Medical Policy
Genetic Testing of CADASIL Syndrome

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Policy Number: 357
BCBSA Reference Number: 2.04.75
NCD/LCD: Local Coverage Determination (LCD): Molecular Pathology Procedures (L35000)

Related Policies
Preimplantation Genetic Testing, #088

Policy
Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity

Genetic testing of NOTCH3 to confirm the diagnosis of CADASIL syndrome in a patient 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; and
- The diagnosis of CADASIL is inconclusive following alternate methods of testing, including skin biopsy and magnetic resonance imaging.

For individuals who are asymptomatic with a family member with a diagnosis of CADASIL syndrome:
- 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.
- If the family member’s genetic status is unknown, genetic testing of NOTCH3 may be considered MEDICALLY NECESSARY.

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

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.

Medicare HMO BlueSM and Medicare PPO BlueSM Members

Medical necessity criteria and coding guidance for Medicare Advantage members living in Massachusetts can be found through the link below.
Local Coverage Determination (LCD): Molecular Pathology Procedures (L35000)

For medical necessity criteria and coding guidance for Medicare Advantage members living outside of Massachusetts, please see the Centers for Medicare and Medicaid Services website for information regarding your specific jurisdiction at https://www.cms.gov.

Prior Authorization Information
Pre-service approval is required for all inpatient services for all products. See below for situations where prior authorization may be required or may not be required for outpatient services. Yes indicates that prior authorization is required. No indicates that prior authorization is not required. N/A indicates that this service is primarily performed in an inpatient setting.

<table>
<thead>
<tr>
<th>Service Type</th>
<th>Commercial Managed Care (HMO and POS)</th>
<th>Commercial PPO and Indemnity</th>
<th>Medicare HMO Blue℠</th>
<th>Medicare PPO Blue℠</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outpatient</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

CPT Codes / HCPCS Codes / ICD Codes
Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member’s contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member.

Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.

The following codes are included below for informational purposes only; this is not an all-inclusive list.

The above medical necessity criteria MUST be met for the following codes to be covered for Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity:

<table>
<thead>
<tr>
<th>CPT codes:</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>81406</td>
<td>Molecular pathology procedure, Level 7 (eg, analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons, cytogenomic array analysis for neoplasia)</td>
</tr>
</tbody>
</table>

Description
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 1).
Table 1. 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 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 (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. \(^1\) 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 MRI parameters. \(^2\)

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

• Examination of brain tissue for the presence of GOM 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.\(^10\)\(^ \quad \)

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). Some studies have indicated that the clinical variability in CADASIL presentation, particularly with regard to the development of white matter hyperintensities on MRI, may be related to genetic modifiers outside the NOTCH3 locus, but the specific role of these modifiers is not well-delineated.

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). In 2012, Pescini et al published a study that attempted to identify clinical factors that increase the likelihood of a pathogenic variant 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.

Summary

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.

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 in the 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.

Given the high clinical sensitivity of genetic testing for CADASIL and the severity of the condition but no direct evidence on improvements in outcomes, clinical input was obtained. Input provided strong consensus that genetic testing for CADASIL syndrome is medically necessary when the diagnosis cannot be made on the basis of clinical presentation, magnetic resonance imaging, and skin biopsy results. In these cases, NOTCH3 testing can confirm the diagnosis of CADASIL with a high degree of certainty.

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 a meaningful 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 a meaningful improvement in the net health outcome.

Given the high clinical sensitivity of genetic testing for CADASIL and the severity of the condition but no direct evidence about improvements in outcomes, clinical input was obtained. Input provided strong consensus that testing is medically necessary for a first- or a second-degree relative, when there is a known pathogenic variant in the family. In these cases, NOTCH3 testing can predict the future development of CADASIL to permit earlier initiation of surveillance for symptoms and determine the likelihood of an affected offspring.

### Policy History

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
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<tr>
<td>1/2016</td>
<td>New references added from BCBSA National medical policy.</td>
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<tr>
<td>6/2015</td>
<td>Local Coverage Determination (LCD): Molecular Pathology Procedures (L34506) added.</td>
</tr>
<tr>
<td>12/2014</td>
<td>New references added from BCBSA National medical policy.</td>
</tr>
<tr>
<td>6/2014</td>
<td>Added “and” between the 2 bullets in the medical policy statement to clarify that both conditions should be met for the testing to be medically necessary.</td>
</tr>
<tr>
<td>1/2014</td>
<td>Revised description of 81406.</td>
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<tr>
<td>12/2012</td>
<td>Updated to add new CPT code 81406.</td>
</tr>
<tr>
<td>9/1/12</td>
<td>New medical policy describing ongoing non-coverage.</td>
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### Information Pertaining to All Blue Cross Blue Shield Medical Policies

Click on any of the following terms to access the relevant information:
- [Medical Policy Terms of Use](#)
- [Managed Care Guidelines](#)
- [Indemnity/PPO Guidelines](#)
- [Clinical Exception Process](#)
- [Medical Technology Assessment Guidelines](#)

### References

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