



Louisiana

Genetic Testing of CADASIL Syndrome

Policy # 00319

Original Effective Date: 10/19/2011

Current Effective Date: 12/20/2017

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When Services Are Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider genetic testing of *NOTCH3* to confirm the diagnosis of CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy) syndrome in a patient to be **eligible for coverage** 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 section); and
- The diagnosis of CADASIL is inconclusive following alternate methods of testing, including skin biopsy and magnetic resonance imaging (MRI).

Based on review of available data, the Company may consider genetic testing to confirm the diagnosis of CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy) syndrome for individuals who are asymptomatic with a family member (first- and second-degree relative) with a diagnosis of CADASIL syndrome to be **eligible for coverage** under either of the following conditions:

- Targeted genetic testing of the known *NOTCH3* familial variant if there is a family member with a known variant; or
- Genetic testing of *NOTCH3* if the family member's genetic status is unknown (see Policy Guidelines section).

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers genetic testing of *NOTCH3* to confirm the diagnosis of CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy) syndrome in all other situations to be **investigational**.*

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.

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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 (Pescini et al, 2012)

Features	No. With <i>NOTCH3</i> Variant	Percent With <i>NOTCH3</i> 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

Human Genome Variation Society (HGVS) nomenclature is used to report information on variants found in DNA and serves as an international standard in deoxyribonucleic acid (DNA) diagnostics. It is being implemented for genetic testing medical evidence review updates starting in 2017 (see Table PG2). HGVS nomenclature is recommended by HGVS, the Human Variome Project, and the HUMAN Genome Organization (HUGO).

The American College of Medical Genetics and Genomics (ACMG) and Association for Molecular Pathology (AMP) standards and guidelines for interpretation of sequence variants represent expert opinion from ACMG, AMP, and 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

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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.

Background/Overview

CADASIL

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 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
<ul style="list-style-type: none"> • Sporadic SVD with or without hypertension the main risk factor • Multiple sclerosis • Primary angiitis of the central nervous system 	<ul style="list-style-type: none"> • Fabry disease • Cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy • Familial SVD caused by heterozygous variants in the <i>HTRA1</i> gene • Some forms of leukodystrophy

SVD: small vessel disease.



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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 MRI findings, are extremely important in diagnosing CADASIL. The clinical features and mode of inheritance (autosomal dominant versus 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/Source 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 MRI parameters.
- 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. GOM accumulates directly in vascular smooth muscle cells and, when present, is considered a hallmark of the disease. 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%.
- Examination of brain tissue for the presence of GOM 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 GOM 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

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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 with regard to the development of white matter hyperintensities on MRI, 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 is an individualized assessment depends on numerous factors such as family history, symptoms, imaging results, and other specialized testing (e.g., skin biopsy). In 2012, Pescini et al published a study that attempted to identify clinical factors that increase the likelihood of a pathogenic variant being present, with increasing likelihood with the presence of 1 or several factors, including migraine, migraine with aura, transient ischemic attack (TIA)/stroke, psychiatric disturbance, cognitive decline, leukoencephalopathy (with greater risk for leukoencephalopathy extending to the temporal pole or external capsule), and subcortical infarcts.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

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). Genetic testing of *NOTCH3* is available under the auspices of CLIA. Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, the U.S. FDA has chosen not to require any regulatory review of this test.

Centers for Medicare and Medicaid Services (CMS)

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

Rationale/Source

See the Appendix Table 1 for genetic testing categories.

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

Following is a summary of the key literature. Literature that describes the analytic validity, clinical validity, and clinical utility of *NOTCH3* testing was sought.

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TESTING INDIVIDUALS WITH SUSPECTED CADASIL SYNDROME

Clinical Context and Test Purpose

The purposes of genetic testing of symptomatic individuals with suspected CADASIL syndrome are to establish the diagnosis of CADASIL without skin biopsy or other invasive testing and to aid in reproductive planning, when the diagnosis cannot be made clinically.

The questions addressed in this evidence review are: In individuals with suspected CADASIL, does the use of genetic testing result in changes in management or outcome improvements, including eliminating the need for skin biopsy to confirm diagnosis of CADASIL, aid in preimplantation genetic testing to determine likelihood of an affected offspring, or alter reproductive planning decisions?

The following PICOTS were used to select literature to inform this review.

Patients

The relevant population of interest includes individuals with suspected CADASIL.

Interventions

The relevant intervention of interest is genetic testing for *NOTCH3* variants.

Comparators

The relevant comparator of interest is standard clinical management without genetic testing.

Outcomes

The potential beneficial outcome of primary interest would be changes in management associated with improved outcomes initiated based on confirming a genetic diagnosis of CADASIL. Reductions in skin biopsies or other invasive tests to confirm diagnosis of CADASIL are also potential beneficial outcomes.

Potential harmful outcomes are those resulting from a false-positive or false-negative test results. False-positive test results can lead to inappropriate initiation of treatments or psychological harm after receiving positive test results. False-negative test results can lead to lack of medical or neurologic treatments or surveillance.

Timing

The time frame for outcome measures varies from short-term development of symptoms to long-term changes in disease status and outcomes.

Setting

Patients suspected of CADASIL are actively managed by neurologists or psychiatrists due to ischemic episodes, cognitive deficits, migraines with aura, or psychiatric disturbances. Genetic testing is used to confirm a diagnosis of CADASIL. Referral for genetic counseling is important for explanation of genetic disease, heritability, genetic risk, test performance, and possible outcomes.

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Analytic Validity

Limited relevant primary data on analytic validity were identified. The test is generally done by gene sequencing analysis, which is expected to have high analytic validity when performed under optimal conditions.

Fernandez et al (2015) described the development of a next-generation sequencing (NGS) protocol for *NOTCH3* and *HTRA1* genes in 70 patients referred for clinical suspicion of CADASIL, all of whom had previously undergone Sanger sequencing of exons 3 and 4 of the *NOTCH3* gene. *NOTCH3* variants were detected in 6 patients using NGS, including 2 variants previously detected with Sanger sequencing and 4 variants in exons 6, 11, and 19.

Clinical Validity

Several retrospective and prospective studies have examined the association between *NOTCH3* variants and CADASIL, as shown in Table 2. Studies have been divided into 2 categories: Part 1: Diagnostic studies, in which 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.

The results of the clinical validity studies 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 ranging from 90% to 100%. Limited data on specificity derive from testing small numbers of healthy controls, and no false-positive *NOTCH3* 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.

Testing Strategy

Identification of a *NOTCH3* pathogenic variant establishes a diagnosis of CADASIL. For individuals suspected of CADASIL:

- Perform targeted sequencing and analysis of specific *NOTCH3* exons (e.g., exon 4 only, exons 2-6) OR
- Perform general testing of *NOTCH3* exons (e.g., exons 2-24 or all 33 exons).
- If no *NOTCH3* pathogenic variant is identified, skin biopsy is warranted for immunohistochemical staining for Notch3 protein and/or electron microscopy for GOM.

Table 2. Association Between *NOTCH3* and CADASIL Diagnosis: Results From Studies Supporting *NOTCH3* Genotyping Test Claims

Study	Patients Evaluated	<i>NOTCH3</i> Exons Sequenced	Results	Specificity
Part 1: Diagnostic studies			Diagnostic Yield	Specificity

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Mosca et al (2011)	<p>Patients: 140 with clinical suspicion of CADASIL (Italian, Chinese)</p> <p>Selection: History of premature strokes; migraine with aura; vascular dementia; suggestive MRI findings; consistent family history; or combination of the previous criteria</p>	Direct sequencing of exons 2-8, 10, 14, 19-20, 22	<p>Patients: 14 with pathogenic variants located in 10 different exons. 126 patients free of pathogenic variants</p> <p>Family members: Analysis of 15 additional family members identified 11 of the same pathogenic variants</p>	NR
Lee et al (2009)	<p>Patients: 39 with suspected CADASIL (Chinese); 100 healthy elderly controls ≥80 y</p> <p>Selection: Suggestive MRI findings and at least 1 of the following: young age at onset, cognitive decline, psychiatric disorders, or consistent family history</p>	Direct sequencing of exons 2-23	<p>Patients: 9 different SNVs identified in 21/39 patients</p> <p>Family members: No data</p>	<ul style="list-style-type: none"> • 100% • No variants in 100 healthy elderly controls
Markus et al (2002)	<p>Patients: 83 with suspected CADASIL (U.K.)</p> <p>Selection: Patients were <60 y with recurrent lacunar stroke with leukoaraiosis on neuroimaging. Migraine, psychiatric disorders, or dementia could occur but were not essential.</p>	Direct sequencing of exons 3-4; SSCP of exons 2, 5-23	<p>Patients: 15 different SNVs identified in 48 families with 116 symptomatic patients, 73% in exon 4, 8% in exon 3, 6% in exons 5 and 6</p> <p>Family members: No data</p>	NR
Choi et al (2013)	<p>Patients: 151 consecutive patients (Korean) with acute ischemic stroke</p> <p>Selection: History of acute ischemic stroke, neurologic exam, cranial computed tomography, or MRI</p>	Bidirectional sequencing of exons 3, 4, 6, 11, 18	<p>Patients: 6 (4%) were found with identical <i>NOTCH3</i> variant (R544C; exon 11). Of these, all had preexisting lacunar infarction, 5 (83.3%) had grade 2-3 white-matter hyperintensity lesions, and a history of hypertension; history of stroke and dementia was higher</p>	NR

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			in patients with variants Family members: No data	
Yin et al (2015)	Patients: 47 subjects from 34 families (Chinese) diagnosed with suspected CADASIL Diagnosis/selection: MRI abnormalities and presence of >1 typical symptom (e.g., migraine, stroke, cognitive deficits, psychiatric symptoms) or presence of atypical symptoms with positive family history	Testing method per Joutel et al: exons 3 and 4 screened first; if no variants detected, remaining exons analyzed	Patients: 6 known familial variants identified in 8 families and 2 novel pathogenic variants identified in 2 families (exons 3 and 4), and 1 VUS identified in 1 family (exon 2). Overall <i>NOTCH3</i> pathogenic variant prevalence: 29.4%.	NR
Abramycheva et al (2015)	Patients: 30 unrelated patients with suspected CADASIL	Direct sequencing of exons 2-23 via PCR	Patients: 16 SNVs identified in 18 unrelated patients, 12 of which had been previously described and 4 were novel (<i>C194G</i> , <i>V252M</i> , <i>C338F</i> , <i>C484G</i>)	NR
Maksemous et al (2016)	Patients: 44 with suspected clinical diagnosis of CADASIL previously screened for standard sequencing exons (3, 4) and/or (2, 11, 18, 19) by Sanger sequencing and classified as negative for known pathogenic variants	Custom NGS panel	Patients: 6 typical CADASIL pathogenic variants identified in 7/44 patients	NR

Part 2: Clinical validity studies

			Sensitivity	Specificity
Peters et al (2005)	Patients: 125 unrelated patients diagnosed with CADASIL Diagnosis/selection: Skin biopsy-proven CADASIL patients	Bidirectional sequencing of all exons	Sensitivity: 96% Patients: 54 distinct variants in 120 (96.0%) of the 125 patients. In 5 (4.0%) patients, no variants identified. Family members: No data	NR
Tikka et al (2009)	Patients: 131 patients from 28 families diagnosed with CADASIL (Finnish, Swedish, French)	Direct sequencing of exons 2-24	Sensitivity: 100% Patients: 131 CADASIL patients	<ul style="list-style-type: none"> • 100% • No pathogenic

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	Diagnosis/selection: EM examination of skin biopsy was performed; 26 asymptomatic controls from CADASIL families		were pathogenic variant-positive Family members: No data No pathogenic variant reported per family or per unrelated individual	variants in 26 negative controls
Dotti et al (2005)	Patients: 28 unrelated, consecutively diagnosed patients with CADASIL (Italian) Diagnosis/selection: Patients were diagnosed via clinical and MRI	DHPLC, followed by confirmatory sequencing of identified pathogenic variants	Sensitivity: 100% Patients: All 28 had pathogenic variants	NR
Joutel et al (1997)	Patients: 50 unrelated patients with a clinical suspicion of CADASIL and 100 healthy controls Diagnosis/selection: History of recurrent strokes, migraine with aura, vascular dementia, or a combination; brain MRI with suggestive findings; and consistent familial history	SSCP or heteroduplex analysis of all exons, followed by confirmatory sequencing of identified variants	Sensitivity: 90% Patients: 45/50 CADASIL patients had variants	<ul style="list-style-type: none"> • 100% • No variants in 100 healthy controls

DHPLC: denaturing high-performance liquid chromatography; EM: electron microscope; MRI: magnetic resonance imaging; NGS: next-generation sequencing; NR: not reported; PCR: polymerase chain reaction; SNV: single-nucleotide variant; SSCP: single-stranded conformational polymorphism; VUS: variant of uncertain significance.

Section Summary: Clinical Validity

The clinical sensitivity of genetic testing is high given that *NOTCH3* is the only gene for which pathogenic variants are known to cause CADASIL. In clinical situations where diagnosis of CADASIL cannot be confirmed by other methods (clinical presentation, MRI findings, skin biopsy), identification of a pathogenic variant in *NOTCH3* establishes a diagnosis of CADASIL.

Clinical Utility

Genetic testing of individuals with suspected CADASIL may have clinical utility by:

- Establishing a diagnosis of CADASIL in an individual with signs and symptoms of the disease, particularly when there are other disorders being considered, without the need for skin biopsy.
- Informing the reproductive decision-making process in preimplantation testing, prenatal (in utero) testing, or altering reproductive planning decisions when a *NOTCH3* pathogenic variant is present in a parent.

The clinical specificity of genetic testing for CADASIL is high, and false-positive results have not been reported in studies of clinical validity. Therefore, a positive genetic test in a patient with clinical signs and symptoms of CADASIL is sufficient to confirm the diagnosis with a high degree of certainty. The clinical sensitivity is also relatively high, in the range of 90% to 100% for patients with a clinical diagnosis of CADASIL. This indicates that a negative test reduces the likelihood that CADASIL is present. However,

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because false-negative tests do occur, a negative test is less definitive in ruling out CADASIL. Whether a negative test is sufficient to rule out CADASIL depends on the pretest likelihood that CADASIL is present.

Pescini et al (2012) published a study that attempted to identify clinical factors that increase the likelihood of a pathogenic variant being present and therefore might be helpful in selecting patients for testing. The authors first performed a systematic review to determine the frequency with which clinical and radiologic factors are associated with a positive genetic test. Evidence was identified from 15 clinical series of patients with CADASIL. Table 3 summarizes the pooled frequency of clinical and radiologic features.

Table 3: Clinical and Radiologic Features in Patients With *NOTCH3* Variants

Features	No. With <i>NOTCH3</i> Variant	Percent With <i>NOTCH3</i> 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.

Using these frequencies, a preliminary scoring system was developed and tested in 61 patients with *NOTCH3* pathogenic variants, and in 54 patients with phenotypic features of CADASIL who were *NOTCH3*-negative. With the addition of family history and age at onset of TIA/stroke, a scoring system as provided in Table 3. 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%).

Currently, no specific clinical treatment for CADASIL has established efficacy. Supportive care in the form of practical help, emotional support, and counseling are appropriate for affected individuals and their families. Four studies were found that addressed the efficacy of potential treatments for CADASIL.

A 2008 double-blind, placebo-controlled trial evaluated the efficacy and safety of donepezil hydrochloride (HCl) in individuals with CADASIL. The trial showed donepezil HCl had no effect on the primary cognitive end point, the cognitive subscale of the Vascular AD Assessment Scale score in patients with CADASIL and cognitive impairment.

Another study (2010) assessed the efficacy and tolerance of a 24-week therapy with acetazolamide 250 mg/d to improve cerebral hemodynamics in CADASIL patients (n=16). Treatment with acetazolamide resulted in a significant increase of blood mean flow velocity (MFV) in the middle cerebral artery (MCA)

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(57.68 cm/s) compared with MFV in the MCA at rest before treatment (67.12 cm/s; $p=0.001$). During the treatment period, none of the subjects developed new neurologic symptoms, and the original symptoms in these patients (e.g., headaches, dizziness) were relieved.

A third study (2007) evaluated the use of 3-hydroxy-3-methylglutaryl-coenzyme A-reductase inhibitors (statins) in 24 CADASIL subjects treated with atorvastatin for 8 weeks. Treatment was started at 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 treatment. There was no significant treatment effect on MFV ($p=0.5$) or cerebral vasoreactivity, as assessed by hypercapnia ($p=0.5$) or intravenous L-arginine ($p=0.4$) in the overall cohort. However, an inverse correlation was found between vasoreactivity at baseline and changes of both CO_2 - 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.

De Maria et al (2014) reported on the results of a randomized, double-blinded trial comparing sapropterin with placebo for adults with CADASIL. Sapropterin is a synthetic analogue of tetrahydrobiopterin, which is an essential cofactor in nitric oxide synthesis in endothelial cells. Given nitric oxide's role in cerebrovascular function, the authors hypothesized that sapropterin supplementation would improve cerebral endothelium-dependent vasodilation in CADASIL patients. Endothelial dysfunction was assessed using the reactive hyperemia peripheral arterial tonometry (RH-PAT) response, which has been shown to be impaired in patients with CADASIL syndrome. Peripheral arterial tonometry is a noninvasive, quantitative test that measures changes in digital pulse volume during reactive hyperemia and evaluates the endothelial function of resistance arteries and nitric oxide-mediated changes in microvascular response. The study randomized 61 subjects from 38 families, 32 to sapropterin and 29 to placebo. In intention-to-treat analysis, there was no significant difference in change in RH-PAT response (mean difference, 0.19; 95% confidence interval, -0.18 to 0.56). Both groups demonstrated improvements in RH-PAT levels during the study, but, after results were adjusted for age, sex, and clinical characteristics, the improvement was not associated with treatment.

Section Summary: Clinical Utility

Direct evidence for the clinical utility of genetic testing of individuals with suspected CADASIL is lacking. No specific clinical treatment for CADASIL has established efficacy. However, a chain of evidence for the clinical validity of *NOTCH3* pathogenic variants in establishing a diagnosis of CADASIL leading to initiation of supportive care in the form of practical help, emotional support, and counseling may provide a chain of evidence for potential clinical utility.

TARGETED FAMILIAL VARIANT TESTING IN ASYMPTOMATIC RELATIVES OF PATIENTS WITH CADASIL

Clinical Context and Test Purpose

The purposes of targeted familial variant testing of asymptomatic individuals with family members who have CADASIL are to screen at-risk individuals and predict development of disease, to determine the need for surveillance, and to aid in reproductive planning.

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Louisiana

Genetic Testing of CADASIL Syndrome

Policy # 00319

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The questions addressed in this evidence review are: In asymptomatic relatives of a patient with CADASIL, does use of targeted genetic testing for a known familial variant lead to improved outcomes, including changes in surveillance, preimplantation genetic testing to determine likelihood of an affected offspring, or alter reproductive planning decisions?

The following PICOTS were used to select literature to inform this review.

Patients

The relevant population of interest includes asymptomatic relatives of patients with CADASIL.

Interventions

The relevant intervention of interest is targeted familial variant testing of *NOTCH3*.

Comparators

The relevant comparator of interest is standard clinical management without genetic testing.

Outcomes

The potential beneficial outcomes of primary interest would be confirming or excluding the need for surveillance or changes in reproductive decision making. A negative genetic test result would eliminate the need for surveillance to detect development of symptoms and disease. A positive genetic test result would confirm a need for active surveillance and inform the reproductive decision process.

Potential harmful outcomes are those resulting from a false-positive or false-negative test results. False-positive test results can lead to unnecessary medical or neurologic surveillance of asymptomatic individuals. False-negative test results can lead to lack of medical or neurologic surveillance.

Timing

The time frame for outcome measures varies from short-term surveillance of asymptomatic individuals for development of signs or symptoms of CADASIL to long-term development of disease.

Setting

Asymptomatic individuals with family members with CADASIL may be referred to medical geneticist for investigation of genetic status for carrying a known familial variant. Referral for genetic counseling is important for explanation of genetic disease, heritability, genetic risk, test performance, and possible outcomes.

Analytic Validity

See the analytic validity discussion in the Testing Individuals With Suspected CADASIL section.

Clinical Validity

See the clinical validity discussion in the Testing Individuals With Suspected CADASIL section.

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Testing Strategy

Identification of a *NOTCH3* pathogenic variant establishes a diagnosis of CADASIL in both symptomatic and asymptomatic individuals. For testing in asymptomatic individuals with family members who have CADASIL:

- When the proband's *NOTCH3* pathogenic variant is known, conduct targeted familial variant testing to determine genetic status

The testing strategy described is a general approach for targeted genetic testing for a known pathogenic variant previously identified in a family member (familial variant) with CADASIL.

Clinical Utility

Genetic testing of asymptomatic individuals with family members who have CADASIL may have clinical utility by:

- Confirming or excluding the need for surveillance based on the presence or absence of a known familial variant.
- Informing the reproductive decision-making process in preimplantation testing, prenatal (in utero) testing, or altering reproductive planning decisions when a known *NOTCH3* familial variant is present in a parent.

Genetic counseling is recommended to discuss the impact of positive or negative test results, followed by molecular testing if desired. At present, for an asymptomatic individual, knowledge of familial variant status will generally not lead to any management changes that can prevent or delay the onset of the disorder. Avoiding tobacco use may be 1 factor that delays onset of disease, but this is a general recommendation that is not altered by genetic testing. However, a negative test may preclude the need for surveillance for complications. Genetic testing may also assist reproductive decision making.

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.

Section Summary: Clinical Utility

Direct evidence for the clinical utility of genetic testing of asymptomatic relatives of patients with CADASIL is lacking. No specific clinical treatment for CADASIL has established efficacy. However, a chain of evidence can be developed to for potential clinical utility, particularly for reproductive decision-making process for preimplantation and/or prenatal testing.

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GENETIC TESTING OF *NOTCH3* IN ASYMPTOMATIC RELATIVES OF PATIENTS WITH CADASIL

Clinical Context and Test Purpose

The purposes of genetic testing of *NOTCH3* in asymptomatic individuals with family members with CADASIL whose genetic status is unknown are to screen at-risk individuals and to predict development of disease, determine the need for surveillance, and to aid in reproductive planning.

The questions addressed in this evidence review are: In asymptomatic relatives of a patient with CADASIL whose genetic status is unknown, does use of *NOTCH3* genetic testing lead to improved outcomes, including changes in surveillance, preimplantation genetic testing to determine likelihood of an affected offspring, or alter reproductive planning decisions?

The following PICOTS were used to select literature to inform this review.

Patients

The relevant population of interest includes asymptomatic relatives of patients with CADASIL whose genetic status is unknown.

Interventions

The relevant intervention of interest is genetic testing of *NOTCH3* variants.

Comparators

The relevant comparator of interest is standard clinical management without genetic testing.

Outcomes

The potentially beneficial outcomes of primary interest would be confirming or excluding the need for surveillance or changes in reproductive decision making. A negative genetic test result would eliminate the need for surveillance to detect development of symptoms and disease. A positive genetic test result would confirm a need for active surveillance and also inform the reproductive decision-making process.

Potential harmful outcomes are those resulting from a false-positive or false-negative test results. False-positive test results can lead to unnecessary medical or neurologic surveillance of asymptomatic individuals. False-negative test results can lead to lack of medical or neurologic surveillance.

Timing

The time frame for outcome measures varies from short-term surveillance of asymptomatic individuals for development of signs or symptoms of CADASIL to long-term development of disease.

Setting

Asymptomatic individuals with family members who have CADASIL may be referred to medical geneticist for investigation of genetic status for carrying a known familial variant. Referral for genetic counseling is

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important for explanation of genetic disease, heritability, genetic risk, test performance, and possible outcomes.

Analytic Validity

See the analytic validity discussion in the Testing Individuals With Suspected CADASIL section.

Clinical Validity

See the clinical validity discussion in the Testing Individuals With Suspected CADASIL section.

Testing Strategy

For testing in asymptomatic individuals with family members who have CADASIL whose genetic status is unknown:

- Perform targeted sequencing and analysis of specific *NOTCH3* exons (e.g., exon 4 only, exons 2-6) OR
- Perform general testing of *NOTCH3* exons (e.g., exons 2-24 or all 33 exons)

This testing strategy to perform sequence analysis of multiple *NOTCH3* exons to identify pathogenic variants is a general approach for genetic testing for *NOTCH3*.

Clinical Utility

Genetic testing of asymptomatic individuals with family members who have CADASIL may have clinical utility by:

- Confirming or excluding the need for surveillance based on the presence or absence of a *NOTCH3* pathogenic variant.

Informing the reproductive decision-making process in preimplantation testing, prenatal (in utero) testing, or altering reproductive planning decisions when a known *NOTCH3* pathogenic variant is present in a parent. Preimplantation testing is addressed elsewhere.

Section Summary: Clinical Utility

Similar to the case where there is a known family variant associated with CADASIL, direct evidence for the clinical utility of genetic testing of asymptomatic relatives of patients with CADASIL is lacking. However, a chain of evidence can be developed to support the clinical utility of testing, as outlined above.

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

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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 a meaningful 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 (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 a meaningful 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 (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 a meaningful improvement in the net health outcome.

References

1. Blue Cross and Blue Shield Association, Medical Policy Reference Manual, "Genetic Testing of CADASIL Syndrome", 2.04.75, 4:2017.
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):2049-2051. 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):107-111. PMID 12756589

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- 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
- 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
- Malandrini A, Gaudio C, Gambelli S, et al. Diagnostic value of ultrastructural skin biopsy studies in CADASIL. *Neurology.* Apr 24 2007;68(17):1430-1432. PMID 17452591
- 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
- Markus HS, Martin RJ, Simpson MA, et al. Diagnostic strategies in CADASIL. *Neurology.* Oct 22 2002;59(8):1134-1138. PMID 12395806
- 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
- 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
- Lesnik Oberstein SAJ, Boon EMJ, Dichgans M. CADASIL. *GeneReviews.* 2016. PMID 20301673
- 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
- Chabriat H, Joutel A, Dichgans M, et al. Cadasil. *Lancet Neurol.* Jul 2009;8(7):643-653. PMID 19539236
- 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
- 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
- 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
- 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
- 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
- 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
- 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 leukoencephalopathy (CADASIL). *J Neurol Sci.* Feb 15 2015;349(1-2):196-201. PMID 25623805
- 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
- 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
- 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
- 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
- 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
- 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
- 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
- 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

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Original Effective Date: 10/19/2011
Current Effective Date: 12/20/2017

29. 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

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10/06/2011	Medical Policy Committee review
10/19/2011	Medical Policy Implementation Committee approval. New policy.
11/01/2012	Medical Policy Committee review
11/28/2012	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
02/19/2013	Coding updated
12/12/2013	Medical Policy Committee review
12/18/2013	Medical Policy Implementation Committee approval. Coverage changed from investigational to eligible for coverage for certain indications. Title changed.
12/04/2014	Medical Policy Committee review
12/17/2014	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
08/03/2015	Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
12/03/2015	Medical Policy Committee review
12/16/2015	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
12/01/2016	Medical Policy Committee review
12/21/2016	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
12/07/2017	Medical Policy Committee review
12/20/2017	Medical Policy Implementation Committee approval. The policy is revised with updated genetics nomenclature. "Mutations" changed to "variants" in policy statements. Added "Notch 3" to all policy statements. Eligible for coverage statement added for testing in asymptomatic and presymptomatic family members of individuals with CADASIL. Investigational statement intent remains unchanged, altered for clarification. Policy Guidelines section added to the policy.

Next Scheduled Review Date: 12/2018

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Code Type	Code
CPT	81406
HCPCS	No codes
ICD-10 Diagnosis	All related diagnoses

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- A. In accordance with nationally accepted standards of medical practice;
- B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient’s illness, injury or disease; and
- C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient’s illness, injury or disease.

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APPENDIX

Appendix Table 1. Categories of Genetic Testing

Category	Addressed
1. Testing of an affected individual’s germline to benefit the individual	

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Category	Addressed
1a. Diagnostic	X
1b. Prognostic	
1c. Therapeutic	
2. Testing cancer cells from an affected individual to benefit the individual	
2a. Diagnostic	
2b. Prognostic	
2c. Therapeutic	
3. Testing an asymptomatic individual to determine future risk of disease	X
4. Testing of an affected individual's germline to benefit family members	
5. Reproductive testing	
5a. Carrier testing: preconception	
5b. Carrier testing: prenatal	
5c. In utero testing: aneuploidy	
5d. In utero testing: familial variants	
5e. In utero testing: other	
5f. Preimplantation testing with in vitro fertilization	

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