Genetic Testing for CADASIL Syndrome

Description of Procedure or Service

Mutations 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 mutations 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 clinical presentation of CADASIL is variable, and 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 determining the diagnosis of CADASIL. 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, by direct sequencing of selected exons or of exons 2-24 of the NOTCH3 gene.
- Examination of brain tissue for the presence of GOM. GOM was originally described as limited to brain vessels. Examination of brain biopsy or autopsy after death was an early gold standard for diagnosis. In some cases, peripheral staining for GOM has been absent even though positive results were seen in brain vessels.
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**NOTCH3 mutations**

Mutations in NOTCH3 have been identified as the underlying cause of CADASIL. In almost all cases, the mutations 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.

Mutations in the NOTCH3 gene have been differentiated into those that are causative of the CADASIL syndrome and those that are of uncertain significance. Causative mutations affect conserved cysteine residues within 34 epidermal growth factor (EGF)-like repeat domains in the extracellular portion of the NOTCH3 protein. More than 150 causative mutations have been reported in at least 500 pedigrees. NOTCH3 has 33 exons, but all CADASIL mutations 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 mutations 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 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 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.

**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.
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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.

When Genetic Testing for CADASIL Syndrome is not covered

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

The evidence for the use of genetic testing for mutations associated with CADASIL syndrome in individuals with suspected CADASIL syndrome includes retrospective and prospective studies evaluating the clinical validity and yield of NOTCH3 mutation testing. Relevant outcomes are overall survival, test accuracy and validity, other test performance measures, changes in reproductive decision making, change in disease status, and morbid events. The clinical validity studies demonstrate that a NOTCH3 mutation 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 mutations 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. There may be potential clinical utility for genetic testing to diagnose CADASIL in patients whose diagnosis cannot be confirmed by other methods (clinical presentation, magnetic resonance imaging [MRI] findings, skin biopsy). However, no direct evidence was identified demonstrating outcome improvements associated with genetic testing for CADASIL. A strong chain of indirect evidence cannot be constructed given the lack of evidence demonstrating the potential for changes in management that might occur following a diagnosis of CADASIL. The evidence is insufficient to determine the effects of the technology on health outcomes.

The evidence for the use of genetic testing for mutations 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, other test performance measures, 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 pathologic mutation 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. The evidence is insufficient to determine the effects of the technology on health outcomes.

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...
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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


Specialty Matched Consultant Advisory Panel review 4/2015

Medical Director review 4/2015


Medical Director review 3/2016

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
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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)


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


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.