



FEP Medical Policy Manual

FEP 2.04.75 Genetic Testing of CADASIL Syndrome

Annual Effective Policy Date: July 1, 2024

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Related Policies:

None

Genetic Testing of CADASIL Syndrome

Description

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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 individuals with suspected CADASIL and their family members.

OBJECTIVE

The objective of this evidence review is to determine whether genetic testing improves the net health outcome in individuals with suspected CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy) syndrome and in asymptomatic individuals with family members who have CADASIL syndrome.

POLICY STATEMENT

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

- Clinical signs, symptoms, and imaging results are consistent with CADASIL, indicating that the pretest probability of CADASIL is at least in the moderate-to-high range (see the Policy Guidelines section); and
- The diagnosis of CADASIL is inconclusive following alternative 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 section) may be considered **medically necessary**.

Genetic testing for a *NOTCH3* variant to confirm the diagnosis of CADASIL syndrome in all other situations is considered **investigational**.

POLICY GUIDELINES

Genetic testing for *NOTCH3* comprises targeted sequencing of specific exons (eg, exon 4 only, exons 2-6), general sequencing of *NOTCH3* exons (eg, 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 cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is present in 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 <i>NOTCH3</i> Variant	Percent With <i>NOTCH3</i> Variant	Points
<i>Clinical</i>			
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
<i>Radiologic</i>			
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

Adapted from Pescini et al (2012)
LE: leukoencephalopathy; No: number.

Genetics Nomenclature Update

The 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 evidence review updates in 2017 (see Table PG2). The Society's nomenclature is recommended by the Human Variome Project, the Human Genome Organisation, and by the Human Genome Variation Society itself.

The American College of Medical Genetics and Genomics and the Association for Molecular Pathology standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations, in addition to the 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 individuals 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.

BENEFIT APPLICATION

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

Screening (other than the preventive services listed in the brochure) is not covered. Please see Section 6 General exclusions.

Benefits are available for specialized diagnostic genetic testing when it is medically necessary to diagnose and/or manage a patient's existing medical condition. Benefits are not provided for genetic panels when some or all of the tests included in the panel are not covered, are experimental or investigational, or are not medically necessary.

FDA 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 (FDA) has chosen not to require any regulatory review of this test.

RATIONALE

Summary of Evidence

For individuals with suspected cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (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*. 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. 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 (eg, 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 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. 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 (eg, 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.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in "Supplemental Information" if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

No guidelines with US representation or that were informed by a systematic review were identified. One position statement was identified.

American Heart Association

In a 2023 scientific statement, the American Heart Association reviewed the current clinical, genetic, and imaging aspects of CADASIL to provide prevention, management, and therapeutic considerations to support future treatment recommendations.³¹ In consideration of when to test for *NOTCH3* mutations, they state to "[c]onsider gene testing in patients with small vessel stroke before 55 y[ears] of age with a paucity of vascular risk factors (eg, normotensive, nondiabetic, nonsmoker) or positive family history of CADASIL."

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

REFERENCES

1. Yuan L, Chen X, Jankovic J, et al. CADASIL: A NOTCH3-associated cerebral small vessel disease. *J Adv Res*. Jan 02 2024. PMID 38176524
2. Joutel A, Favrole P, Labauge P, et al. Skin biopsy immunostaining with a Notch3 monoclonal antibody for CADASIL diagnosis. *Lancet*. Dec 15 2001; 358(9298): 2049-51. PMID 11755616
3. Lesnik Oberstein SA, van Duinen SG, van den Boom R, et al. Evaluation of diagnostic NOTCH3 immunostaining in CADASIL. *Acta Neuropathol*. Aug 2003; 106(2): 107-11. PMID 12756589
4. Muqtadar H, Testai FD. Single gene disorders associated with stroke: a review and update on treatment options. *Curr Treat Options Cardiovasc Med*. Jun 2012; 14(3): 288-97. PMID 22528196
5. del Ro-Espnola A, Mendiroz M, Domingues-Montanari S, et al. CADASIL management or what to do when there is little one can do. *Expert Rev Neurother*. Feb 2009; 9(2): 197-210. PMID 19210195
6. Malandrini A, Gaudio C, Gambelli S, et al. Diagnostic value of ultrastructural skin biopsy studies in CADASIL. *Neurology*. Apr 24 2007; 68(17): 1430-2. PMID 17452591
7. Brulin P, Godfraind C, Leteurtre E, et al. Morphometric analysis of ultrastructural vascular changes in CADASIL: analysis of 50 skin biopsy specimens and pathogenic implications. *Acta Neuropathol*. Sep 2002; 104(3): 241-8. PMID 12172909
8. Markus HS, Martin RJ, Simpson MA, et al. Diagnostic strategies in CADASIL. *Neurology*. Oct 22 2002; 59(8): 1134-8. PMID 12395806
9. Choi JC, Lee KH, Song SK, et al. Screening for NOTCH3 gene mutations among 151 consecutive Korean patients with acute ischemic stroke. *J Stroke Cerebrovasc Dis*. Jul 2013; 22(5): 608-14. PMID 22133740
10. Mosca L, Marazzi R, Ciccone A, et al. NOTCH3 gene mutations in subjects clinically suspected of CADASIL. *J Neurol Sci*. Aug 15 2011; 307(1-2): 144-8. PMID 21616505
11. Hack RJ, Rutten J, Lesnik Oberstein SAJ. In: Adam MP, Feldman J, Mirzaa GM, et al., eds. *GeneReviews*, Seattle, WA: University of Washington; 2019.
12. Donahue CP, Kosik KS. Distribution pattern of Notch3 mutations suggests a gain-of-function mechanism for CADASIL. *Genomics*. Jan 2004; 83(1): 59-65. PMID 14667809
13. Chabriat H, Joutel A, Dichgans M, et al. Cadasil. *Lancet Neurol*. Jul 2009; 8(7): 643-53. PMID 19539236
14. Hack RJ, Gravesteijn G, Cerfontaine MN, et al. Three-tiered EGFR domain risk stratification for individualized NOTCH3-small vessel disease prediction. *Brain*. Jul 03 2023; 146(7): 2913-2927. PMID 36535904
15. Opher C, Gonik M, Duering M, et al. Genome-wide genotyping demonstrates a polygenic risk score associated with white matter hyperintensity volume in CADASIL. *Stroke*. Apr 2014; 45(4): 968-72. PMID 24578207

16. Dup C, Guey S, Biard L, et al. Phenotypic variability in 446 CADASIL patients: Impact of NOTCH3 gene mutation location in addition to the effects of age, sex and vascular risk factors. *J Cereb Blood Flow Metab.* Jan 2023; 43(1): 153-166. PMID 36254369
17. Pescini F, Nannucci S, Bertaccini B, et al. The Cerebral Autosomal-Dominant Arteriopathy With Subcortical Infarcts and Leukoencephalopathy (CADASIL) Scale: a screening tool to select patients for NOTCH3 gene analysis. *Stroke.* Nov 2012; 43(11): 2871-6. PMID 22996955
18. Lee YC, Liu CS, Chang MH, et al. Population-specific spectrum of NOTCH3 mutations, MRI features and founder effect of CADASIL in Chinese. *J Neurol.* Feb 2009; 256(2): 249-55. PMID 19242647
19. Yin X, Wu D, Wan J, et al. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy: Phenotypic and mutational spectrum in patients from mainland China. *Int J Neurosci.* 2015; 125(8): 585-92. PMID 25105908
20. Joutel A, Vahedi K, Corpechot C, et al. Strong clustering and stereotyped nature of Notch3 mutations in CADASIL patients. *Lancet.* Nov 22 1997; 350(9090): 1511-5. PMID 9388399
21. Abramychewa N, Stepanova M, Kalashnikova L, et al. New mutations in the Notch3 gene in patients with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL). *J Neurol Sci.* Feb 15 2015; 349(1-2): 196-201. PMID 25623805
22. Maksemous N, Smith RA, Haupt LM, et al. Targeted next generation sequencing identifies novel NOTCH3 gene mutations in CADASIL diagnostics patients. *Hum Genomics.* Nov 24 2016; 10(1): 38. PMID 27881154
23. Gorukmez O, Gorukmez O, Topak A, et al. NOTCH3 Variants in Patients with Suspected CADASIL. *Ann Indian Acad Neurol.* 2023; 26(4): 484-490. PMID 37970308
24. Peters N, Opherck C, Bergmann T, et al. Spectrum of mutations in biopsy-proven CADASIL: implications for diagnostic strategies. *Arch Neurol.* Jul 2005; 62(7): 1091-4. PMID 16009764
25. Tikka S, Mykknen K, Ruchoux MM, et al. Congruence between NOTCH3 mutations and GOM in 131 CADASIL patients. *Brain.* Apr 2009; 132(Pt 4): 933-9. PMID 19174371
26. Dotti MT, Federico A, Mazzei R, et al. The spectrum of Notch3 mutations in 28 Italian CADASIL families. *J Neurol Neurosurg Psychiatry.* May 2005; 76(5): 736-8. PMID 15834039
27. Dichgans M, Markus HS, Salloway S, et al. Donepezil in patients with subcortical vascular cognitive impairment: a randomised double-blind trial in CADASIL. *Lancet Neurol.* Apr 2008; 7(4): 310-8. PMID 18296124
28. De Maria R, Campolo J, Frontali M, et al. Effects of sapropterin on endothelium-dependent vasodilation in patients with CADASIL: a randomized controlled trial. *Stroke.* Oct 2014; 45(10): 2959-66. PMID 25184356
29. Huang L, Yang Q, Zhang L, et al. Acetazolamide improves cerebral hemodynamics in CADASIL. *J Neurol Sci.* May 15 2010; 292(1-2): 77-80. PMID 20227091
30. Peters N, Freilinger T, Opherck C, et al. Effects of short term atorvastatin treatment on cerebral hemodynamics in CADASIL. *J Neurol Sci.* Sep 15 2007; 260(1-2): 100-5. PMID 17531269
31. Meschia JF, Worrall BB, Elahi FM, et al. Management of Inherited CNS Small Vessel Diseases: The CADASIL Example: A Scientific Statement From the American Heart Association. *Stroke.* Oct 2023; 54(10): e452-e464. PMID 37602377

POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:

Date	Action	Description
March 2012	New policy	
December 2012	Replace policy	Updated with literature review and updated references. Policy statement unchanged.
December 2013	Replace policy	Policy updated with literature review. Reference 13 added. Medically necessary statement added for patients with high likelihood of disorder, in whom diagnosis cannot be made by other methods. Title revised to include all genetic testing for CADASIL syndrome and "syndrome" added to title and policy statements.
December 2014	Replace policy	Policy updated with literature review through September 6, 2014. References 14, 16, and 24 added. Policy statement unchanged.
June 2017	Replace policy	Policy updated with literature review through February 23, 2017; reference 20 added. The policy is revised with updated genetics nomenclature. "Mutations" changed to "variants" in policy statements. Requirement for skin biopsy removed from medically necessary policy statement for testing of symptomatic patients; medically necessary statements added for testing in asymptomatic and presymptomatic family members of individuals with CADASIL.
June 2018	Replace policy	Policy updated with literature review through February 5, 2018; no references added. Statements removed for testing in asymptomatic and presymptomatic family members of individuals with CADASIL due to benefit application of testing to diagnose and/or manage a patient's existing medical condition.
June 2019	Replace policy	Policy updated with literature review through February 5, 2019; no references added. Policy statements unchanged.
June 2020	Replace policy	Policy updated with literature review through April 2, 2020; European Academy of Neurology consensus recommendations added. Policy statement changed to remove skin biopsy requirement prior to genetic testing.
June 2021	Replace policy	Policy updated with literature review through February 25, 2021; no references added. Policy statements unchanged.
June 2022	Replace policy	Policy updated with literature review through January 17, 2022; no references added. Policy statements unchanged.
June 2023	Replace policy	Policy updated with literature review through January 16, 2023; no references added. Minor editorial refinement to policy statement; intent unchanged.
June 2024	Replace policy	Policy updated with literature review through February 29, 2024; references added. Policy statements unchanged.

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