BlueCross BlueShield Federal Employee Program.

FEP 2.04.75 Genetic Testing of CADASIL Syndrome

Effective Date: July 15, 2018

Related Policies: None

Genetic Testing of CADASIL Syndrome

Description

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

FDA REGULATORY STATUS

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). Exome or genome sequencing tests as a clinical service are available under the auspices of CLIA. Laboratories that offer LDTs must be licensed by 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.

POLICY STATEMENT

Genetic testing for a *NOTCH3* variant to confirm the diagnosis of CADASIL syndrome in a patient may be considered **medically necessary** under the following conditions:

- Clinical signs, symptoms, skin biopsy, 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 skin biopsy and magnetic resonance imaging.

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.

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 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	277/277	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

LE: leukoencephalopathy.

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 is being implemented for genetic testing medical evidence review updates starting in 2017 (see Table PG2). The Society's nomenclature is recommended 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 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

Genetic counseling is primarily aimed at patients who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual's family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

BENEFIT APPLICATION

Screening of asymptomatic individuals (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.

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

RATIONALE

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*. 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 in the exclude other conditions in a differential diagnosis. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Given the high clinical sensitivity of genetic testing for CADASIL and the severity of the condition but no direct evidence on improvements in outcomes, genetic testing for CADASIL syndrome is medically necessary when the diagnosis cannot be made by clinical presentation, magnetic resonance imaging, and skin biopsy results. In these cases, *NOTCH3* testing can confirm the diagnosis of CADASIL with a high degree of certainty.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

The European Federation of Neurological Societies' 2010 guidelines on the molecular diagnosis of channelopathies, epilepsies, migraine, stroke, and dementias noted that most *NOTCH3* pathogenic variants occurred within exons 3 and 4 and suggested direct sequencing of these 2 exons if clinical suspicion is high.[27]

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

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

REFERENCES

1. 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):2049-2051. PMID 11755616
2. 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):107-111. PMID 12756589
3. 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):288-297. PMID 22528196
4. del Rio-Espinola A, Mendioroz 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
5. Malandrini A, Gaudiano C, Gambelli S, et al. Diagnostic value of ultrastructural skin biopsy studies in CADASIL. Neurology. Apr 24 2007;68(17):1430-1432. PMID 17452591
6. 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):241-248. PMID 12172909
7. Markus HS, Martin RJ, Simpson MA, et al. Diagnostic strategies in CADASIL. Neurology. Oct 22 2002;59(8):1134-1138. PMID 12395806
8. 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. Nov 29 2013;22(5):608-614. PMID 22133740
9. 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):144-148. PMID 21616505
10. Lesnik Oberstein SAJ, Boon EMJ, Dichgans M. CADASIL. GeneReviews. 2016. PMID 20301673
11. 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
12. Chabriat H, Joutel A, Dichgans M, et al. Cadasil. Lancet Neurol. Jul 2009;8(7):643-653. PMID 19539236
13. Opherk 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):968-972. PMID 24578207
14. 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):2871-2876. PMID 22996955
15. Fernandez A, Gomez J, Alonso B, et al. A next-generation sequencing of the NOTCH3 and HTRA1 genes in CADASIL patients. J Mol Neurosci. Jul 2015;56(3):613-616. PMID 25929831
16. 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):249-255. PMID 19242647
17. 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. Sep 1 2015;125(8):585-592. PMID 25105908
18. 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):1511-1515. PMID 9388399

19. Abramycheva N, Stepanova M, Kalashnikova L, et al. New mutations in the Notch3 gene in patients with cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy (CADASIL). J Neurol Sci. Feb 15 2015;349(1-2):196-201. PMID 25623805
20. 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
21. Peters N, Opherk C, Bergmann T, et al. Spectrum of mutations in biopsy-proven CADASIL: implications for diagnostic strategies. Arch Neurol. Jul 2005;62(7):1091-1094. PMID 16009764
22. Tikka S, Mykkanen K, Ruchoux MM, et al. Congruence between NOTCH3 mutations and GOM in 131 CADASIL patients. Brain. Apr 2009;132(Pt 4):933-939. PMID 19174371
23. 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):736-738. PMID 15834039
24. 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):310-318. PMID 18296124
25. 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
26. Peters N, Freilinger T, Opherk C, et al. Effects of short term atorvastatin treatment on cerebral hemodynamics in CADASIL. J Neurol Sci. Sep 15 2007;260(1-2):100-105. PMID 17531269
27. 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):2959-2966. PMID 25184356
28. Burgunder JM, Finsterer J, Szolnoki Z, et al. EFNS guidelines on the molecular diagnosis of channelopathies, epilepsies, migraine, stroke, and dementias. Eur J Neurol. May 2010;17(5):641-648. PMID 20298421

POLICY HISTORY

Date	Action	Description
March 2012	New Policy	
December 2012	Update Policy	Updated with literature review and updated references. Policy statement unchanged.
December 2013	Update 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	Update Policy	Policy updated with literature review through September 6, 2014. References 14, 16, and 24 added. Policy statement unchanged.
June 2017	Update 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	Update 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.