Genetic Testing of CADASIL Syndrome

Policy Number: AHS – M2069 – Genetic Testing for CADASIL Syndrome

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Policy Description

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) (Tournier-Lasserve et al., 1993) is a genetic small vessel disease in which mutations in the Notch Receptor 3 (NOTCH3) gene located on chromosome 19 (Joutel et al., 1996) result in a clinical syndrome of adult-onset migraines (frequently with aura), progressive strokes, and cognitive decline in adults leading to severe functional impairment by the seventh decade of life (Opherk, Peters, Herzog, Luedtke, & Dichgans, 2004; Zhu & Nahas, 2016).

Related Policies

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<th>Policy Number</th>
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<td>AHS-M2145</td>
<td>General Genetic Testing, Germline Disorders</td>
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Indications and/or Limitations of Coverage

Application of coverage criteria is dependent upon an individual’s benefit coverage at the time of the request

1. Genetic testing to confirm the diagnosis of CADASIL syndrome MEETS COVERAGE CRITERIA under the following conditions:
   a. 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 for further details)
   b. Individuals in which the diagnosis of CADASIL is inconclusive following a combination of clinical presentation, magnetic resonance imaging (MRI) findings, and skin biopsy findings.

2. Genetic testing for CADASIL syndrome in asymptomatic individuals who have a first- or second-degree relative diagnosed with CADASIL syndrome MEETS COVERAGE CRITERIA.
The following does not meet coverage criteria due to a lack of available published scientific literature confirming that the test(s) is/are required and beneficial for the diagnosis and treatment of a patient’s illness.

3. Genetic testing for CADASIL syndrome in all other situations **DOES NOT MEET COVERAGE CRITERIA.**

**Scientific Background**

CADASIL is the most common hereditary small vessel disease and is characterized by granular osmiophilic material deposits surrounding blood vessels, a prominent thickening of the vessel wall by extracellular matrix accumulation, and a progressive loss of vascular smooth muscle cells (VSMCs) (Fernandez-Susavila et al., 2018; Ferrante, Cudrici, & Boehm, 2019; Monet-Lepretre et al., 2013). Small vessel diseases such as this are an important cause of stroke and vascular cognitive decline in adults (Chabriat, Joutel, Dichgans, Tournier-Lasserve, & Bousser, 2009). VSMC dysfunction may be caused by mutations in the NOTCH3 gene, leading to irregularities in VSMC proliferation, cell cycle affliction, senescence and cellular apoptosis (Dziewulska, Nycz, Rajczewska-Oleszkiewicz, Bojakowski, & Sulejczak, 2018).

Currently, no efficient treatment options to cure or prevent CADASIL syndrome are available (Hack, Rutten, & Lesnik Oberstein, 2019; NORD, 2019); however, recent studies have shown proof of concept for a novel application of exon skipping and are a first step towards the development of a rational therapeutic approach to treat up to 94% of CADASIL-causing mutations (Rutten, Dauwerse, Peters, et al., 2016). Further, neurofilament light chains have now been identified as a promising CADASIL biomarker and can be detected in the serum of affected patients (Ferrante et al., 2019).


CADASIL usually presents with one or more of the following: dementia, psychiatric disturbances, migraine, and recurrent strokes (Chabriat et al., 2009; Dichgans et al., 1998; M.Wang, 2018). Rarer symptoms including lumbaro, humpback, and Parkinson syndrome (Cao et al., 2019; Lim, Millar, & Zaman, 2019). Migraine with aura occurs in nearly one-half of CADASIL cases and is often the initial manifestation of the disease (Guey et al., 2016). Subcortical ischemic attacks begin at a mean age of 47 and present as lacunar syndromes (Adib-Samii, Brice, Martin, & Markus, 2010; Dichgans et al., 1998). Accumulation of lacunae, which impact executive performance and function independence, strongly correlate to clinical severity (Ling et al., 2017). Cognitive impairment associated with CADASIL is progressive; a profile of frontal lobe dysfunction, declarative memory impairment suggestive of a retrieval deficit, and relatively preserved language is often evident with this disease (Harris & Filley, 2001). A concurrent stepwise deterioration due to recurrent strokes is also common (Rutten & Lesnik Oberstein, 2016). Mood disturbances are reported in approximately 30% of individuals (Adib-Samii et al., 2010; Dichgans et al., 1998). Further, apathy, which may be independent of depression, is reported in 40% of individuals (Reyes et al., 2009).

Genetic linking of the disorder to chromosome 19 was first recognized in 1993, and the identification of the NOTCH3 gene from the CADASIL mapped region was later discovered in 1996 (Ping & Zhao, 2018). While CADASIL was originally diagnosed via neuroimaging techniques such as magnetic resonance imaging (MRI), the identification of the distinctive missense mutations in NOTCH3 has allowed genetic testing to debut as the current gold standard for CADASIL diagnostics (Rutten & Lesnik Oberstein, 2016). However, MRI testing for
the detection of cerebral white matter changes in the brain is still used to assist in CADASIL diagnoses; most often, MRI imaging is used as a diagnostic measure before symptoms present (Ferrante et al., 2019).

Missense mutations in the \textit{NOTCH3} gene typically lead to the gain or loss of a cysteine, therefore resulting in an unpaired number of cysteine residues in one of 34 highly conserved epidermal growth factor-like repeat (EGFr) domains (Joutel et al., 1996; Papakonstantinou et al., 2019; Rutten et al., 2014). This leads to an increased multimerization tendency of mutant \textit{NOTCH3} (Duering et al., 2011), toxic accumulation of the protein and extracellular matrix in disulfide cross-linked detergent-insoluble aggregates (Monet-Lepretre et al., 2013), altered neurovascular coupling (Huneau et al., 2018), and ultimately reduced cerebral blood flow, recurrent stroke, and vascular dementia (Rutten et al., 2016). However, certain \textit{NOTCH3} mutations do not present with a cysteine change; this type of non-cysteine mutation can cause a great loss of structure in the \textit{NOTCH3} protein (Papakonstantinou et al., 2019).

More than 200 \textit{NOTCH3} mutations have been reported since its original discovery in the development of CADASIL syndrome in 1996; some of these mutations result in a phenotypic change while some present as a silent mutation. A few prevalent \textit{NOTCH3} variants include the 34 identified in EGFr. EGFr 1–6 pathogenic variants are more common in the CADASIL population than EGFr 7–34 pathogenic variants; unfortunately, patients with EGFr 1–6 variants tend to present with more severe symptoms and phenotypes (Papakonstantinou et al., 2019; Rutten et al., 2018). These severe symptoms include stroke onset an average of 12 years earlier and overall lower survival rates (Papakonstantinou et al., 2019).

The prevalence of the disease has been estimated to be at 0.8 to 5 per 100,000 individuals (Moreton, Razvi, Davidson, & Muir, 2014; Narayan, Gorman, Kalaria, Ford, & Chinnery, 2012; Razvi, Davidson, Bone, & Muir, 2005); however, many suspect that these numbers are underestimates. A more recent investigation of the frequency of the characteristic missense \textit{NOTCH3} mutations in a public database found a total prevalence of 3.4/1000 (Rutten et al., 2016).

\textit{Analytical Validity}

There are no established diagnostic criteria for CADASIL. The phenotype is highly variable, and although imaging may be suggestive, no characteristic is pathognomonic; genetic testing remains the gold standard for diagnosis (Rutten & Lesnik Oberstein, 2016; Wang, 2018). As a heterozygous pathogenic variant in the \textit{NOTCH3} protein coding gene is well established as a main reason for CADASIL development, a CADASIL diagnosis is generally delivered based on molecular genetic testing or electron microscopy and immunohistochemistry results. Molecular genetic testing approaches may include both gene-targeted testing and in-depth genomic testing, such as exome sequencing and genome sequencing (Hack et al., 2019; Papakonstantinou et al., 2019).

Immunohistochemistry combined with electron microscopy of skin biopsy can be useful when molecular testing is not definitive (Rutten & Lesnik Oberstein, 2016). Immunohistochemistry assay of a skin biopsy sample for the accumulation of \textit{NOTCH3} protein in the walls of small blood vessels (Joutel et al., 2001) has an estimated sensitivity and specificity at 85-90% and 95-100%, respectively (Lesnik Oberstein et al., 2003). Detection of granular osmiophilic material deposits (GOM) containing the ectodomain of the \textit{NOTCH3} gene by electron microscopy (del Rio-Espinola et al., 2009; Muqtadar & Testai, 2012) had a sensitivity of 45% and a specificity of 100% (Brulin, Godfraind, Leteurtre, & Ruchoux, 2002; Malandrini et al., 2007; Markus et al., 2002).

MRI is useful to demonstrate radiologic features of CADASIL, including recent lunar infarctions and white matter hyperintensities. Computed tomography (CT) scans are less sensitive than MRI in this regard (Dichgans, 2018). MRI may also provide prognostic information. Brain lesions in CADASIL patients tend to precede symptoms by 10 to 15 years; however, a normal MRI in the fourth decade of life should not automatically rule out CADASIL syndrome even though
most patients exhibit an abnormal MRI by age 35 (Samoes et al., 2016). White matter hyperintensities on MRI can be visualized in those aged 21 years and older, and lesion volume correlates with the level of disability and three year clinical course of CADASIL (Jouvent et al., 2016). Isolated T2 hyperintensities involving the temporal poles can differentiate CADASIL from chronic microvascular ischemia due to hypertension with a sensitivity and specificity of 95% and 80%, respectively (O’ Sullivan et al., 2001). Cerebral microbleeds visible on T2 weighted MRI images detected in 36% of patients with CADASIL were independently associated with an increased risk of incident ischemic stroke and may be a marker for a subgroup of patients with CADASIL who have a more severe or advanced form of the disease (Puy et al., 2017).

Clinical Validity and Utility

One study has reported that the sequence analysis of \textit{NOTCH3} is 95-100% sensitive and 100% specific to establish the diagnosis of CADASIL (Dotti et al., 2005; Peters et al., 2005; Tikka et al., 2009; Yin et al., 2015). A preliminary scale was proposed to screen for patients who should undergo \textit{NOTCH3} gene analysis with a sensitivity of 96.7% and a specificity of 74.2% (Pescini et al., 2012). Another study of Russian patients with clinically suspected CADASIL concluded that careful assessment of genealogical, clinical, and neuroimaging data in patients with lacunar stroke can help select patients with a high probability of finding mutations on genetic screening (Abramycheva et al., 2015). In the absence of clinical features suggestive of CADASIL, screening of patients with lacunar stroke, leukoarosis, and migraine have low yield (de Vries, Frants, Ferrari, & van den Maagdenberg, 2009; Dong et al., 2003).

As individual symptoms and disease severity span a wide spectrum, it must be noted that symptom onset alone cannot warrant a CADASIL syndrome diagnosis. Researchers previously screened 123 patients who exhibited two common CADASIL symptoms: lacunar stroke and transient ischemic attack. These participants were genetically tested for CADASIL; it was determined that only 12.5% had a \textit{NOTCH3} mutation, showing that common CADASIL symptoms are shared with many other disorders (Bersano et al., 2018). This highlights the importance of genetic testing as a diagnostic measure. Further, three features were found to be significantly associated with a CADASIL diagnosis: “A family history of stroke, the presence of dementia and external capsule lesions on MRI” (Bersano et al., 2018).

Predictive Testing of At-Risk Family Members

For an asymptomatic individual, knowledge of mutation status will generally not lead to any management changes that can prevent or delay the onset of the disorder. Avoiding tobacco use may be a factor that delays onset of disease, but this is a general recommendation that is not altered by genetic testing. Goldman (2015) has suggested that asymptomatic family members follow the guidelines for presymptomatic testing for Huntington disease (HDSA, 2016).

CADASIL genetic testing may assist decision making in areas such as employment choices and reproductive decision making. However, the impact of these decisions on health outcomes is uncertain. Further, the testing of asymptomatic at-risk individuals with nonspecific or equivocal symptoms is not useful in predicting age of onset, severity, type of symptoms, or rate of progression in asymptomatic individuals (Rutten & Lesnik Oberstein, 2016). Initial data from Reyes, Kurtz, Herve, Tournier-Lasserve, and Chabriat (2012) show that predictive testing is rarely requested and has a high dropout rate.

Di Donato et al. (2017) state that the MRI of an unaffected family member could have a similar impact to a genetic test because MRIs are able to accurately predict CADASIL disease development before symptoms present. Therefore, the potential implications of MRI testing should be shared before this type of testing is completed.
Guidelines and Recommendations

**American Heart Association and American Stroke Association (Powers et al., 2018; Smith et al., 2017)**

The American Heart association and American Stroke Association do not provide any recommendations on rare genetic causes of cerebral small vessel disease, such as CADASIL, but they do provide suggestions on when rare genetic causes could be suspected. And, they suggest that the diagnosis could be made on the basis of testing for mutations in the NOTCH3 gene (Powers et al., 2018; Smith et al., 2017).

**European Federation of Neurological Societies (Burgunder et al., 2010)**

The European Federation of Neurological Societies guideline on the molecular diagnosis of channelopathies, epilepsies, migraine, stroke, and dementias notes that most NOTCH3 mutations occur within exons 3 and 4 and suggests direct sequencing of these 2 exons if clinical suspicion is high (Burgunder et al., 2010).

**U.S. Preventive Services Task Force (USPSTF) (USPSTF, 2019)**

As of 10/21/2019, the USPSTF has not published guidelines for the genetic testing of CADASIL patients.

**State and Federal Regulations, as applicable**

No U.S. Food and Drug Administration-cleared tests were found with the keyword “NOTCH3” as of 10/18/2019; a total of 23 U.S. Food and Drug Administration-cleared tests were found with the keyword “genotyping.” Additionally, many labs have developed specific tests that they must validate and perform in house. NOTCH3 sequencing is therefore a laboratory developed test (LDT). These LDTs are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA ‘88). As an LDT, the U. S. Food and Drug Administration has not approved or cleared this test; however, FDA clearance or approval is not currently required for clinical use.

**Applicable CPT/HCPCS Procedure Codes**

<table>
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<th>Code Description</th>
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| 81406       | Molecular pathology procedure, level 7  

Gene:  

**NOTCH3** (notch 3) (eg, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy [CADASIL]), targeted sequence analysis (eg, exons 1-23).


Procedure codes appearing in Medical Policy documents are included only as a general reference tool for each policy. They may not be all-inclusive.
Evidence-based Scientific References


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Ping, S., & Zhao, L.-R. (2018). *Current Understanding of Pathology and Therapeutic Status for CADASIL.*


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