The following Protocol contains medical necessity criteria that apply for this service. It is applicable to Medicare Advantage products unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. **Preauthorization is required.** Please note that payment for covered services is subject to eligibility and the limitations noted in the patient’s contract at the time the services are rendered.

**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, 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.

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 two 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)

**Regulatory Status**

As of August 2012, there are no manufactured test kits for detecting **NOTCH3** gene mutations; therefore, this testing has not been reviewed by the U.S. Food and Drug Administration (FDA). Rather, **NOTCH3** gene sequencing is a laboratory-developed test (LDT), offered by clinical laboratories licensed under Clinical Laboratory improvement Act (CLIA) for high-complexity testing.

**Related Protocol**

Preimplantation Genetic Testing

**Policy (Formerly Corporate Medical Guideline)**

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 (see Policy Guidelines).
- 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 considered **investigational**.

**Policy Guideline**

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.

Pescini et al published a study in 2013 that attempted to identify clinical factors that increase the likelihood of a pathologic mutation being present. (13) The following table 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, as this score resulted in a high sensitivity (96.7%) and a moderately high specificity (74.2%).
Features

<table>
<thead>
<tr>
<th>Features</th>
<th>Number With NOTCH3 Mutation</th>
<th>Percent With NOTCH3 Mutation</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 stroke/stroke</td>
<td>380/526</td>
<td>72%</td>
<td>1 (2 if &lt; 50 years old)</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>
<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>

Services that are the subject of a clinical trial do not meet our Technology Assessment Protocol criteria and are considered investigational. For explanation of experimental and investigational, please refer to the Technology Assessment Protocol.

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. Some of this Protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.

**References**

We are not responsible for the continuing viability of web site addresses that may be listed in any references below.


