetic status is unknown improve net health outcomes?

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is asymptomatic individuals with relatives who have CADASIL and whose genetic status is unknown.

Interventions

The test being considered is genetic testing of *NOTCH3* variants.
Asymptomatic individuals with family members who have CADASIL may be referred to a medical geneticist for investigation of genetic status for carrying a known familial variant. Referral for genetic counseling is important for the explanation of genetic disease, heritability, genetic risk, test performance, and possible outcomes.

Comparators

The following practice is currently being used: standard clinical management without genetic testing.

Outcomes

The potentially beneficial outcomes of primary interest would be confirming or excluding the need for surveillance or changes in reproductive decision making. A negative genetic test result would eliminate the need for surveillance to detect the development of symptoms and disease. A positive genetic test result would confirm a need for active surveillance and also inform the reproductive decision-making process.

Potential harmful outcomes are those resulting from a false-positive or false-negative test result. False-positive test results can lead to unnecessary medical or neurologic surveillance of asymptomatic individuals. False-negative test results can lead to lack of medical or neurologic surveillance.

The time frame for outcome measures varies from short-term surveillance of asymptomatic individuals for the development of signs or symptoms of CADASIL to long-term development of the disease.

Study Selection Criteria

For the evaluation of clinical validity of the tests, studies that met the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores)
- Included a suitable reference standard
- Patient/sample clinical characteristics were described
- Patient/sample selection criteria were described
- Included a validation cohort separate from development cohort

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

See the clinical validity discussion in the *Testing Individuals With Suspected CADASIL Syndrome section.*

Testing Strategy

For testing in asymptomatic individuals with family members who have CADASIL whose genetic status is unknown:

- Perform targeted sequencing and analysis of specific *NOTCH3* exons (e.g., exon 4 only, exons 2- 6) OR
- Perform general testing of *NOTCH3* exons (e.g., exons 2-24 or all 33 exons).

This testing strategy to perform sequence analysis of multiple *NOTCH3* exons to identify pathogenic variants is a general approach for genetic testing for *NOTCH3*.

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, more effective therapy, or avoid unnecessary therapy or testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

No randomized trials were identified addressing outcomes managed with CADASIL testing.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.
Genetic testing of asymptomatic individuals with family members who have CADASIL may have clinical utility by:

- Confirming or excluding the need for surveillance based on the presence or absence of a *NOTCH3* pathogenic variant.
- Informing the reproductive decision-making process in preimplantation testing, prenatal (in utero) testing, or altering reproductive planning decisions when a known *NOTCH3* pathogenic variant is present in a parent. Preimplantation testing is addressed elsewhere (evidence review 4.02.05).

Section Summary: Clinically Useful
Similar to the case where there is a known family variant associated with CADASIL, direct evidence for the clinical utility of genetic testing of asymptomatic relatives of individuals with CADASIL is lacking. However, a chain of evidence can be developed to support the clinical utility of testing, as outlined above.

Supplemental Information
The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Clinical Input From Physician Specialty Societies and Academic Medical Centers
2013 Input
While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

In response to requests, input was received from 1 physician specialty society and 3 academic medical centers while this policy was under review in 2013. Most reviewers disagreed with the statement that genetic testing to confirm the diagnosis of CADASIL was investigational. All reviewers expressed support for testing to confirm the diagnosis in select patients, particularly when the diagnosis of CADASIL is inconclusive, and when the pretest likelihood of CADASIL is moderate to high. In addition to consensus among reviewers, contextual factors in support of medical necessity are present for this indication, ie, there is a highly suggestive chain of evidence; high-quality trials are unlikely to be performed, and there is a potential for reducing harms by avoiding additional testing and avoiding anticoagulants and antiplatelet agents when the disease is present.

Reviewers also agreed with the recommendation that testing is medically necessary for a first- or second-degree relative when there is a known pathogenic variant (familial variant) in the family. For this indication, contextual factors in support of medical necessity were not present. High-quality trials are unlikely to be performed.

2020 Input
Clinical consultation was obtained in 2020 indicating that skin biopsy prior to NOTCH3 testing is not necessary; skin biopsy should be reserved for patients where NOTCH3 genetic testing is inconclusive (e.g. variants of uncertain significance).

Practice Guidelines and Position Statements
Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

No guidelines or position statements with US representation or that were informed by a systematic review were identified.

U.S. Preventive Services Task Force Recommendations
Not applicable.

Medicare National Coverage
There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials

One currently ongoing trial that might influence this review is listed in Table 4.

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT04310098	Cerebral Autosomal Dominant Arteriopathy With Subcortical Infarcts and Leukoencephalopathy Registry Study	1000	Mar 2049

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Documentation for Clinical Review

Please provide the following documentation:

- History and physical and/or consultation notes including:
  o Specific clinical signs and symptoms
  o Family history for CADASIL, including Family relationship(s): (maternal or paternal), (family member [e.g., sibling, aunt, grandparent]), (living or deceased) (if applicable)
  ○ Imaging results (e.g., MRI) if applicable
  ○ Reason for Request
  ○ Laboratory testing/other specialized testing (e.g., skin biopsy)

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy.

The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.

Type	Code	Description
CPT®	81406	Molecular pathology procedure level 7
HCPCS	None	

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action	Reason
09/27/2013	BCBSA Medical Policy adoption	Medical Policy Committee
03/14/2014	Title changed from Notch3 Genotyping for Diagnosis of CADASIL	Medical Policy Committee
04/09/2014	Administrative Update	Administrative Review
06/30/2015	Coding update	Administrative Review
01/01/2017	Policy revision without position change	Medical Policy Committee
12/01/2017	Policy revision with position change	Medical Policy Committee
06/01/2018	Policy revision without position change	Medical Policy Committee
07/01/2019	Policy revision without position change	Medical Policy Committee
06/01/2023	Policy reactivated. Previously archived from 06/01/2020 to 05/31/2023.	Medical Policy Committee

Definitions of Decision Determinations

Medically Necessary: Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the Member's illness, injury, or disease.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements and Feedback (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

We are interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California or Blue Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration.

For utilization and medical policy feedback, please send comments to: MedPolicy@blueshieldca.com

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.

Appendix A

POLICY STATEMENT	
BEFORE	**AFTER** **Blue font: Verbiage Changes/Additions**
Reactivated Policy **Policy Statement:** N/A	**Genetic Testing of CADASIL Syndrome 2.04.75** **Policy Statement:** I. Genetic testing for a NOTCH3 variant to confirm the diagnosis of cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) syndrome in an individual may be considered **medically necessary** under the following conditions: A. Clinical signs, symptoms, and imaging results are consistent with CADASIL, indicating that the pretest probability of CADASIL is at least in the moderate-to-high range (see the Policy Guidelines section); and B. The diagnosis of CADASIL is inconclusive following alternative methods of testing, including magnetic resonance imaging. For individuals who are asymptomatic with a family member with a diagnosis of CADASIL syndrome: II. If there is a family member (first- and second-degree relative) with a known variant, targeted genetic testing of the known *NOTCH3* familial variant may be considered **medically necessary**. III. If the family member's genetic status is unknown, genetic testing of *NOTCH3* (see Policy Guidelines section) may be considered **medically necessary**. IV. Genetic testing for a *NOTCH3* variant to confirm the diagnosis of CADASIL syndrome in all other situations is considered **investigational**.