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## Medical Policy



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**\*Current Policy Effective Date: 11/1/22**  
(See policy history boxes for previous effective dates)

### **Title: Genetic Testing of CADASIL Syndrome**

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#### **Description/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 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 (Table 1):

**Table 1. Differential Diagnosis of CADASIL**

<b>Acquired Disorders</b>	<b>Inherited Disorders</b>
<ul style="list-style-type: none"><li>• Sporadic SVD with or without hypertension as the main risk factor</li><li>• Multiple sclerosis</li><li>• Primary angiitis of the central nervous system</li></ul>	<ul style="list-style-type: none"><li>• Fabry disease</li><li>• Cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy</li><li>• Familial SVD caused by heterozygous variants in the <i>HTRA1</i> gene</li><li>• Some forms of leukodystrophy</li></ul>

CADASIL: cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; 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 versus 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 selected 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 (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 the NOTCH3 protein in the walls of small blood vessels.<sup>1</sup> 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.<sup>2</sup>
- Detection of granular osmiophilic material in the same skin biopsy sample by electron microscopy. The major component of GOM is the ectodomain of the *NOTCH3* gene product.<sup>3</sup> Granular osmiophilic material accumulates directly in vascular smooth muscle cells and, when present, is considered a hallmark of the disease.<sup>4</sup> However, granular osmiophilic material 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%.<sup>5-7</sup>
- Examination of brain tissue for the presence of granular osmiophilic material was originally described as limited to brain blood vessels.<sup>8</sup> Examination of brain biopsy or autopsy after death was an early criterion standard for diagnosis. In some cases, peripheral staining for granular osmiophilic material 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 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.<sup>9</sup>

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 (EGF)-like repeats, traverses the membrane once, and has an intracellular domain required for signal transduction.<sup>10</sup>

Variants in the *NOTCH3* gene have been differentiated into those that are 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.<sup>10,11</sup> 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).<sup>12</sup> 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.<sup>13</sup>

The probability that CADASIL is present is an individualized assessment depends on numerous factors such as family history, symptoms, imaging results, and other specialized testing (eg, skin biopsy). Pescini et al (2012) attempted to identify clinical factors that increase the likelihood of a pathologic mutation being present, with increasing likelihood with the presence of 1 or several factors, including 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.<sup>14</sup>

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## **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* mutation 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 (FDA) has chosen not to require any regulatory review of this test.

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## **Medical Policy Statement**

Genetic testing of CADASIL syndrome is considered established in select patient populations who meet clinical criteria. This testing may be a useful diagnostic option when indicated.

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## **Inclusionary and Exclusionary Guidelines (Clinically based guidelines that may support individual consideration and pre-authorization decisions)**

### **Inclusions**

- Genetic testing of *NOTCH3* to confirm a diagnosis of CADASIL syndrome is considered established when clinical signs, symptoms, and imaging results (MRI) are suggestive of CADASIL syndrome.
- Genetic testing of (*NOTCH3*) of an asymptomatic individual who has a first- or second-degree relative with CADASIL syndrome is established when:
  - There is a family member (first- or second-degree) with a known variant, targeted genetic testing of the known *NOTCH3* familial variant is considered established.
  - The family member's genetic status is unknown, genetic testing of *NOTCH3* is considered established.

*Note:* First-degree relative: parent, full-sibling, child

Second-degree relative: grandparent, grandchild, aunt, uncle, nephew, niece, half-sibling

**Exclusions:**

- All other situations not addressed in the inclusions above are excluded.

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**CPT/HCPCS Level II Codes** *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)*

**Established codes:**

81406\*

\*Code 81406 includes: *NOTCH3* (notch 3) (eg, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy [CADASIL]), targeted sequence analysis (eg, exons 1-23).

**Other codes (investigational, not medically necessary, etc.):**

N/A

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**Rationale**

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.

**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 question addressed in this evidence review is: 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 diagnosis of CADASIL are also potential beneficial outcomes.

Potential harmful outcomes are those resulting from a false-positive or false-negative test results. False-positive test results can lead to 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 outcomes measures varies from 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 patients 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 (eg, exon 4 only, exons 2–6) OR
- Perform general testing of *NOTCH3* exons (eg, exons 2-24 or all 33 exons)
- If no *NOTCH3* pathogenic variant is identified, 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	<i>NOTCH3</i> Exons Sequenced	Results	
<i>Part 1: Diagnostic Studies</i>			<i>Diagnostic Yield</i>	<i>Specificity</i>
Mosca et al (2011) <sup>9</sup>	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) <sup>15</sup>	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) <sup>7</sup>	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) <sup>8</sup>	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 <i>NOTCH3</i> variant (R544C; exon11). 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) <sup>16</sup>	Patients: 47 subjects from 34 families (Chinese) diagnosed with suspected CADASIL Diagnosis/selection: MRI abnormalities and presence of >1 typical symptom (eg,	Testing method per Joutel et al(1997) <sup>17</sup> : exons 3 and 4 screened first; if no variants	Patients: 6 knownfamilial variants identified in 8 families and 2 novel pathogenic variants identified in 2 families (exons 3 and 4),and 1	NR

	migraine, stroke, cognitive deficits, psychiatric symptoms) or presence of atypical symptoms with positive family history	detected, remaining exons analyzed	VUS identified in 1 family (exon 2). Overall <i>NOTCH3</i> pathogenic variant prevalence: 29.4%	
Abramycheva et al (2015) <sup>18</sup>	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) <sup>19</sup>	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
<b>Part 2: Clinical Validity Studies</b>			<b>Sensitivity</b>	<b>Specificity</b>
Peters et al (2005) <sup>20</sup>	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) <sup>21</sup>	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) <sup>22</sup>	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) <sup>17</sup>	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 diagnosis of CADASIL cannot be confirmed by other methods (clinical presentation, magnetic resonance imaging [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 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 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 a patient with clinical signs and symptoms of CADASIL is sufficient to confirm the diagnosis with a high degree of certainty. The clinical sensitivity is also relatively high, in the range of 90% to 100% for patients with a clinical diagnosis of CADASIL. This indicates that a negative test reduces the likelihood that CADASIL is present. However, because false-negative tests do occur, a negative test is less definitive in ruling out CADASIL. Whether a negative test is sufficient to rule out CADASIL depends on the pretest likelihood that CADASIL is present.

Pescini et al (2012) attempted to identify clinical factors that increase the likelihood of a pathologic mutation being present and therefore might be helpful in selecting patients for testing.<sup>14</sup> 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 3 summarizes the pooled frequency of clinical and radiologic features.

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

Features	No. With <i>NOTCH3</i> Variant	Percent With <i>NOTCH3</i> Variant	Points
<i>Clinical</i>			
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
<i>Radiologic</i>			
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)<sup>14</sup>

LE: leukoencephalopathy.

Using these frequencies, a preliminary scoring system was developed and tested in 61 patients with *NOTCH3* pathogenic 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 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 patients 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.<sup>3,10</sup> 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.<sup>23</sup> The trial showed donepezil hydrochloride had no effect on the primary cognitive end point, 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).<sup>24</sup> 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;  $p=.001$ ). During the treatment period, none of the subjects developed new neurologic symptoms, and the original symptoms in these patients (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.<sup>25</sup> 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 ( $p=.5$ ) or cerebral vasoreactivity, as assessed by hypercapnia ( $p=.5$ ) or intravenous L-arginine ( $p=.4$ ) in the overall cohort. However, an inverse correlation was found between vasoreactivity at baseline and changes of both CO<sub>2</sub>- and L-arginine-induced vasomotor response (both  $p<.05$ ). 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 the results of a randomized, double-blinded trial comparing sapropterin with placebo for adults with CADASIL.<sup>26</sup> 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 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 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 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 (see medical policy, *Genetic Testing - Preimplantation*).

### **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 question addressed in this evidence review is: 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 patients 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 results. 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 eligibility criteria described in the first indication were considered.

### **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 here 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 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 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 (see medical policy, *Genetic Testing-Preimplantation*).

Genetic counseling is recommended to discuss the impact of positive or negative test results, followed by molecular testing if desired.<sup>4</sup> 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 patients with CADASIL is lacking. No specific clinical treatment for CADASIL has established efficacy. However, a chain of evidence can be developed to 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, to predict development of disease, to determine the need for surveillance and to aid in reproductive planning.

The question addressed in this evidence review is: 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 patients 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 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 results. False-positive test results can lead to unnecessary medical or neurological surveillance of asymptomatic individuals. False-negative test results can lead to lack of medical or neurological surveillance.

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

### **Study Selection Criteria**

For the evaluation of clinical validity of the tests, studies that met the eligibility criteria described in the first indication were considered.

### **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 (eg, exon 4 only, exons 2–6) OR
- Perform general testing of *NOTCH3* exons (eg, 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 (see Policy, *Genetic Testing-Preimplantation*).

## Section Summary: Clinical Utility

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 patients with CADASIL is lacking. However, a chain of evidence can be developed to support the clinical utility of testing, as outlined above.

## Summary of Evidence

For individuals with suspected CADASIL syndrome who receive *NOTCH3* genetic testing, the evidence includes case reports, case series, and genotype-phenotype correlation studies evaluating the clinical validity and genetic testing yield for *NOTCH3*. Relevant outcomes are overall survival, test accuracy and validity, changes in reproductive decision making, change in disease status, and morbid events. The clinical validity studies have 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 of 90% to 100%. Limited data on specificity derives from testing small numbers of healthy controls, and no false-positive *NOTCH3* pathogenic variants have been reported in these populations. The diagnostic yield studies have reported a variable yield, ranging from 10% to 54%. These lower numbers likely reflect testing in heterogeneous populations that include patients with other disorders. No direct evidence was identified demonstrating outcome improvements associated with genetic testing for CADASIL. However, a chain of evidence can be constructed to demonstrate that identification of a *NOTCH3* pathogenic variant establishes the diagnosis of CADASIL without the need for a skin biopsy and reduces the need for other diagnostic tests used to exclude other conditions in a differential diagnosis. The evidence is sufficient to determine that the technology results in improvement in the net health outcome.

For individuals who are asymptomatic with family members who have CADASIL syndrome who receive targeted genetic testing for a known *NOTCH3* familial variant, 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 asymptomatic 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 disease onset. A chain of evidence can be constructed to demonstrate that identification of a *NOTCH3* familial 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. The evidence is sufficient to determine that the technology results in improvement in the net health outcome.

For individuals who are asymptomatic with family members who have CADASIL syndrome whose genetic status is unknown who receive *NOTCH3* 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 asymptomatic family members of an individual with known CADASIL whose genetic status is unknown, knowledge of the presence of a *NOTCH3* pathogenic 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 disease onset. 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. The evidence is sufficient to determine that the technology results in improvement in the net health outcome.

## **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 Received through Physician Specialty Societies and Academic Medical Centers**

**2013**

In response to requests made by the Blue Cross Blue Shield Association, input was received from 1 physician specialty society and 3 academic medical centers while their policy was under review in 2013. Most reviewers disagreed with 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 pathologic 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**

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 (eg, 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.

**Ongoing and Unpublished Clinical Trials**

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

**Table 4. Summary of Key Trials**

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



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## Government Regulations

### National:

There is no national coverage determination addressing genetic testing for CADASIL syndrome.

### Local:

There is no active local coverage determination or article that addresses genetic testing of CADASIL syndrome, or genetic testing of *NOTCH3*.

Palmetto GBA MoIDX has no LCD regarding *NOTCH3* or CADASIL.

There is a retired Wisconsin Physicians Service Insurance Corporation Article, MoIDX: Excluded Test List (A55247), which lists 81406 for *NOTCH3*, tsa.

*(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)*

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## Related Policies

Genetic Testing – Preimplantation  
Genetic Testing and Counseling

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*The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through 6/30/22, the date the research was completed.*

### Joint BCBSM/BCN Medical Policy History

<b>Policy Effective Date</b>	<b>BCBSM Signature Date</b>	<b>BCN Signature Date</b>	<b>Comments</b>
5/1/12	2/21/12	2/21/12	Joint policy established
7/1/13	4/16/13	4/22/13	Routine maintenance - Replaced unlisted procedure code with new CPT code 81406 (effective 1/1/13). Updated references.
11/1/14	8/19/14	8/19/14	Policy status changed from experimental/investigational to established.  Title changed from "Genetic Testing - NOTCH3 Genotyping for Diagnosis of CADASIL" to "Genetic Testing of CADASIL Syndrome."
7/1/16	4/19/16	4/19/16	Routine maintenance
7/1/17	6/7/17	6/6/17	Routine maintenance. Updated inclusions regarding testing of family members.
5/1/18	2/20/18	2/20/18	Routine maintenance. Policy status to EST. Updated inclusions: incorporation of CADASIL scale; genetic testing allowed if highly suggestive based on scale and to avoid skin biopsy; exclusions updated. References updated. Updated Medicare information.
5/1/19	2/19/19		Routine maintenance
5/1/20	2/18/20		Routine maintenance
5/1/21	4/1/21		Routine maintenance. Inclusions/exclusions: reference to skin biopsy deleted. Ref 28 added. Inclusions edited.
11/1/21	8/17/21		Routine maintenance
11/1/22	8/16/22		Routine maintenance (ls)

Next Review Date: 3rd Qtr, 2023

**BLUE CARE NETWORK BENEFIT COVERAGE  
POLICY: GENETIC TESTING OF CADASIL SYNDROME**

**I. Coverage Determination:**

<b>Commercial HMO (includes Self-Funded groups unless otherwise specified)</b>	Covered; criteria apply
<b>BCNA (Medicare Advantage)</b>	See Government Regulations section.
<b>BCN65 (Medicare Complementary)</b>	Coinsurance covered if primary Medicare covers the service.

**II. Administrative Guidelines:**

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.