MEDICAL POLICY

POLICY TITLE	GENETIC TESTING OF CADASIL SYNDROME
POLICY NUMBER	MP 2.247

Effective Date:	12/1/2023

I. POLICY

Genetic testing of *NOTCH3* to confirm the diagnosis of cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) syndrome may be considered **medically necessary** under the following conditions:

- Clinical signs, symptoms, and imaging results are consistent with CADASIL, indicating that the pre-test probability of CADASIL is at least in the moderate to high range (see Policy Guidelines); **and**
- The diagnosis of CADASIL is inconclusive following alternate methods of testing, including magnetic resonance imaging.

For individuals who are asymptomatic with a family member with a diagnosis of CADASIL syndrome:

- If there is a family member (first- and second-degree relative) with a known variant, targeted genetic testing of the known *NOTCH3* familial variant may be considered **medically necessary**
- If the family member's genetic status is unknown, genetic testing of *NOTCH3* (see Policy Guidelines) may be considered **medically necessary**.

Genetic testing of *NOTCH3* to confirm the diagnosis of CADASIL syndrome in all other situations is considered **investigational**. There is insufficient evidence to support a general conclusion concerning the health outcomes or benefits associated with this listed procedure.

Policy Guidelines

Genetic testing of *NOTCH3* comprises targeted sequencing of specific exons (e.g., exon 4 only, exons 2-6), general sequencing of *NOTCH3* exons (e.g., exons 2-24 or all 33 exons), or targeted testing for known *NOTCH3* pathogenic variants. Skin biopsy should be reserved for patients where NOTCH3 genetic testing is inconclusive (e.g. variants of uncertain significance).

The probability that CADASIL is present if an individualized assessment depends on numerous factors such as family history, symptoms, imaging results, and other specialized testing such as skin biopsy.

Pescini et al (2012) attempted to identify clinical factors that increase the likelihood of a pathogenic variant being present. Table PG1 summarizes the pooled frequency of clinical and radiologic features, and the points assigned for each finding. The authors recommended that a

total score of 14 be used to select patients for testing, because this score resulted in a high sensitivity (96.7%) and a moderately high specificity (74.2%).

Table PG1. Pooled Frequency of Clinical and Radiologic Features

Features	No. With *NOTCH3* Variant	Percent With *NOTCH3* Variant	Points
Clinical			
Migraine	239/463	52%	1
Migraine with aura	65/85	76%	3
Transient ischemic attack/stroke	380/526	72%	1 (2 if <50 y)
Psychiatric disturbance	106/380	28%	1
Cognitive decline	188/434	43%	3
Radiologic			
LE	*277Pescini/*277	100%	3
LE extended to temporal pole	174/235	74%	1
LE extended to external capsule	228/303	75%	5
Subcortical infarcts	210/254	83%	2

Genetics Nomenclature Update

Human Genome Variation Society nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. It was implemented for genetic testing medical policy updates starting in 2017 (see Table PG2). The Society's nomenclature is recommended by by the Human Variome Project, the Human Genome Organization, and by the Human Genome Variation Society itself.

The American College of Medical Genetics and Genomics and Association for Molecular Pathology standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations, in addition tothe College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table PG3 shows the recommended standard terminology—"pathogenic," "likely pathogenic," "uncertain significance," "likely benign," and "benign"—to describe variants identified that cause Mendelian disorders.

Table PG2. Nomenclature to Report on Variants Found in DNA

Previous	Updated	Definition
Mutation	Disease-associated variant	Disease-associated change in the DNA sequence
	Variant	Change in the DNA sequence

	Familial variant	Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives

Table PG3. ACMG-AMP Standards and Guidelines for Variant Classification

Variant Classification	Definition
Pathogenic	Disease-causing change in the DNA sequence
Likely pathogenic	Likely disease-causing change in the DNA sequence
Variant of uncertain significance	Change in DNA sequence with uncertain effects on disease
Likely benign	Likely benign change in the DNA sequence
Benign	Benign change in the DNA sequence

ACMG: American College of Medical Genetics and Genomics; AMP: Association for Molecular Pathology.

Genetic Counseling

Experts recommend formal genetic counseling for patients who are at risk for inherited disorders and who wish to undergo genetic testing. Interpreting the results of genetic tests and understanding risk factors can be difficult for some patients; genetic counseling helps individuals understand the impact of genetic testing, including the possible effects the test results could have on the individual or their family members. It should be noted that genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing; further, genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

Cross-reference:

MP 7.009 Preimplantation Genetic Testing

II. PRODUCT VARIATIONS

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This policy is only applicable to certain programs and products administered by Capital BlueCross and subject to benefit variations as discussed in Section VI. Please see additional information below.

FEP PPO: Refer to FEP Medical Policy Manual. The FEP Medical Policy manual can be found at: https://www.fepblue.org/benefit-plans/medical-policies-and-utilization-management-guidelines/medical-policies.

III. DESCRIPTION/BACKGROUND

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Variants in the NOTCH3 gene have been causally associated with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL). Genetic testing is available to determine if pathogenic variants exist in the NOTCH3 gene for patients with suspected CADASIL and their family members.

CADASIL

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is an uncommon, autosomal dominant disease, though it is the most common cause of hereditary stroke and hereditary vascular dementia in adults. CADASIL syndrome is an adult-onset, disabling systemic condition, characterized by a migraine with aura, recurrent lacunar strokes, progressive cognitive impairment, and psychiatric disorders. The overall prevalence of the disease is unknown in the general population.

Diagnosis

The differential diagnosis of CADASIL includes the following conditions (see Table 1).

Table 1. Differential Diagnosis of CADASIL

Acquired Disorders	Inherited Disorders
• Sporadic SVD with or without hypertension as the main risk factor • Multiple sclerosis • Primary angiitis of the central nervous system	• Fabry disease • Cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy • Familial SVD caused by heterozygous variants in the *HTRA1* gene • Some forms of leukodystrophy

SVD: small vessel disease.

Since the clinical presentation of CADASIL varies, the condition may be confused with multiple sclerosis, Alzheimer dementia, and Binswanger disease. The specific clinical signs and symptoms, along with family history and brain magnetic resonance imaging findings, are extremely important in diagnosing CADASIL. The clinical features and mode of inheritance (autosomal dominant vs autosomal recessive) help to distinguish CADASIL from other inherited disorders in a differential diagnosis.

When the differential diagnosis includes CADASIL, various diagnostic tests are available:

- Genetic testing, by direct sequencing of select exons or of exons 2 through 24 of the *NOTCH3* gene (see the Rationale section). Identification of a *NOTCH3* pathogenic variant definitively establishes a diagnosis of CADASIL without the need for additional diagnostic testing (e.g., skin biopsy)
- Immunohistochemistry assay of a skin biopsy sample, using a monoclonal antibody with reactivity against the extracellular domain of the *NOTCH3* receptor. Positive immunostaining reveals the accumulation of the *NOTCH3* protein in the walls of small blood vessels. Lesnick Oberstein et al (2003) estimated the sensitivity and specificity at 85% to 90% and 95% to 100%, respectively, for 2 observers of the test results in a population of patients and controls correlated with clinical, genetic, and magnetic resonance imaging parameters
- Detection of granular osmiophilic material in the same skin biopsy sample by electron microscopy. The major component of granular osmiophilic material is the ectodomain of

the *NOTCH3* gene product. Granular osmiophilic material accumulates directly in vascular smooth muscle cells and, when present, is considered a hallmark of the disease. However, granular osmiophilic material may not be present in all biopsy samples. Sensitivity has been reported as low as 45% and 57% but specificity is generally near or at 100%.

- Examination of brain tissue for the presence of granular osmiophilic material was originally described as limited to brain blood vessels. Examination of brain biopsy or autopsy after death was an early criterion standard for diagnosis. In some cases, peripheral staining for granular osmiophilic material has been absent even though positive results were seen in brain blood vessels.

NOTCH3 Variants

Variants in *NOTCH3* have been identified as the underlying cause of CADASIL. In almost all cases, the pathogenic variants lead to loss or gain of a cysteine residue that can lead to increased reactivity of the NOTCH3 protein, resulting in ligand-binding and toxic effects.

The *NOTCH3* gene is found on chromosome 19p13.2-p13.1 and encodes the third discovered human homologue of the *Drosophila melanogaster* type I membrane protein NOTCH. The NOTCH3 protein consists of 2321 amino acids, primarily expressed in vascular smooth muscle cells, and plays an important role in the control of vascular transduction. It has an extracellular ligand-binding domain of 34 epidermal growth factor (EGF)-like repeats, traverses the membrane once, and has an intracellular domain required for signal transduction.

Variants in the *NOTCH3* gene have been differentiated into those causative of the CADASIL syndrome (pathogenic variants) and those of uncertain significance. Pathogenic variants affect conserved cysteine residues within 34 EGF-like repeat domains in the extracellular portion of the NOTCH3 protein. More than 150 pathogenic variants have been reported in at least 500 pedigrees. *NOTCH3* has 33 exons but all CADASIL variants reported to date have occurred in exons 2 to 24, which encode the 34 EGF-like repeats, with strong clustering in exons 3 and 4, which encode EGF receptors 2 to 5 (>40% of variants in >70% of families occur in these exons). Some studies have indicated that the clinical variability in CADASIL presentation, particularly about the development of white-matter hyperintensities on magnetic resonance imaging, may be related to genetic modifiers outside the *NOTCH3* locus but the specific role of these modifiers is not well-delineated.

The probability that CADASIL is present in an individualized assessment depends on numerous factors such as family history; symptoms, imaging results, and other specialized testing (e.g., skin biopsy). Pescini et al (2012) attempted to identify clinical factors that increase the likelihood of a pathogenic variant being present, with increasing likelihood with the presence of one or several factors, including a migraine, migraine with aura, transient ischemic attack/stroke, psychiatric disturbance, cognitive decline, leukoencephalopathy (with greater risk for leukoencephalopathy extending to the temporal pole or external capsule), and subcortical infarcts.

Regulatory Status

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). Genetic testing of *NOTCH3* is available under the auspices of the CLIA. Laboratories that offer laboratory-developed tests must be licensed by the CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

IV. RATIONALE

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Summary of Evidence

For individuals with suspected CADASIL syndrome who receive *NOTCH3* genetic testing, the evidence includes case reports, case series, and genotype-phenotype correlation studies evaluating the clinical validity and genetic testing yield *for NOTCH3*. The relevant outcomes are overall survival, test accuracy and validity, changes in reproductive decision making, change in disease status, and morbid events. The clinical validity studies have demonstrated that a *NOTCH3* pathogenic variant is found in a high percentage of patients with a clinical diagnosis of CADASIL, with studies reporting a clinical sensitivity of 90% to 100%. Limited data on specificity derives from testing small numbers of healthy controls, and no false-positive *NOTCH3* pathogenic variants have been reported in these populations. The diagnostic yield studies have reported a variable yield, ranging from 10% to 54%. These lower numbers likely reflect testing in heterogeneous populations that include patients with other disorders. No direct evidence was identified demonstrating outcome improvements associated with genetic testing for CADASIL. However, a chain of evidence can be constructed to demonstrate that identification of a *NOTCH3* pathogenic variant establishes the diagnosis of CADASIL without the need for a skin biopsy and reduces the need for other diagnostic tests used to exclude other conditions in a differential diagnosis. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who are asymptomatic with family members who have CADASIL syndrome who receive targeted genetic testing for a known *NOTCH3* familial variant, the evidence is limited. The relevant outcomes are overall survival, test accuracy and validity, changes in reproductive decision making, change in disease status, and morbid events. For asymptomatic family members of an individual with known CADASIL, knowledge of the presence of a familial variant may lead to changes in lifestyle decisions for the affected individual (e.g., reproduction, employment). However, the impact of these lifestyle decisions on health outcomes is uncertain, and there are no interventions for asymptomatic individuals that are known to delay or prevent disease onset. A chain of evidence can be constructed to demonstrate that identification of a *NOTCH3* familial variant predicts future development of CADASIL in an asymptomatic individual, eliminates the need for additional diagnostic testing, allows for earlier monitoring for development of systems, aids in reproductive planning, and helps determine the likelihood of an affected offspring. The evidence is sufficient to determine that the technology results in in an improvement in the net health outcome.

For individuals who are asymptomatic with family members who have CADASIL syndrome whose genetic status is unknown who receive *NOTCH3* genetic testing, the evidence is limited. The relevant outcomes are overall survival, test accuracy and validity, changes in reproductive decision making, change in disease status, and morbid events. For asymptomatic family members of an individual with known CADASIL whose genetic status is unknown, knowledge of the presence of a *NOTCH3* pathogenic variant may lead to changes in lifestyle decisions for the affected individual (e.g., reproduction, employment). However, the impact of these lifestyle decisions on health outcomes is uncertain, and there are no interventions for asymptomatic individuals that are known to delay or prevent disease onset. A chain of evidence can be constructed to demonstrate that identification of a *NOTCH3* pathogenic variant predicts future development of CADASIL in an asymptomatic individual, eliminates the need for additional diagnostic testing, allows for earlier monitoring for development of systems, aids in reproductive planning, and helps determine the likelihood of an affected offspring. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

V. DEFINITIONS

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AUTOSOMAL DOMINANT is a gene on one of the non-sex chromosomes that is always expressed, even if only one copy is present. The chance of passing the gene to offspring is 50% for each pregnancy.

GENOTYPE is the specific genetic makeup of an individual, usually in the form of DNA.

LEUKOENCEPHALOPATHY refers to any of a group of diseases affecting the white substance of the brain.

MUTATION is a permanent structural alteration in DNA.

VI. BENEFIT VARIATIONS

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The existence of this medical policy does not mean that this service is a covered benefit under the member's health benefit plan. Benefit determinations should be based in all cases on the applicable health benefit plan language. Medical policies do not constitute a description of benefits. A member's health benefit plan governs which services are covered, which are excluded, which are subject to benefit limits and which require preauthorization. There are different benefit plan designs in each product administered by Capital Blue Cross. Members and providers should consult the member's health benefit plan for information or contact Capital Blue Cross for benefit information.

VII. DISCLAIMER

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Capital Blue Cross's medical policies are developed to assist in administering a member's benefits, do not constitute medical advice, and are subject to change. Treating providers are solely responsible for medical advice and treatment of members. Members should discuss any medical policy related to their coverage or condition with their provider and consult their benefit information to determine if the service is covered. If there is a discrepancy between this medical

policy and a member's benefit information, the benefit information will govern. If a provider or a member has a question concerning the application of this medical policy to a specific member's plan of benefits, please contact Capital Blue Cross' Provider Services or Member Services. Capital Blue Cross considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.

VIII. CODING INFORMATION

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Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

Covered when Medically Necessary:

Procedure Codes								
81406								

ICD-10-CM Diagnosis Codes	Description
A81.2	Progressive multifocal leukoencephalopathy
E75.25	Metachromatic leukodystrophy
E75.27	Pelizaeus-Merzbacher disease
F01.50	Vascular dementia without behavioral disturbance
F01.51	Vascular dementia with behavioral disturbance
F06.31	Mood disorder due to known physiological condition with depressive features
F06.32	Mood disorder due to known physiological condition with major depressive-like epis
F06.4	Anxiety disorder due to known physiological condition
F06.8	Other specified mental disorders due to known physiological condition
G43.001	Migraine without aura, not intractable, with status migrainosus
G43.009	Migraine without aura, not intractable, without status migrainosus
G43.011	Migraine without aura, intractable, with status migrainosus
G43.019	Migraine without aura, intractable, without status migrainosus
G43.101	Migraine with aura, not intractable, with status migrainosus
G43.109	Migraine with aura, not intractable, without status migrainosus
G43.111	Migraine with aura, intractable, with status migrainosus
G43.119	Migraine with aura, intractable, without status migrainosus
G43.401	Hemiplegic migraine, not intractable, with status migrainosus
G43.409	Hemiplegic migraine, not intractable, without status migrainosus
G43.411	Hemiplegic migraine, intractable, with status migrainosus
G43.419	Hemiplegic migraine, intractable, without status migrainosus
G43.501	Persistent migraine aura without cerebral infarction, not intractable, with status migrainosus

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ICD-10-CM Diagnosis Codes	Description
G43.509	Persistent migraine aura without cerebral infarction, not intractable, without status migrainosus
G43.511	Persistent migraine aura without cerebral infarction, intractable, with status migrainosus
G43.519	Persistent migraine aura without cerebral infarction, intractable, without status migrainosus
G43.601	Persistent migraine aura with cerebral infarction, not intractable, with status migrainosus
G43.609	Persistent migraine aura with cerebral infarction, not intractable, without status migrainosus
G43.611	Persistent migraine aura with cerebral infarction, intractable, with status migrainosus
G43.619	Persistent migraine aura with cerebral infarction, intractable, without status migrainosus
G43.801	Other migraine, not intractable, with status migrainosus
G43.809	Other migraine, not intractable, without status migrainosus
G43.811	Other migraine, intractable, with status migrainosus
G43.819	Other migraine, intractable, without status migrainosus
G43.E01	Chronic migraine with aura, not intractable, with status migrainosus
G43.E09	Chronic migraine with aura, not intractable, without status migrainosus
G43.E11	Chronic migraine with aura, intractable, with status migrainosus
G43.E19	Chronic migraine with aura, intractable, without status migrainosus
G45.8	Other transient cerebral ischemic attacks and related syndromes
G45.9	Transient cerebral ischemic attack, unspecified
I63.311	Cerebral infarction due to thrombosis of right middle cerebral artery
I63.312	Cerebral infarction due to thrombosis of left middle cerebral artery
I63.313	Cerebral infarction due to thrombosis of bilateral middle cerebral arteries
I63.321	Cerebral infarction due to thrombosis of right anterior cerebral artery
I63.322	Cerebral infarction due to thrombosis of left anterior cerebral artery
I63.323	Cerebral infarction due to thrombosis of bilateral anterior arteries
I63.331	Cerebral infarction due to thrombosis of right posterior cerebral artery
I63.332	Cerebral infarction due to thrombosis of left posterior cerebral artery
I63.333	Cerebral infarction due to thrombosis of bilateral posterior cerebral arteries
I63.341	Cerebral infarction due to thrombosis of right cerebellar artery
I63.342	Cerebral infarction due to thrombosis of left cerebellar artery
I63.343	Cerebral infarction due to thrombosis of bilateral cerebellar arteries
I63.39	Cerebral infarction due to thrombosis of other cerebral artery
I63.411	Cerebral infarction due to embolism of right middle cerebral artery
I63.412	Cerebral infarction due to embolism of left middle cerebral artery

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ICD-10-CM Diagnosis Codes	Description
I63.413	Cerebral infarction due to embolism of bilateral middle cerebral arteries
I63.421	Cerebral infarction due to embolism of right anterior cerebral artery
I63.422	Cerebral infarction due to embolism of left anterior cerebral artery
I63.423	Cerebral infarction due to embolism of bilateral anterior cerebral arteries
I63.431	Cerebral infarction due to embolism of right posterior cerebral artery
I63.432	Cerebral infarction due to embolism of left posterior cerebral artery
I63.433	Cerebral infarction due to embolism of bilateral posterior cerebral arteries
I63.441	Cerebral infarction due to embolism of right cerebellar artery
I63.442	Cerebral infarction due to embolism of left cerebellar artery
I63.443	Cerebral infarction due to embolism of bilateral cerebellar arteries
I63.49	Cerebral infarction due to embolism of other cerebral artery
I63.511	Cerebral infarction due to unspecified occlusion or stenosis of right middle cerebral artery
I63.512	Cerebral infarction due to unspecified occlusion or stenosis of left middle cerebral artery
I63.513	Cerebral infarction due to unspecified occlusion or stenosis of bilateral middle arteri
I63.521	Cerebral infarction due to unspecified occlusion or stenosis of right anterior cerebral artery
I63.522	Cerebral infarction due to unspecified occlusion or stenosis of left anterior cerebral artery
I63.523	Cerebral infarction due to unspecified occlusion or stenosis of bilateral anterior arter
I63.531	Cerebral infarction due to unspecified occlusion or stenosis of right posterior cerebra artery
I63.532	Cerebral infarction due to unspecified occlusion or stenosis of left posterior cerebral artery
I63.533	Cerebral infarction due to unspecified occlusion or stenosis of bilateral posterior arteries
I63.541	Cerebral infarction due to unspecified occlusion or stenosis of right cerebellar artery
I63.542	Cerebral infarction due to unspecified occlusion or stenosis of left cerebellar artery
I63.543	Cerebral infarction due to unspecified occlusion or stenosis of bilateral cerebellar arteries
I63.59	Cerebral infarction due to unspecified occlusion or stenosis of other cerebral artery
I67.3	Progressive vascular leukoencephalopathy
I63.81	Other cerebral infarction due to occlusion or stenosis of small artery
I63.89	Other cerebral infarction
I67.850	Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy
R41.81	Age-related cognitive decline
R41.82	Altered mental status, unspecified

IX. REFERENCES

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X. POLICY HISTORY

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MP 2.247	**CAC 4/24/12 New policy**. Adopting BCBSA. This testing was considered medically necessary in MP 2.242 Genetic Testing for Inherited Disease prior to the 12/1/11 revision when the table was deleted. Now investigational.
	6/4/13 CAC- Consensus review. Administrative code review complete.
	CAC 3/25/14 Minor revision. Changed testing from investigational to medically necessary with criteria. Added rationale section. Updated references.
	CAC 3/24/15 Minor review. Added "and" between the 2 bullets in the medical policy statement to clarify that both conditions should be met for the testing to be medically necessary. Updated references and rationale. Policy coded.
	CAC 3/29/16 Consensus review. No change to policy statements. References and rationale updated. Coding reviewed.
	11/15/16 Admin Update Variation Reformatting

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1/1/17 Admin Update New diagnosis codes added effective 10/1/16
CAC 3/28/17 Consensus review. Policy statements unchanged. Appendix added. Rationale section updated. Coding Reviewed
CAC 7/25/17 Minor revision. • NOTCH3 was added to the 1st medically necessary statement to further define the type of genetic testing. • Skin biopsy added as a medically necessary requirement (1st bullet of the 1st medically necessary policy statement). • Revised with updated genetics nomenclature. “Mutations” changed to “variants” within the policy. And • A medically necessary statement was added for testing in asymptomatic and family members of individuals with CADASIL. Description/Background, Cross Reference, Rationale, and Reference sections updated. Coding reviewed
4/9/18 Consensus review. No change to the policy statements. References reviewed and rationale revised. Appendix removed.
10/1/18 Admin Update: Removed deleted ICD-10 codes and added new ICD-10 codes effective 10/1/18.
5/8/19 Consensus review. No change to policy statements. Background, summary of evidence, and references updated.
4/10/2020 Consensus Review. No change to policy statement. References checked and updated. Coding checked with no changes.
5/19/2021 Minor Review. To align with BCBSA’s policy stance, skin biopsy was taken out as a MN requirement in the 1st and 2nd bullet point. Updated Policy Guidelines and References. No changes to coding.
5/19/2022 Consensus Review. References updated. Coding reviewed.
10/01/2023 Admin update. New ICD10 codes added to policy from new code review.
08/31/2023 Consensus review. No change to policy statement. Production Variation language and Background updated.

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