

Genetic Testing of CADASIL Syndrome

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I. Policy Description

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a genetic small vessel disease in which mutations in the Notch Receptor 3 (*NOTCH3*) gene located on chromosome 19 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.

II. 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 cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (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**.

III. 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). Small vessel diseases such as this are an important cause of stroke and vascular cognitive decline in adults. VSMC dysfunction may be caused by mutations in the *NOTCH3* gene, leading to irregularities in VSMC proliferation, cell cycle affliction, senescence, and cellular apoptosis.

Individual symptoms, onset, and disease severity span a wide spectrum. 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. CADASIL usually presents with one or more of the following: dementia, psychiatric disturbances, migraine, and recurrent strokes. Rarer symptoms include lumbago, humpback, and Parkinson syndrome. Migraine with aura occurs in 55% of CADASIL cases and is often the initial manifestation of the disease. Subcortical ischemic attacks begin at a mean age of 47 years and present as lacunar syndromes. Accumulation of lacunae, which impact executive performance and function independence, strongly correlate to clinical severity. 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. A concurrent stepwise deterioration due to recurrent strokes is also common. Mood disturbances are reported in approximately 30% of individuals. Further, apathy, which may be independent of depression, is reported in 40% of individuals.

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. 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. 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.

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. This leads to an increased multimerization tendency of mutant NOTCH3, toxic accumulation of the protein and extracellular matrix in disulfide cross-linked detergent-insoluble aggregates, altered neurovascular coupling, and ultimately reduced cerebral blood flow, recurrent stroke, and vascular dementia. 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.

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. These severe symptoms include stroke onset an average of 12 years earlier and overall lower survival rates.

The prevalence of the disease has been estimated to be at 0.8 to 5 per 100,000 individuals; 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.

Currently, no efficient treatment options to cure or prevent CADASIL syndrome are available; 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.

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. 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.

Immunohistochemistry combined with electron microscopy of skin biopsy can be useful when molecular testing is not definitive. Immunohistochemistry assay of a skin biopsy sample for the accumulation of *NOTCH3* protein in the walls of small blood vessels has an estimated sensitivity and specificity at 85-90% and 95-100%, respectively. Detection of granular osmiophilic material deposits (GOM) containing the ectodomain of the *NOTCH3* gene by electron microscopy had a sensitivity of 45% and a specificity of 100%.

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. 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. 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. 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. 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.

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.”

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.”

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.

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. 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%. 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. In the absence of clinical features suggestive of CADASIL, screening of patients with lacunar stroke, leukoarosis, and migraine have low yield.

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. 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.”

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.

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 stroke, 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.”

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.

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 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” (R. J. 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.”

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 of 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.”

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.

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. Initial data from Reyes, Kurtz, Herve, Tournier-Lasserre, 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.

IV. 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 on the basis of testing for mutations in the *NOTCH3* gene.

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).

U.S. 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.”

V. State and Federal Regulations, as applicable

DISCLAIMER: If there is a conflict between this Policy and any relevant, applicable government policy for a particular member [e.g., Local Coverage Determinations (LCDs) or National Coverage Determinations (NCDs) for Medicare and/or state coverage for Medicaid], then the government policy will be used to make the determination. For the most up-to-date Medicare policies and coverage, please visit the Medicare search website: <http://www.cms.gov/medicare-coveredatabase/overview-and-quick-search.aspx>. For the most up-to-date Medicaid policies and coverage, visit the applicable state Medicaid website.

No U.S. Food and Drug Administration-cleared tests were found with the keyword “NOTCH3” as of 10/05/2021; a total of 25 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.

VI. Important Reminder

The purpose of this Medical Policy is to provide a guide to coverage. This Medical Policy is not intended to dictate to providers how to practice medicine. Nothing in this Medical Policy is intended to discourage or prohibit providing other medical advice or treatment deemed appropriate by the treating physician.

Benefit determinations are subject to applicable member contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

This Medical Policy has been developed through consideration of the medical necessity criteria under Hawaii’s Patients’ Bill of Rights and Responsibilities Act (Hawaii Revised Statutes §432E-1.4), or for QUEST Integration members under Hawaii Administrative Rules (HAR 1700.1-42), generally accepted standards of medical practice and review of medical literature and government approval status. HMSA has determined that services not covered under this Medical Policy will not be medically necessary under Hawaii law in most cases. If a treating physician disagrees with HMSA’s determination as to medical necessity in a given case, the physician may request that HMSA reconsider the application of the medical necessity criteria to the case at issue in light of any supporting documentation.

Genetic testing is covered for level 1 or 2A recommendations of the National Comprehensive Cancer Network (NCCN and in accordance with Hawaii’s Patients’ Bill of Rights and Responsibilities Act (Hawaii Revised Statutes §432E-1.4) or for QUEST members, the Hawaii Administrative Rules (HAR 1700.1-42).

VII. Evidence-based Scientific References

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VIII. Policy History

Policy approved by Medical Directors	9/20/2022
Policy approved at UMC	12/16/2022
Policy effective	6/1/2023

Updated Lines of Business	12/18/2023
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