Genetic Testing for CADASIL Syndrome

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.

Background
Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is an uncommon, autosomal dominant disease. It is the most common cause of hereditary stroke and hereditary vascular dementia in adults. The CADASIL syndrome is an adult-onset, disabling systemic condition, characterized by migraine with aura, recurrent lacunar strokes, progressive cognitive impairment, and psychiatric disorders. The overall prevalence of the disease is unknown in the general population.

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

<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>SVD: small vessel disease.</td>
<td>• Some forms of leukodystrophy</td>
</tr>
</tbody>
</table>

The clinical presentation of CADASIL varies, the condition may be confused with multiple sclerosis, Alzheimer dementia, andBinswanger disease. The specific clinical signs and symptoms, along with family history and brain magnetic resonance imaging (MRI) findings, are extremely important in determining the diagnosis of 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 other tests are available for diagnosis:

- Immunohistochemistry assay of a skin biopsy sample, using a monoclonal antibody with reactivity against the extracellular domain of the NOTCH3 receptor. Positive immunostaining reveals the accumulation of NOTCH3 protein in the walls of small blood vessels.
- 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. GOM accumulates directly in vascular smooth muscle cells and, when present, is considered a hallmark of the disease. 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%.
Genetic Testing for CADASIL Syndrome

- Genetic testing, by direct sequencing of selected exons or of exons 2-24 of the NOTCH3 gene. Identification of a NOTCH3 pathogenic variant has been shown to establish diagnosis of CADASIL without the need for additional diagnostic testing (eg, skin biopsy).
- Examination of brain tissue for the presence of GOM was originally described as limited to brain vessels. 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 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 could lead to increased reactivity of the NOTCH3 protein, resulting in ligand-binding and toxic effects.

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

Variants in the NOTCH3 gene have been differentiated into those that are causative of the CADASIL syndrome (pathogenic variants) and those that are of uncertain significance. Pathogenic variants affect conserved cysteine residues within 34 epidermal growth factor (EGF)-like repeat domains in the extracellular portion of the NOTCH3 protein. 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 2–24, which encode the 34 EGF-like repeats, with strong clustering in exons 3 and 4, which encode EGFR 2–5 (>40% of variants in >70% of families occur in these exons). Some studies indicate 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, depending on numerous factors such as family history, symptoms, imaging results, and other specialized testing such as skin biopsy. In 2012, Pescini et al 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, leukoencephalopathy (with greater risk for leukoencephalopathy extending to the temporal pole or external capsule), and subcortical infarcts.

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

***Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.

Policy

BCBSNC will provide coverage for genetic testing for CADASIL syndrome when the medical criteria and guidelines shown below are met.
Genetic Testing for CADASIL Syndrome

Benefits Application
This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When Genetic Testing for CADASIL Syndrome is covered
Genetic testing to confirm the diagnosis of CADASIL syndrome may be considered medically necessary under the following conditions:

- Clinical signs, symptoms, and imaging results are consistent with CADASIL, indicating that the pre-test probability of CADASIL is at least in the moderate to high range.
- The diagnosis of CADASIL is inconclusive following alternate methods of testing, including MRI and skin biopsy.

For individuals who are asymptomatic with a family member diagnosed with CADASIL syndrome:
- If there is a family member (first- and second-degree relative) with a known familial variant.
- If the family member’s genetic status is unknown.

When Genetic Testing for CADASIL Syndrome is not covered
Genetic testing for CADASIL syndrome in all other situations is considered investigational.

Policy Guidelines
The evidence for the use of genetic testing in individuals with suspected CADASIL syndrome includes case reports, case series and genotype-phenotype correlation studies evaluating the clinical validity and yield of 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 demonstrate 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 is from testing small numbers of healthy controls, and no false-positive NOTCH3 pathogenic variants have been reported in these populations. The diagnostic yield studies report a variable diagnostic yield, ranging from 10% to 54%. These lower numbers likely reflect testing in heterogeneous populations that include patients with other disorders. However, no direct evidence was identified demonstrating outcome improvements associated with genetic testing for CADASIL. 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 the differential diagnosis. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

The evidence for the use of targeted genetic testing for known NOTCH3 familial variant, associated with CADASIL syndrome in individuals, who are asymptomatic with family members with CADASIL syndrome 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 (e.g., reproduction, employment). However, the impact of these lifestyle decisions on health outcomes is uncertain, and there are no interventions for asymptomatic individuals that are known to delay or prevent the onset of disease. A chain of evidence can be constructed to demonstrate that identification of a NOTCH3 familial variant predicts future development of CADASIL in 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 health outcome.
Genetic Testing for CADASIL Syndrome

The evidence for individuals who are asymptomatic with family members with CADASIL syndrome whose genetic status is unknown who receive genetic testing of NOTCH3, is limited. Relevant outcomes are overall survival, test accuracy and validity, changes in reproductive decision making, changes 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 the onset of disease. 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.

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable service codes: 81406, 81479, G0452

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources

For policy titled NOTCH3 Genotyping for Diagnosis of CADASIL


Medical Director review 8/2012

Specialty Matched Consultant Advisory Panel review 1/2013

For policy re-titled Genetic Testing for CADASIL Syndrome


Medical Director review 11/2013

Specialty Matched Consultant Advisory Panel review 1/2014

Genetic Testing for CADASIL Syndrome

Specialty Matched Consultant Advisory Panel review 4/2015
Medical Director review 4/2015
Medical Director review 3/2016
Medical Director review 4/2017

Policy Implementation/Update Information

For policy titled NOTCH3 Genotyping for Diagnosis of CADASIL

9/4/12 New policy developed. NOTCH3 testing for the diagnosis of CADASIL is considered investigational.
Medical Director review 8/2012. Notification given 9/4/2012 for effective date of 12/11/2012. (mco)

1/1/13 Deleted the following statement from the Billing/Coding section: “There is not a specific code for this
test; however, a series of molecular diagnostic codes such as 83891, 83898, 83904, 83909 and 83912
may be used.” Added 81406, 81479, G0452 to Billing/Coding section.

2/12/13 Specialty Matched Consultant Advisory Panel review 1/2013. No changes to Policy Statements. (mco)

For policy re-titled Genetic Testing for CADASIL Syndrome

12/10/13 Policy re-titled from “NOTCH3 Genotyping for CADASIL” to “Genetic Testing for CADASIL
Syndrome”. “When Covered” revised from “Not Applicable” to “Genetic testing to confirm the
diagnosis of CADASIL syndrome may be considered medically necessary under the following
conditions: 1)Clinical signs, symptoms, and imaging results are consistent with CADASIL,
indicating that the pre-test probability of CADSIL is at least in the moderate to high range. 2) The
diagnosis of CADASIL is inconclusive following alternate methods of testing, including MRI and
skin biopsy. “When not Covered” revised to state: “Genetic testing for CADASIL syndrome in all
other situations, including but not limited to testing of asymptomatic patients who have a first or second
degree relative with CADASIL, is considered investigational.” Policy Guidelines updated. References
updated. Medical Director review 11/2013. (mco)


11/11/14 References updated. Description section updated. Policy Guidelines section updated. No change to
Policy Statements. (td)

statements remain unchanged. (td)

12/30/15 Description section updated. Policy Guidelines section extensively revised. References updated. Policy
Statement remains unchanged. (td)

review 3/2016. (td)
Genetic Testing for CADASIL Syndrome


Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.