Medicare Policy – 12.04.75

Genetic Testing of CADASIL Syndrome

BCBSA Ref. Policy: 2.04.75
Effective Date: July 1, 2017
Last Revised: June 13, 2017
Replaces: 2.04.75

Related Medical Policies:
12.04.305 Preimplantation Genetic Testing in Embryos

Policy Coverage Criteria

Introduction

CADASIL syndrome is a condition that affects the small blood vessels, especially in the brain. It leads to stroke, other brain injury (especially in a deep part of the brain called white matter), and dementia. The term CADASIL comes from the formal name of the syndrome: cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy. In CADASIL, the blood vessel walls within the brain get thicker. Damaged blood vessels restrict the blood flow, which cause migraine headaches and eventually lead to strokes. Repeated strokes cause damage in the brain, resulting in dementia. CADASIL is caused by a genetic change in the NOTCH3 gene. This gene is involved with how blood vessels are formed and how they work. This genetic change can be passed from parent to child. This medical policy describes when genetic testing for CADASIL syndrome may be considered medically necessary.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.
Testing Intent

Medicating Necessity

Confirm diagnosis of CADASIL of the individual with signs, symptoms, etc. Genetic testing of NOTCH3 to confirm the diagnosis of CADASIL syndrome may be considered medically necessary under the following conditions:

- Clinical signs, symptoms, skin biopsy and imaging results are consistent with CADASIL, indicating that the pretest probability of CADASIL is at least in the moderate-to-high range (see Related Information for screening tool).

AND

- The diagnosis of CADASIL is inconclusive following alternative methods of testing, including skin biopsy and magnetic resonance imaging.

Confirm diagnosis of CADASIL in asymptomatic individuals with a diagnosed family member Genetic testing of NOTCH3 for asymptomatic individuals who have a family member with a diagnosis of CADASIL syndrome may be considered medically necessary:

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

- If the affected family member’s genetic status is unknown.

Investigational

Genetic testing of NOTCH3 to confirm the diagnosis of CADASIL syndrome in all other situations is considered investigational.

Coding

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>CPT</td>
<td></td>
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<tr>
<td>81406</td>
<td>Molecular pathology procedure, Level 7 (e.g., analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons, cytogenomic array analysis for neoplasia). This CPT code includes: NOTCH3 (notch 3) (e.g., cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy [CADASIL]), targeted sequence analysis (e.g., exons 1-23)</td>
</tr>
<tr>
<td>Code</td>
<td>Description</td>
</tr>
<tr>
<td>---------</td>
<td>----------------------------------------------------------</td>
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<tr>
<td>81479</td>
<td>Unlisted molecular pathology procedure</td>
</tr>
<tr>
<td>81599</td>
<td>Unlisted multianalyte assay with algorithmic analysis</td>
</tr>
</tbody>
</table>

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## Related Information

### Definition of Terms

**Degrees of relationship:** Close blood relatives on the same side of the family (mother or father) include:

- First-degree relatives are parents, siblings, and children.
- Second-degree relatives are grandparents, aunts, uncles, nieces, nephews, grandchildren, and half-siblings.
- Third-degree relatives are great-grandparents, great-aunts, great-uncles, great-grandchildren, and first cousins.


**Neurogenic locus notch homolog protein 3 (NOTCH3) gene:** The protein that this gene codes for is thought to be essential for the maintenance of smooth muscle cells that surround small blood vessels, including those that supply blood to the brain.

### Genetic Counseling

Genetic counseling is primarily aimed at patients who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing,
including the possible impact of the information on the individual’s family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

Clinical and Radiologic Features: NOTCH3 Variants

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

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

Pescini et al (2012) attempted to identify clinical factors that increase the likelihood of a pathogenic variant being present. Table 1 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 1. Pooled Frequency of Clinical and Radiologic Features (Pescini et al, 2012)

<table>
<thead>
<tr>
<th>Features</th>
<th>Number with NOTCH3 variant</th>
<th>Percent with NOTCH3 variant</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical features</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Migraine</td>
<td>239/463</td>
<td>52%</td>
<td>1</td>
</tr>
<tr>
<td>Migraine with aura</td>
<td>65/85</td>
<td>76%</td>
<td>3</td>
</tr>
<tr>
<td>Transient ischemic attack /stroke</td>
<td>380/526</td>
<td>72%</td>
<td>1 (2 if &lt;50 y.o.)</td>
</tr>
<tr>
<td>Psychiatric disturbance</td>
<td>106/380</td>
<td>28%</td>
<td>1</td>
</tr>
<tr>
<td>Cognitive decline</td>
<td>188/434</td>
<td>43%</td>
<td>3</td>
</tr>
<tr>
<td><strong>Radiologic features</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukoencephalopathy (LE)</td>
<td>277/277</td>
<td>100%</td>
<td>3</td>
</tr>
<tr>
<td>LE extended to temporal pole</td>
<td>174/235</td>
<td>74%</td>
<td>1</td>
</tr>
</tbody>
</table>
### Features

<table>
<thead>
<tr>
<th>Features</th>
<th>Number with NOTCH3 variant</th>
<th>Percent with NOTCH3 variant</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>LE extended to external capsule</td>
<td>228/303</td>
<td>75%</td>
<td>5</td>
</tr>
<tr>
<td>Subcortical infarcts</td>
<td>210/254</td>
<td>83%</td>
<td>2</td>
</tr>
</tbody>
</table>

LE leukoencephalopathy.

### Evidence Review

#### 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 for patients with suspected CADASIL and their family members to determine if pathogenic variants exist in the NOTCH3 gene.

#### Background

**CADASIL**

CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy) 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 (see Table 2).
Table 2. Differential Diagnosis of CADASIL

<table>
<thead>
<tr>
<th>Acquired Disorders</th>
<th>Inherited Disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sporadic SVD with or without hypertension as the main risk factor</td>
<td>Fabry disease</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>Cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy</td>
</tr>
<tr>
<td>Primary angiitis of the central nervous system</td>
<td>Familial SVD caused by heterozygous variants in the HTRA1 gene</td>
</tr>
<tr>
<td></td>
<td>Some forms of leukodystrophy</td>
</tr>
</tbody>
</table>

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 (MRI) 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. 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 (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.\(^1\)
- Detection of granular osmiophilic material (GOM) in a skin biopsy sample using electron microscopy. The major component of GOM is the ectodomain of the \( NOTCH3 \) gene product.\(^2\) GOM accumulates directly in vascular smooth muscle cells and, when present, is considered a hallmark of the disease.\(^4\) However, GOM may not be present in all biopsy samples. Sensitivity has been reported as low as 45% and 57%, but specificity is generally near or at 100%.\(^5\)\(^-\)\(^7\)
- Examination of brain tissue for the presence of GOM 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 variants lead to loss or gain of a cysteine residue that could lead to increased reactivity of the NOTCH3 protein, resulting in ligand-binding and toxic effects.\(^9\)

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

Variants in the NOTCH3 gene have been differentiated into those that are causative of the CADASIL syndrome and those that are of uncertain significance. Causative variants affect conserved cysteine residues within 34 epidermal growth factor (EGF)-like repeat domains in the extracellular portion of the NOTCH3 protein.\(^10,11\) More than 150 causative variants have been reported in at least 500 pedigrees. NOTCH3 has 33 exons, but all CADASIL variants reported to date have occurred in exons 2-24, which encode the 34 EGF-like repeats, with strong clustering in exons 3 and 4, which encode EGFR 2-5. More than 40% of variants in > 70% of families occur in these exons.\(^12\) Some studies indicate that the clinical variability in CADASIL presentation, particularly with regard to the development of white matter hyper-intensities on MRI, 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 is an individualized assessment, depending on numerous factors such as family history, symptoms, imaging results, and other specialized testing such as skin biopsy. In 2013, Pescini et al\(^14\) published a study that attempted to identify clinical factors that increase the likelihood of a pathologic mutation being present, with increasing likelihood with the presence of one or several factors, including migraine, migraine with aura, transient ischemic attack/stroke, psychiatric disturbance, cognitive decline, leukencephalopathy (with greater risk for leukencephalopathy extending to the temporal pole or external capsule), and subcortical infarcts.\(^14\)
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. It also reduces the need for other diagnostic tests to exclude other conditions in a differential diagnosis. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

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 symptoms, aids in reproductive planning, and helps determine the likelihood of having an affected offspring. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For asymptomatic individuals with family members who have CADASIL syndrome and whose genetic status is unknown, the evidence for doing NOTCH3 genetic testing is limited. Relevant outcomes are overall survival, test accuracy and validity, changes in reproductive decision making, change in disease status, and morbid events. 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 a meaningful improvement in the net health outcome.

Ongoing and Unpublished Clinical Trials

A search of ClinicalTrials.gov in March 2017 did not identify any ongoing or unpublished trials that would likely influence this review.

Clinical Input Received from Physician Specialty Societies and Academic Medical Centers

While the various physician specialty societies and academic medical centers may provide appropriate reviewers who collaborate with and make recommendations during this process, 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 one 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 was investigational to confirm the diagnosis of CADASIL. All reviewers expressed support for testing to confirm the diagnosis in selected patients, particularly when the diagnosis of CADASIL is inconclusive following other diagnostic testing, and when the pre-test likelihood of CADASIL being present is moderate to high. In addition to consensus among the reviewers, contextual factors in support of medical necessity are present for this indication, ie, there is a highly suggestive indirect 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 mutation in the family. For this indication, contextual factors in support of medical necessity were not present. High-quality trials are unlikely to be performed, but other contextual criteria were lacking.
Practice Guidelines and Position Statements

European Federation of Neurological Societies (EFNS)

The EFNS’s 2010 guideline on the molecular diagnosis of channelopathies, epilepsies, migraine, stroke, and dementias notes that most NOTCH3 pathogenic variants occur within exons 3 and 4 and suggests direct sequencing of these 2 exons if clinical suspicion is high.28

Medicare National Coverage

There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

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 Amendments (CLIA). Genetic testing of NOTCH3 is available under the auspices of CLIA. Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

References


10. Lesnik Oberstein SAJ, Boon EMJ, Dichgans M. CADASIL. GeneReviews. 2016. PMID 20301673


History

<table>
<thead>
<tr>
<th>Date</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>10/11/11</td>
<td>New policy; add to Pathology/Laboratory section. Policy created with literature search through September 2011, considered investigational.</td>
</tr>
<tr>
<td>05/24/12</td>
<td>Policy renumbered to 12.04.75 (previously 2.04.75) and reassigned to new Genetic Testing category.</td>
</tr>
<tr>
<td>11/27/12</td>
<td>Replace policy – Rationale section revised based on a literature review through August 2012. Reference 8 added; others renumbered or removed. Policy statement unchanged. CPT codes 83891-83912 will be deleted effective 12/31/12 and replaced by 81200-81479, effective 1/1/13.</td>
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<tr>
<td>01/14/13</td>
<td>Coding update. CPT codes 83890 – 83913 deleted as of 12/31/12; CPT codes 81200 – 81479 and 81599, effective 1/1/13, are added to the policy.</td>
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<tr>
<td>05/14/13</td>
<td>Update Related Policies. Add 12.04.91.</td>
</tr>
<tr>
<td>12/09/13</td>
<td>Replace policy. Removed Notch3 Genotyping from policy title to be more inclusive of all genetic testing for CADASIL syndrome. Policy statement changed from Investigational to Medically Necessary for genetic testing to confirm the diagnosis when other methods are inconclusive. Rationale updated with literature review through September 2013 and results of BC clinical vetting. Reference 18 added; others renumbered or removed. Policy statements changed as noted. CPT code range 81200 – 81479 removed; replaced with specific code 81406. CPT codes 83891-83912 removed; these are now deleted.</td>
</tr>
<tr>
<td>12/17/14</td>
<td>Annual Review. Policy updated with literature review through September 6, 2014. References 14, 16, and 24 added. Policy statement unchanged. ICD-9 and ICD-10 diagnosis and procedure codes removed; these do not relate to policy adjudication.</td>
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</table>
| 07/01/17 | Annual Review, approved June 13, 2017. Policy moved into new format. Policy updated with literature review through February 23, 2017; reference 20 added. The policy is
revised with updated genetics nomenclature. "Mutations" changed to "variants" in policy statements. Medically necessary statements added for testing in asymptomatic and presymptomatic family members of individuals with CADASIL.

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