BlueCross BlueShield of North Carolina

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# Corporate Medical Policy

# Genetic Testing of CADASIL Syndrome AHS – M2069

**File Name:** genetic_testing_of_cadasil_syndrome
**Origination:** 01/01/2019
**Last Review:** 1/2023

## Description of Procedure or Service

**Description**

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a genetic small vessel disease in which mutations in notch receptor 3 (NOTCH3), 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 et al., 2004; Zhu & Nahas, 2016).

******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 of CADASIL syndrome when it is determined to be medically necessary because 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.

## When Genetic Testing of CADASIL Syndrome is covered

1. For individuals who have received genetic counseling and who have received a clinical diagnosis of cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) or for whom a definitive diagnosis cannot be made without genetic testing, genetic testing of *NOTCH3* to confirm the diagnosis of CADASIL is considered medically necessary.

2. For asymptomatic individuals who have a first- or second-degree relative diagnosed with CADASIL syndrome, the following genetic testing is considered medically necessary:

    A. Testing restricted to the known familial *NOTCH3* mutation
    B. Comprehensive *NOTCH3* sequencing only if the specific familial mutation is unknown

## When Genetic Testing of CADASIL Syndrome is not covered

Genetic testing of CADASIL syndrome in all other situations is considered investigational.

## Policy Guidelines

**Background**

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (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 et al., 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 et al., 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 et al., 2018).

Individual symptoms, onset, and disease severity span a wide spectrum (Wang, 2018). Thus, descriptions of hereditary multi-infarct dementia, chronic familial vascular encephalopathy, and familial subcortical dementia, originally thought to be separate disorders, represent early reports of this condition (Dichgans, 2022). 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 include lumbago, humpback, and Parkinson syndrome (Cao et al., 2019; Lim et al., 2019). Migraine with aura occurs in 55% of CADASIL cases and is often the initial manifestation of the disease (Di Donato et al., 2017). Subcortical ischemic attacks begin at a mean age of 47 years and present as lacunar syndromes (Adib-Samii et al., 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 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 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 NOTCH3 mutations do not present with a cysteine change; this type of non-cysteine mutation can cause a great loss of structure in the NOTCH3 protein (Papakonstantinou et al., 2019).

More than 200 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 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 five per 100,000 individuals (Moreton et al., 2014; Narayan et al., 2012; Razvi et al., 2005); however, many suspect that these numbers are underestimates. A more recent investigation of the frequency of the characteristic missense CADASIL mutations in a public database found a total prevalence of 3.4/1000 (Rutten et al., 2016).

Currently, no efficient treatment options to cure or prevent CADASIL syndrome are available (Hack et al., 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 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).

***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 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 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 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 et al., 2002; Malandrini et al., 2007; Markus et al., 2002).

Magnetic resonance imaging (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, 2022). 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).

Guo et al. (2021) studied the role of NOTCH3 gene mutations and variants in Alzheimer Disease (AD) and subcortical vascular dementia (SVaD). CADASIL is a common etiology of SVaD. 667 AD patients, 96 SVaD patients, and 365 healthy control participants, all recruited from the Southern Han Chinese population, were included in the study. The authors performed targeted capture sequencing on

NOTCH3 and adjacent intron regions. “Five known pathogenic variants (p.R182C, p.C201S, p.R544C, p.R607C, and p.R1006C) and two novel likely pathogenic variants (p.C201F and p.C1061F) were detected in 16 SVaD patients.” No pathogenic variants were found in AD patients. The authors concluded that the “findings broaden the mutational spectrum of NOTCH3 and validate the pathogenic role of NOTCH3 mutations in SVaD, but do not support the notion that NOTCH3 variation influences the risk of AD” (Guo et al., 2021).

Cho et al. (2021) performed an analysis on whole-exome sequencing data from 200,632 participants in the UK Biobank. The authors note that CADASIL is considered rare, but there is a higher frequency of cysteine-altering NOTCH3 variants which could increase risk of apparently sporadic lacunar stroke. The authors compared frequency of stroke, vascular dementia, clinical features of CADASIL, and MRI white matter hyperintensity volume between carriers and non-carriers of 67 cysteine-altering NOTCH3 variants. “NOTCH3 variant carriers had increased risk of stroke (OR: 2.33, p=0.0004) and vascular dementia (OR: 5.00, p=0.007), and increased white matter hyperintensity volume (standardised difference: 0.52, p<0.001) and white matter ultrastructural damage on diffusion MRI (standardised difference: 0.72, p<0.001).” The authors concluded that “cysteine-changing NOTCH3 variants are more common in the general population than expected from CADASIL prevalence and are risk factors for apparently 'sporadic' stroke and vascular dementia” (Cho et al., 2021).

Gravesteijn et al. (2021) studied the effect of NOTCH3 variant position on NOTCH3 protein aggregation load. Vascular NOTCH3 aggregation was measured in skin biopsies and brain tissue from CADASIL patients. “CADASIL patients with an EGFr 7-34 variant have significantly less vascular NOTCH3 aggregation than patients with an EGFr 1-6 variant.” The authors concluded that NOTCH3 variant position may be a factor that underlies differences in CADASIL disease severity (Gravesteijn et al., 2021).

***Clinical Validity and Utility***

One study has reported that the sequence analysis of 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 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 et al., 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 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).

CADASIL was first diagnosed by visualizing granular osmiophilic material (GOM) in the tunica media of small arteries through light microscopy. Although GOM deposit is the pathological hallmark of CADASIL, NOTCH3 genetic sequencing is the confirmative diagnostic tool. While most genetic tests use Sanger sequencing methods to target specific NOTCH3 exons, next-generation sequencing (NGS) and whole exome sequencing (WES) have proven to deliver greater efficacy. One study has reported that NGS and WES have increased sensitivity to detect low frequency variants of NOTCH3 mutations compared to Sanger sequencing. Through Sanger sequencing, 10.8% of tests were able to identify NOTCH3 mutations compared to 15.8% of tests identifying mutations through next-

generation sequencing. With NGS, the results were in concordance with Sanger sequencing, but it extended the capacity to detect mutations and previously unreported variants. As diagnostic sequencing techniques continue to advance, NGS and WES may play an important role in identifying other genes involved with CADASIL (Dunn et al., 2020).

Rutten et al. (2018) analyzed the effect of NOTCH3 pathogenic variant (PV) location on CADASIL disease variability. The authors correlated PV position with brain MRI lesion load, age of first stoke, and survival on 664 European CADASIL patients. "CADASIL patients with an EGFr 1–6 pathogenic variant have a 12-year earlier onset of stroke than those with an EGFr 7–34 pathogenic variant, lower survival, and higher white matter hyperintensity volumes." The authors concluded that NOTCH3 PV location is "the most important determinant of CADASIL disease severity"(Rutten et al., 2018).

Mukai et al. (2020) correlated genotypes and phenotypes of 179 Japanese CADASIL probands. The authors identified 68 mutations, "p.Cys388Arg, p.Cys435Phe, p.Gly481Cys, p.Cys743Tyr, and p.Cys1009Phe were novel ones." The authors then analyzed genotype-phenotype correlations on the three most common mutations. "p.Arg141Cys showed typical CADASIL phenotypes, whereas p.Arg75Pro showed mild and atypical phenotypes, a low frequency of stroke/TIA [transient ischemic attack], high frequency of hypertension, and low frequency of temporal pole lesions. p.Arg182Cys showed various initial symptoms other than stroke/TIA." The authors also studied mutation location and the age of stroke/TIA onset, and found that mutations of EGFr 1-6 (excluding p.Arg75Pro) were significantly correlated with a younger age of stroke/TIA onset than mutations in EGFr 7-43. The authors concluded that the data clarified genotype-phenotype correlations and the effect of mutation location on the age of stroke/TIA onset in Japanese CADASIL probands (Mukai et al., 2020).

Hack et al. (2020) performed a cross-sectional study using 118 participants with a NOTCH3 cysteine altering variant and 184 age- and sex-matched control participants. Clinical, neuroimaging, and whole-exome data was compared. There was no difference in dementia, mild cognitive impairment, migraine with aura, or depression prevalence. Participants with a NOTCH3 cysteine altering variant had a higher had a higher risk of stroke, white matter hyperintensity, and lacunas after age 65. The authors note that the classic mid-adult onset CADASIL phenotype was not reported, suggesting "NOTCH3 variants do not only cause the rate and more severe hereditary CADASIL but are much more commonly associated with a milder [cerebral small vessel disease] SVD phenotype, specifically when these variants are located in EGFr 7 to 35" (Hack et al., 2020).

Liu et al. (2021) tracked clinical and MRI data of three patients from a family in China over seven years. Genetic tests confirmed CADASIL diagnosis on all three participants, including a novel mutation of p.C533S on exon 10 of NOTCH3. The same heterozygous mutations were detected across family members. The authors conclude that there is "distinct heterogeneity of CADASIL patients in the same family with the same mutation" (Liu et al., 2021).

Chen et al. (2021) assessed the diagnostic utility of using NGS and MRI data for the diagnosis of adult onset leukodystrophy. The authors used a panel of 200 neurodegeneration-related genes and an MRI brain-based diagnostic algorithm from 45 patients with young-onset cognitive impairment with leukodystrophy. All the patients with an established genetic diagnosis had MRI brain patterns consistent with their diagnosis. 51.4% of patients with MRI changes consistent with vascular cognitive impairment secondary to small vessel disease (VCI-SVD) had pathogenic variants: 89.5% of which were pathogenic NOTCH3 and 11.5% of which were HTRA1 variants. The authors concluded that the results "demonstrated a high diagnostic utility incorporating a targeted neurodegeneration gene panel and MRI-based diagnostic algorithms in young-onset cognitive impairment patients with leukodystrophy" (Chen et al., 2021).

*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 et al. (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**

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. They suggest that the diagnosis could be made based on testing for mutations in the *NOTCH3* gene (Kleindorfer et al., 2021; Powers et al., 2019; Smith et al., 2017).

**European Federation of Neurological Societies**

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).

**United States Preventive Services Task Force**

As of 10/05/2021, the USPSTF has not published guidelines for the genetic testing of CADASIL patients.

**European Academy of Neurology (EAN)**

The European Academy of Neurology (EAN) released guidelines for monogenic cerebral small-vessel disease (cSVD), including diagnosis and management of CADASIL. EAN suggests that the first line diagnosis for CADASIL should be genetic testing, but diagnosis can also be established by skin biopsy with electron microscopy revealing granular osmiophilic material (GOM). Most NOTCH3 variants causing CADASIL are due to a loss or gain of a cysteine in the EGFR repeats. Some non-cysteine changing variants have been reported, but most of these non-cysteine changing variants do not lead to a diseased state. If genetic testing reveals a non-cysteine changing variant, electron microscopy to visualize GOM is a useful tool to confirm CADASIL diagnosis. If the NOTCH3 variant is of unknown significance, CADASIL diagnosis can be established with skin biopsy via electron microscopy or immunohistochemistry of the NOTCH3 extracellular domain. The guideline recommends "considering" a CADASIL diagnosis in any patient with "unexplained symmetrical periventricular WMHs [white matter hyperintensities] and a positive family history of migraine with aura, stroke, mood disorders or dementia." The guideline also notes that CADASIL cannot be ruled out in the presence of "common cerebrovascular risk factors and extensive WMHs" or in "the absence of a medical or family history of migraine with aura." The guideline remarks that "although most patients have a family history, if the clinical and imaging phenotype is consistent with CADASIL the diagnosis should be considered" (Mancuso et al., 2020).

Overall, the EAN remarks that "CADASIL can only be definitively confirmed by genetic testing, revealing a NOTCH3 mutation altering the number of cysteines in one of the 34 EGFr domains of the NOTCH3 protein" (Mancuso et al., 2020).

**Applicable Federal Regulations**

Many labs have developed specific tests that they must validate and perform in house. These laboratory-developed tests (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). LDTs are not approved or cleared by the U. S. Food and Drug Administration; however, FDA clearance or approval is not currently required for clinical use.

## 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*

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

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## Policy Implementation/Update Information

1/1/2019 BCBSNC will provide coverage for genetic testing of CADASIL syndrome when it is determined to be medically necessary because the criteria and guidelines are met. Medical Director review 1/1/2019. Policy noticed 1/1/2019 for effective date 4/1/2019. (jd)

4/1/2019 Description section, policy guidelines and references updated. Medical Director review 4/2019. (jd)

2/11/20 Annual review by Avalon 4th Quarter CAB 2019. CPT code G0452 and code table removed from the Billing/Coding section. No change to policy intent. Medical Director review 12/2019. (jd)

3/31/20 Specialty Matched Consultant Advisory Panel review 3/2020. Medical Director review 3/2020. (jd)

2/9/21 Annual review by Avalon 4th Quarter CAB 2020. Minor revisions; no change to policy intent. Medical Director review 1/2021. (jd)

3/31/21 Specialty Matched Consultant Advisory Panel review 3/2021. Medical Director review 3/2021. (jd)

2/8/22 Reviewed by Avalon 4th Quarter 2021 CAB. Under the When Covered section, added the following to item #1 for clarity: "cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy"; no change to policy intent. Description, policy guidelines, and references updated with minor revisions. Medical Director review 1/2022. (jd)

2/7/23 Reviewed by Avalon 4th Quarter 2022 CAB. Description, Policy Guidelines and References sections updated. Related Policies section removed. When Covered section edited for clarity, no change to policy statement. Medical Director review 1/2023. (tm)