Protocol

Genetic Testing of CADASIL Syndrome

(20475)

Medical Benefit		**Effective Date**: 04/01/15	**Next Review Date**: 11/17
Preauthorization	Yes	**Review Dates**: 01/12, 01/13, 01/14, 11/14, 11/15, 11/16	

Preauthorization is required.

The following Protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient's contract at the time the services are rendered.

Populations	Interventions	Comparators	Outcomes
Individuals: • With suspected CADASIL syndrome	Interventions of interest are: • Genetic testing for mutations associated with CADASIL syndrome	Comparators of interest are: • Standard management without genetic testing	Relevant outcomes include: • Overall survival • Test accuracy • Test validity • Other test performance measures • Changes in reproductive decision making • Change in disease status • Morbid events
Individuals: • Who are asymptomatic with family members with CADASIL syndrome	Interventions of interest are: • Genetic testing for mutations associated with CADASIL syndrome	Comparators of interest are: • Standard management without genetic testing	Relevant outcomes include: • Overall survival • Test accuracy • Test validity • Other test performance measures • Changes in reproductive decision making • Change in disease status • Morbid events

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.

Summary of Evidence

The evidence for the use of genetic testing for mutations associated with CADASIL syndrome in individuals with suspected CADASIL syndrome includes retrospective and prospective studies evaluating the clinical validity and yield of *NOTCH3* mutation testing. Relevant outcomes are overall survival, test accuracy and validity, other test performance measures, changes in reproductive decision making, change in disease status, and morbid events. 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% to 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% to 54%. These lower numbers likely reflect testing in heterogeneous populations that include patients with other disorders. There may be potential clinical utility for genetic testing to diagnose CADASIL in patients whose diagnosis cannot be confirmed by other methods (clinical presentation, magnetic resonance imaging [MRI] findings, skin biopsy). However, no direct evidence was identified demonstrating outcome improvements associated with genetic testing for CADASIL. A strong chain of indirect evidence cannot be constructed given the lack of evidence demonstrating the potential for changes in management that might occur following a diagnosis of CADASIL. The evidence is insufficient to determine the effects of the technology on health outcomes.

The evidence for the use of genetic testing for mutations associated with CADASIL syndrome in individuals who are asymptomatic with family members with CADASIL syndrome is limited. Relevant outcomes are overall survival, test accuracy and validity, other test performance measures, 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 pathologic mutation 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 the onset of disease. The evidence is insufficient to determine the effects of the technology on health outcomes.

Policy

Genetic testing to confirm the diagnosis of CADASIL syndrome may be considered **medically necessary** under the following conditions:

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

Genetic testing for CADASIL syndrome in all other situations, including but not limited to testing of asymptomatic patients who have a first- or second-degree relative with CADASIL, is considered **investigational**.

Policy Guidelines

The probability that CADASIL is present is an individualized assessment depending 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 pathologic mutation 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, as 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	Number With N*OTCH3* Mutation, n/N	Percent With *NOTCH3* Mutation	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 years old)

Features	Number With N*OTCH3* Mutation, n/N	Percent With *NOTCH3* Mutation	Points
Psychiatric disturbance	106/380	28%	1
Cognitive decline	188/434	43%	3
Radiologic			
Leukoencephalopathy (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

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

CADASIL is an uncommon, autosomal dominant disease. 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.

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% to 90% and 95% to 100%, respectively, for two 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
- 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 criterion 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 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-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 two to 24, which encode the 34 EGF-like repeats, with strong clustering in exons three and four, which encode epidermal growth factor receptors two to five (> 40% of mutations in > 70% of families occur in these exons).[12] Some studies indicate 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.[13]

The probability that CADASIL is present is an individualized assessment, depending on numerous factors such as family history, symptoms, imaging results, and other specialized testing such as skin biopsy. In 2012, Pescini et al[14] published a study that attempted to identify clinical factors that increase the likelihood of a pathologic mutation being present, with increasing likelihood with the presence of one or several factors, including migraine, migraine with aura, transient ischemic attack/stroke, psychiatric disturbance, cognitive decline, leukoencephalopathy (with greater risk for leukoencephalopathyextending to the temporal pole or external capsule), and subcortical infarcts.

Regulatory Status

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA). *NOTCH3* mutation testing 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. Food and Drug Administration has chosen not to require any regulatory review of this test.

Related Protocol

Preimplantation Genetic Testing

Services that are the subject of a clinical trial do not meet our Technology Assessment Protocol criteria and are

considered investigational. *For explanation of experimental and investigational, please refer to the Technology Assessment Protocol.*

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. **Some of this Protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.**

References

We are not responsible for the continuing viability of web site addresses that may be listed in any references below.

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