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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 *notch receptor 3* (*NOTCH3*), located on chromosome 19,[1] 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.[2,3]

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. Specifications pertaining to Medicare and Medicaid can be found in the "Applicable State and Federal Regulations" section of this policy document.

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 **MEETS COVERAGE CRITERIA**.

2) For asymptomatic individuals who have a first- or second-degree relative (see Note 1) diagnosed with CADASIL syndrome, the following genetic testing **MEETS COVERAGE CRITERIA**:

   a) Testing restricted to the known familial *NOTCH3* pathogenic/likely pathogenic (P/LP) variant.

   b) Comprehensive *NOTCH3* sequencing only if the specific familial P/LP variant is unknown.

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 an individual's illness.

3) For all other situations not discussed above, genetic testing for CADASIL syndrome **DOES NOT MEET COVERAGE CRITERIA**.

NOTES:

Note 1: First-degree relatives include parents, full siblings, and children of the individual. Second-degree relatives include grandparents, aunts, uncles, nieces, nephews, grandchildren, and half-siblings of the individual.

III. Table of Terminology

Term	Definition
AD	Alzheimer disease
AHA	American Heart Association
ASA	American Stroke Association
CADASIL	Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy
CLIA '88	Clinical Laboratory Improvement Amendments of 1988
CMS	Centers for Medicare and Medicaid Services
cSVD	Cerebral small-vessel disease
CT	Computed tomography
EAN	European Academy of Neurology
EFNS	European Federation of Neurological Studies
EGFr	Epidermal growth factor-like repeat
EMR	Electronic medical records
FDA	Food and Drug Administration
GOM	Granular osmiophilic material
HTRA1	**Serine protease**
LDT	Laboratory-developed test
MCI	Mild cognitive impairment
MRI	Magnetic resonance imaging
NGS	Next-generation sequencing
NORD	National Organization for Rare Disorders
NOTCH3	*Notch receptor 3*
PV	Pathogenic variant
SVD	Small vessel disease
SVaD	Subcortical vascular dementia
T2	Transverse relaxation time
TIA	Transient ischemic attack
USPSTF	United States Preventive Services Task Force
VCI-SVD	Vascular cognitive impairment secondary to small vessel disease
VSMCs	Vascular smooth muscle cells
WES	Whole-exome sequencing
WMHs	White matter hyperintensities

IV. Scientific 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).[4-6] Small vessel diseases such as this are an important cause of stroke and vascular cognitive decline in adults.[7] VSMC dysfunction may be caused by mutations in the *NOTCH3* gene, leading to irregularities in VSMC proliferation, cell cycle affliction, senescence, and cellular apoptosis.[8]

Individual symptoms, onset, and disease severity span a wide spectrum.[9] 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.[10] CADASIL usually presents with one or more of the following: dementia, psychiatric disturbances, migraine, and recurrent strokes.[7,11,12] Rarer symptoms include lumbago, humpback, and Parkinson syndrome.[13] Migraine with aura occurs in 55% of CADASIL cases and is often the initial manifestation of the disease.[14] Subcortical ischemic attacks begin at a mean age of 47 years and present as lacunar syndromes.[11,15] Accumulation of lacunae, which impact executive performance and function independence, strongly correlate to clinical severity.[16] 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.[17] A concurrent stepwise deterioration due to recurrent strokes is also common.[18] Mood disturbances are reported in approximately 30% of individuals.[11,15] Further, apathy, which may be independent of depression, is reported in 40% of individuals.[19]

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.[20] 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.[18] 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.[6]

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.[1,21,22] This leads to an increased multimerization tendency of mutant NOTCH3,[23] toxic accumulation of the protein and extracellular matrix in disulfide cross-linked detergent-insoluble aggregates,[4] altered neurovascular coupling,[24] and ultimately reduced cerebral blood flow, recurrent stroke, and vascular dementia.[25] 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.[22]

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.[22,26] These severe symptoms include stroke onset an average of 12 years earlier and overall lower survival rates.[22]

Variant position is a key severity determinant: EGFr 1-6 pathogenic variants confer earlier stroke, heavier WMH burden, and poorer survival versus EGFr 7-34. Conversely, specific genotypes such as p.Arg75Pro and p.Arg544Cys are repeatedly linked to later onset and a lower frequency of temporal-pole WMHs, and show strong geographic patterns (e.g. Jeju Island and Taiwan for p.Arg544Cys). This helps reconcile why some families exhibit atypical or comparatively mild trajectories despite confirmed NOTCH3 pathogenicity.[27]

The prevalence of the disease has been estimated to be at 0.8 to five per 100,000 individuals.[28-30] However, many suspect that these numbers are underestimated. 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.[25]

Currently, no efficient treatment options to cure or prevent CADASIL syndrome are available;[31,32] 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.[25] Further, neurofilament light chains have now been identified as a promising CADASIL biomarker and can be detected in the serum of affected patients.[6]

Additionally, the multicenter LOMCAD trial is investigating the use of lomerizine hydrochloride, a calcium channel blocker, for blood flow on CADASIL patients. In doing so, the efficacy of lomerizine in preventing recurrent ischemic events can be thoroughly evaluated. Research suggests that this could be a promising agent for stroke prevention by increasing cerebral blood flow. These developments highlight a growing focus on targeted interventions and disease-modifying strategies.[33]

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.[9,18] 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.[22,32]

Immunohistochemistry combined with electron microscopy of skin biopsy can be useful when molecular testing is not definitive.[18] Immunohistochemistry assay of a skin biopsy sample for the accumulation of NOTCH3 protein in the walls of small blood vessels[34] has an estimated sensitivity and specificity at 85-90% and 95-100%, respectively.[35] Detection of granular osmiophilic material deposits (GOM) containing the ectodomain of the *NOTCH3* gene by electron microscopy[36,37] had a sensitivity of 45% and a specificity of 100%.[38-40]

Most pathogenic NOTCH3 mutations are cysteine-altering missense variants within exons 2-24, which encode the 34 EGFrs. These mutations cause the gain or loss of a cysteine residue, resulting in an unpaired number of cysteines and disrupted disulfide bonds. This structural change drives protein misfolding, abnormal multimerization, and toxic extracellular accumulation of NOTCH3. The resulting vascular pathology includes impaired neurovascular coupling, reduced cerebral blood flow, and chronic hypoperfusion, processes that are thought to contribute to stroke recurrence and progressive cognitive decline.[27]

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.[10] 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.[41] 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.[42] 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.[43] 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.[44]

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. A total of 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."[45]

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."[46]

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.[47]

Clinical Utility and Validity

One study has reported that the sequence analysis of *NOTCH3* is 95-100% sensitive and 100% specific to establish the diagnosis of CADASIL.[48-51] 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%.[52] 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.[53] In the absence of clinical features suggestive of CADASIL, screening of patients with lacunar stroke, leukoarosis, and migraine have low yield.[54,55]

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.[56] 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."[56]

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (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.[57]

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."[26]

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.[58]

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."[59]

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."[60]

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. A total of 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."[61]

Anisetti, et al. (2023) gathered the electronic medical records (EMR) of adult patients with confirmed CADASIL disease to analyze the use of a recently proposed grading system. A grade of zero (asymptomatic), Grade One (migraine only), Grade Two (stroke, TIA, or MCI), Grade Three (gait assistance or dementia) or Grade four (bedbound or end-stage) was given to each patient. The inter-rater reliability of grading was also assessed with an 81.8% agreement on ratings. Results showed that those patients who received a lower grade on the CADASIL scale were younger (49.5 vs. 61.9 years) and were less likely to have hypertension and/or diabetes mellitus. Higher ratings were correlated with

increased vascular risk factors. The authors concluded that a CADASIL grading system based on symptoms was a reliable categorization of patients to assess higher vascular risk factor burden.[62]

Boston, et al. (2024) completed a systematic review on the most common *NOTCH3* mutations that cause CADASIL and CADASIL-like cerebral small vessel disease. The authors were aiming to investigate the association between phenotypes and genotypes across the most common *NOTCH3* mutations in CADASIL patients. "The six most common NOTCH3 missense mutations globally were the p.R75P, p.R133C, p.R141C, p.R169C, p.R182C, and p.R544C, of which p.R133C was described to occur most often." p.R75P, p.R141C, p.R182C and p.R544C genotypes were "highly congruent" with white matter hyperintensities on MRI. P.R141C genotype was associated with decreased disease severity. Although there were some associations, overall, "statistical analysis showed there were no overall differences between the phenotypic characteristics of the two common mutations, p.R141C and p.R544C."[63]

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.[65]

Genetic testing for CADASIL 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.[18] 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.

Akrich, et al. (2024) studied the population at risk of CADASIL who had not completed diagnostic procedures, aiming to understand the hesitation. The study included a questionnaire survey with 40 questions about why people choose to undergo or not undergo a genetic test, and what led to that decision. The questionnaire was sent to 883 people, and 359 replied. Of the 359 replies, 197 were from *NOTCH3*-mutation carriers, 81 were from close relatives, and 81 were from individuals at risk of CADASIL. "Results suggest that, far from being a simple, unequivocal path, the decision-making process leading to the choice of diagnosis is initially slowed down by the need to distance oneself from the disease so that it doesn't take over one's life, and then evolves under the influence of a complex tangle between advancing age, the presence of early symptoms, and the personal relationship with uncertainty."[67]

V. Guidelines and Recommendations

American Heart Association (AHA) and American Stroke Association (ASA)

The American Heart Association and American Stroke Association 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.[68-70]

In 2023, the AHA released a scientific statement about the management of inherited central nervous system small vessel diseases, specifically CADASIL. The AHA recommends: "Consider gene testing in patients with small vessel stroke before 55 years of age with a paucity of vascular risk factors (eg, normotensive, nondiabetic, nonsmoker) or positive family history of CADASIL." The AHA also notes that "one should distinguish diagnostic testing in individuals who have clinical manifestations of disease from predictive or presymptomatic testing. In general, children, unless emancipated minors, should not undergo predictive testing because this robs them of the choice of knowing or not knowing their status. The penetrance of *NOTCH3* variants is incomplete and highly variable. Testing and finding mutations in *NOTCH3* can lead to pessimistic prognostication and bias of detecting asymptomatic brain lesions with MRI. This can have life-changing, negative psychological consequences."[71]

European Federation of Neurological Societies (EFNS)

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 three and four and suggests direct sequencing of these two exons if clinical suspicion is high.[72]

United States Preventive Services Task Force (USPSTF)

As of September 19, 2023, 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."[73]

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."[73]

National Organization for Rare Diseases (NORD)

The National Organization for Rare Diseases released diagnosis guidelines on the disease. "CADASIL is based on symptoms, family history, and brain MRI lesions compatible with the disease. The CADASIL diagnosis can only be confirmed by DNA testing of blood samples for characteristic mutations in the *NOTCH3* gene or by identifying granular osmiophilic material (GOM) inclusions on a skin biopsy."[31]

VI. Applicable State and Federal Regulations

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: https://www.cms.gov/medicare-coverage-database/search.aspx For the most up-to-date Medicaid policies and coverage, visit the applicable state Medicaid website.

Food and Drug Administration (FDA)

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.

VII. 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 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).

VIII. Evidence-based Scientific References

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IX. Applicable CPT/HCPCS Procedure Codes

CPT	Code Description
81403	Molecular pathology procedure, Level 4 (eg, analysis of single exon by DNA sequence analysis, analysis of >10 amplicons using multiplex PCR in 2 or more independent reactions, mutation scanning or duplication/deletion variants of 2-5 exons)
81406	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)

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

X. Policy History

Action Date	Action
June 01, 2023	Policy created
March 17, 2026	Policy approved by Medical Directors
March 27, 2026	Policy approved at UMC
August 1, 2026	Policy effective date following notification period