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Medical Policy Manual

Topic: Genetic Testing for CADASIL Syndrome

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Section: Genetic Testing

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IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Mutations 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 mutations exist in the NOTCH3 gene for patients with suspected CADASIL and their family members.

Background

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

The clinical presentation of CADASIL is variable and 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 (MRI) findings, are extremely important in determining the diagnosis of CADASIL. When the differential diagnosis includes CADASIL, various other tests are available for diagnosis:

- 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 NOTCH3 protein in the walls of small blood vessels.[1] Lesnick Oberstein et al. (2003) estimated sensitivity and specificity at 85-90% and 95-100%, respectively, for 2 observers of the test results in a population of patients and controls correlated with clinical, genetic and MRI parameters.[2]

- Detection of granular osmiophilic material (GOM) in the same skin biopsy sample by electron microscopy

  The major component of GOM is the ectodomain of the *NOTCH3* gene product.[3] GOM accumulates directly in vascular smooth muscle cells and, when present, is considered a hallmark of the disease.[4] However, GOM 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%.[5-7]

- Genetic testing by direct sequencing of selected exons or of exons 2-24 of the *NOTCH3* gene (see Scientific Evidence section below)

- Examination of brain tissue for the presence of GOM

  GOM was originally described as limited to brain vessels.[8] Examination of brain biopsy or autopsy after death was an early gold standard for diagnosis. In some cases, peripheral staining for GOM has been absent even though positive results were seen in brain vessels.

NOTCH3 Mutations

Mutations in *NOTCH3* have been identified as the underlying cause of CADASIL. In almost all cases, the mutations lead to loss or gain of a cysteine residue that could lead to increased reactivity of the NOTCH3 protein, resulting in ligand-binding and toxic effects.[9]

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 2,321 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-like repeats, traverses the membrane once, and has an intracellular domain required for signal transduction.[10]

Mutations in the *NOTCH3* gene have been differentiated into those that are causative of the CADASIL syndrome and those that are of uncertain significance. Causative mutations affect conserved cysteine residues within 34 epidermal growth factor (EGF)-like repeat domains in the extracellular portion of the NOTCH3 protein.[10,11] More than 150 causative mutations have been reported in at least 500 pedigrees. *NOTCH3* has 33 exons, but all CADASIL mutations reported to date have occurred in exons 2–24, which encode the 34 EGF-like repeats, with strong clustering in exons 3 and 4, which encode EGFR 2–5 (>40% of mutations in >70% of families occur in these exons).[12]

Regulatory Status

As of August 2012, there are no manufactured test kits for detecting *NOTCH3* gene mutations; therefore, this testing has not been reviewed by the U.S. Food and Drug Administration (FDA). Rather,

NOTCH3 gene sequencing is a laboratory-developed test (LDT), offered by clinical laboratories licensed under Clinical Laboratory improvement Act (CLIA) for high-complexity testing.

MEDICAL POLICY CRITERIA

NOTCH3 testing for the diagnosis of CADASIL is considered **investigational.**

SCIENTIFIC EVIDENCE

Validation of the clinical use of any genetic test focuses on 3 main principles:

1. The analytic validity of the test, which refers to the technical accuracy of the test in detecting a mutation that is present or in excluding a mutation that is absent;
2. The clinical validity of the test, which refers to the diagnostic performance of the test (sensitivity, specificity, positive and negative predictive values) in detecting clinical disease; and
3. The clinical utility of the test, i.e., how the results of the diagnostic test will be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes.

Literature Appraisal

Analytical Validity

No relevant primary data on analytic validity of NOTCH3 testing were identified. The test is generally done by gene sequencing analysis, which is expected to have high analytic validity when performed under optimal conditions.

Clinical Validity

Several retrospective and prospective studies have examined the association between *NOTCH3* genes and cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), as shown in the following table. These have been divided into 2 categories: Part 1, diagnostic studies, in which the patients enrolled were suspected but not confirmed to have CADASIL; and Part 2, clinical validity studies, in which the patients had already been diagnosed with the disease by some method other than genetic testing. The diagnostic studies are more likely to represent the target population in which the test would be used.

Table. Studies of the association of *NOTCH3* with CADASIL diagnosis; results of published studies supporting *NOTCH3* genotyping test claims.

Study	Patients Evaluated	NOTCH3 Exons Evaluated	Results	
Part 1 Diagnostic Studies			**Diagnostic Yield**	**Specificity**
Mosca et al. 2011[9]	Patients: 140 patients with clinical suspicion of CADASIL (Italian and	Direct sequencing of exons 2-8, 10, 14,	Patients: 14 patients with causative mutations located in 10	NR

	Chinese). Patient Selection: History of premature strokes; migraine with aura; vascular dementia; suggestive MRI findings; a consistent family history; or a combination of the above criteria.	19, 20, and 22.	different exons. 126 patients free of pathogenic mutations. Family Members: Analysis of 15 additional family members identified 11 of the same causative mutations.	
Lee et al. 2009[13]	Patients: 39 patients with suspected CADASIL (China). 100 healthy elderly controls 80 years or older. Patient Selection: Suggestive MRI findings and at least one of the following: young age at onset, cognitive decline, psychiatric disorders, or consistent family history.	Direct sequencing of exons 2-23.	Patients: 9 different point mutations identified in 21/39 patients. Family members: No data for additional family members	100% No mutations found in 100 healthy elderly controls.
Markus et al. 2002[7]	Patients: 83 patients with suspected CADASIL (UK). Patient Selection: Patients were younger than 60 years of age with recurrent lacunar stroke with leukoaraiosis on neuroimaging. Migraine, psychiatric disorders, or dementia could occur but were not essential.	Direct sequencing of exons 3-4; SSCP of exons 2, 5-23.	Patients: 15 different point mutations identified in 48 families with a total of 116 symptomatic patients, 73% in exon 4, 8% in exon 3, and 6% in exons 5 and 6. Family Members: No data for additional family members	NR
Choi et al. 2011[8]	Patients: 151 consecutive Korean patients with acute ischemic stroke. Patient Selection: History of acute ischemic stroke, neurologic exam, cranial computed tomography or MRI.	Bidirectional sequencing of exons 3, 4, 6, 11 and 18.	Patients: 6 patients (4%) were found with the identical *NOTCH3* mutation (R544C; exon 11). Of these, all had pre-existing lacunar infarction, 5 (83.3%) had grade 2-3 white-matter hyperintensity lesions, and a history of hypertension; a history of stroke and dementia was higher in patients with mutations. Family Members: No data for additional family	NR

			members	
Part 2 Clinical Validity Studies			**Sensitivity**	**Specificity**
Choi et al. 2013[14]	Patients: 73 unrelated patients diagnosed with CADASIL between 2004-2009. Patient Diagnosis/Selection: Patients were diagnosed via clinical and MRI, and stroke history.	Bidirectional sequencing of R544C (exon 11).	Patients: 65 of 73 Patients (90.3%) had the same R544C genotype.	NR
Peters et al. 2005[15]	Patients: 125 unrelated patients diagnosed with CADASIL. Patient Diagnosis/Selection: Skin biopsy-proven CADASIL pts referred between 1994 and 2003 (German).	Bidirectional sequencing of all exons.	Sensitivity: 96% Patients: 54 distinct mutations in 120 (96.0%) of the 125 patients. In 5 patients (4.0%), no mutation was identified. Family Members: No data for additional family patients	NR
Tikka et al. 2009[16]	Patients: 131 patients from 28 families diagnosed with CADASIL (Finnish, Swedish, and French). Patient Diagnosis/Selection: EM examination of skin biopsy was performed; 26 asymptomatic controls from CADASIL families.	Direct sequencing of exons 2-24.	Sensitivity: 100% Patients: 131 CADASIL patients were mutation positive. Family Members: No data for additional family patients. No mutation reporting per family or per unrelated individual.	100% No mutations were found in the 26 negative controls.
Dotti et al. 2005[17]	Patients: 28 unrelated, consecutively diagnosed patients with CADASIL (Italian). Patient Diagnosis/Selection: Patients were diagnosed via clinical and MRI.	DHPLC, followed by confirmatory sequencing of identified mutations.	Sensitivity: 100%. Patients: All 28 patients had mutations.	NR
Joutel et al.	Patients: 50 unrelated patients with a clinical suspicion of	SSCP or heteroduplex	Sensitivity: 90%	100%

1997[18]	CADASIL and 100 healthy controls. Patient Diagnosis/Selection: History of recurrent strokes, migraine with aura, vascular dementia, or a combination; brain MRI with suggestive findings; and a consistent familial history.	analysis of all exons, followed by confirmatory sequencing of identified mutations.	Patients: 45 of 50 CADASIL patients had mutations.	No mutations were found in 100 healthy controls.

MRI, magnetic resonance imaging; SSCP, single-stranded conformational polymorphism; EM, electron microscope; DHPLC, denaturing high-performance liquid chromatography

The results of the clinical validity studies demonstrate that a *NOTCH3* mutation is found in a high percentage of patients with a clinical diagnosis of CADASIL, with studies reporting a clinical sensitivity of 90-100%. Limited data on specificity is from testing small numbers of healthy controls, and no false positive *NOTCH3* mutations have been reported in these populations. The diagnostic yield studies report a variable diagnostic yield, ranging from 10-54%. These lower numbers likely reflect testing in heterogeneous populations that include patients with other disorders.

Clinical Utility

A single study that addressed the clinical utility of CADASIL testing was identified and described below:

Pescini et al. published a study in 2013 that attempted to identify clinical factors that increase the likelihood of a pathologic mutation being present.[19] The authors first performed a systematic review to determine the frequency with which clinical and radiologic factors were associated with a positive genetic test. Evidence was identified from 15 clinical series of patients with CADASIL. The authors then created a preliminary scale that assigned weighted scores to common disease features based on their frequencies obtained in a pooled analysis of selected international CADASIL series. The accuracy of the scale versus the genetic diagnosis was tested with receiver operating characteristic analysis after the application of this scale to 61 CADASIL and 54 NOTCH3-negative patients (no pathogenic mutation on exons 2-23 of the NOTCH3 gene). Authors noted several limitations of their study, including the construction of the scale. The scale was based on data derived from a pooled analysis of selected international CADASIL series, and not all disease features were included. Further, different combinations of history and clinical features could not be accounted for in the scale. The scale was based on 3 centers with local expertise and therefore the scale may not be generalizable. Because a limited patient population was included in the study, the authors noted the results need to be confirmed and further validated with the application of the scale on larger and different series.

Currently, there is no specific clinical treatment for CADASIL that has established efficacy. There is no recommended clinical treatment for CADASIL. Supportive care in the form of practical help, emotional support, and counseling are appropriate for affected individuals and their families. [10] Three studies were found that addressed treatment efficacy in CADASIL as follows:

- A double-blind, placebo controlled trial that evaluated the efficacy and safety of donepezil hydrochloride (HCl) in individuals with CADASIL was conducted.[20] The study resulted in donepezil HCl having no effect on the primary cognitive endpoint, the vascular AD assessment

scale cognitive subscale (V-ADAS-cog) score in patients with CADASIL who had cognitive impairment.

- Another study evaluated the efficacy and tolerance of a 24-week treatment with 250 mg/d acetazolamide (ACZ), which could be chronically implemented to improve cerebral hemodynamics in CADASIL patients (n=16).[21] Treatment with ACZ resulted in a significant increase of mean blood flow velocity (MFV) in the middle cerebral artery (MCA) compared with MFV in the MCA at rest before treatment (57.68±12.7 cm/s versus 67.12±9.4 cm/s; p=0.001). During the treatment period, none of the subjects developed new neurologic symptoms, and the original symptoms in these patients, such as headaches and dizziness, were relieved.
- A third study evaluated the use of HMG-CoA-reductase-inhibitors (statins) in 24 CADASIL subjects treated with atorvastatin for 8 weeks.[22] Treatment was started with 40 mg, followed by a dosage increase to 80 mg after 4 weeks. Transcranial Doppler sonography measuring MFV in the MCA was performed at baseline and at the end of the treatment period. There was no significant treatment effect on MFV (p=0.5) or cerebral vasoreactivity, as assessed by hypercapnia (p=0.5) and intravenous L-arginine (p=0.4) in the overall cohort. However, an inverse correlation was found between vasoreactivity at baseline and changes of both CO2- and L-arginine-induced vasomotor response (both $p<0.05$). Short-term treatment with atorvastatin resulted in no significant improvement of hemodynamic parameters in the overall cohort of CADASIL subjects.

Predictive testing of at-risk family members.

The clinical utility of predictive testing for at-risk family members has not been established. For an asymptomatic individual, knowledge of mutation status will not generally lead to any management changes that can prevent or delay the onset of the disorder. For example, avoiding tobacco use may be one factor that delays onset of disease, but this is a general recommendation that is not altered by genetic testing.

Clinical Practice Guidelines

No evidence-based clinical practice guidelines were identified which recommend NOTCH3 testing for the diagnosis or management of CADASIL.

Summary

The diagnostic accuracy of NOTCH3 genetic testing cannot be determined with certainty due to the lack of a true gold standard for diagnosis of this disease. The diagnosis of CADASIL can often be made by a combination of clinical presentation, MRI findings, and skin biopsy findings. Though a high percentage of patients in whom CADASIL is diagnosed by clinical methods will have a *NOTCH3* mutation, NOTCH3 genetic testing has uncertain clinical utility. *NOTCH3* testing is not necessary for diagnosis. Further, there is no effective treatment for CADASIL and therefore establishing a definitive diagnosis of CADASIL will not change management. As a result, *NOTCH3* mutation testing for the diagnosis of CADASIL is considered investigational.

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CROSS REFERENCES

Genetic and Molecular Diagnostic Testing, Genetic Testing, Policy No. 20

CODES	NUMBER	DESCRIPTION
CPT	81406	Molecular pathology procedure, Tier 2, Level 7
HCPCS	None	