Medical Policy
Genetic Testing of CADASIL Syndrome

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Policy Number: 357
BCBSA Reference Number: 2.04.75

Related Policies
- Preimplantation Genetic Testing, #088

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

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; and
- The diagnosis of CADASIL is inconclusive following alternate methods of testing, including MRI and skin biopsy.

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 INVESTIGATIONAL.

Prior Authorization Information
See below for situations where prior authorization may be required or may not be required.
Yes indicates that prior authorization is required.
No indicates that prior authorization is not required.

<table>
<thead>
<tr>
<th></th>
<th>Outpatient</th>
<th>Inpatient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Commercial Managed Care (HMO and POS)</td>
<td>No</td>
<td>n/a</td>
</tr>
<tr>
<td>Commercial PPO and Indemnity</td>
<td>No</td>
<td>n/a</td>
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<td>Medicare HMO BlueSM</td>
<td>No</td>
<td>n/a</td>
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<tr>
<td>Medicare PPO BlueSM</td>
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CPT Codes / HCPCS Codes / ICD-9 Codes
The following codes are included below for informational purposes. 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.

CPT Codes

<table>
<thead>
<tr>
<th>CPT codes:</th>
<th>Code Description</th>
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<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>
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Description

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. (1) Lesnick Oberstein et al. (2003) estimated sensitivity and specificity at 85-90% and 95-100%, 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)
- 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. (8) 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.

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. (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 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)

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. (10, 11) 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). (12)

Summary
Pathologic NOTCH mutations are found to be the cause of cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) in the majority of patients with the syndrome. The diagnostic accuracy of genetic testing cannot be determined with certainty due to the lack of a true gold standard for diagnosis of CADASIL. However, a high percentage of patients in whom CADASIL is diagnosed by clinical methods will have a pathologic mutation on genetic testing. Conversely, pathologic NOTCH mutations are not commonly found in unaffected individuals.

Genetic testing has clinical utility for a subset of patients with clinical signs and symptoms of CADASIL, but in whom the diagnosis cannot be made by other methods. The diagnosis of CADASIL can usually be confirmed by a combination of clinical presentation, magnetic resonance imaging (MRI) findings, and skin biopsy findings. In such cases, NOTCH3 testing is not necessary for diagnosis. In other cases, the diagnosis cannot be made on the basis of clinical presentation, MRI, and skin biopsy results. In these cases, NOTCH3 testing can confirm the diagnosis of CADASIL with a high degree of certainty. Based on the available evidence and results of clinical vetting, genetic testing may be considered medically necessary to confirm the diagnosis of CADASIL when there is uncertainty in the diagnosis following alternate testing methods, and there is at least a moderate to high likelihood that CADASIL is present based on clinical and imaging results.

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, for example in the areas of reproduction and 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. Therefore, genetic testing of asymptomatic relatives is considered investigational.

Policy History

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
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<tbody>
<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>
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<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>
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<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