Corporate Medical Policy

Genetic Testing of CADASIL Syndrome AHS – M2069

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Description of Procedure or Service

Description

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) (Tournier-Lasserve et al., 1993) is a genetic small vessel disease in which mutations in the Notch Receptor 3 (*NOTCH3*) gene located on chromosome 19 (Joutel et al., 1996) result in a clinical syndrome of adult-onset migraines (frequently with aura), progressive strokes, and cognitive decline in adults leading to severe functional impairment by the seventh decade of life (Opherk, Peters, Herzog, Luedtke, & Dichgans, 2004; Zhu & Nahas, 2016).

Related Policies

General Genetic Testing, Germline Disorders AHS – M2145

******Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.***

Policy

BCBSNC will provide coverage for genetic testing of CADASIL syndrome when it is determined to be medically necessary because the medical criteria and guidelines shown below are met.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When Genetic Testing of CADASIL Syndrome is covered

1. Genetic testing to confirm the diagnosis of CADASIL syndrome is considered medically necessary under the following conditions:

   A. 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 for further details)
   B. Individuals in which the diagnosis of CADASIL is inconclusive following a combination of clinical presentation, magnetic resonance imaging (MRI) findings, and skin biopsy findings.

2. Genetic testing for CADASIL syndrome in asymptomatic individuals who have a first- or second-degree relative diagnosed with CADASIL syndrome is considered medically necessary.

When Genetic Testing of CADASIL Syndrome is not covered

Genetic testing of CADASIL syndrome in all other situations is considered investigational.

Policy Guidelines

Background

CADASIL is the most common hereditary small vessel disease and is characterized by granular osmiophilic material deposits surrounding blood vessels, a prominent thickening of the vessel wall by extracellular matrix accumulation, and a progressive loss of vascular smooth muscle cells (VSMCs) (Fernandez-Susavila et al., 2018; Ferrante, Cudrici, & Boehm, 2019; Monet-Lepretre et al., 2013). Small vessel diseases such as this are an important cause of stroke and vascular cognitive decline in adults (Chabriat, Joutel, Dichgans, Tournier-Lasserve, & Bousser, 2009). VSMC dysfunction may be caused by mutations in the *NOTCH3* gene, leading to irregularities in VSMC proliferation, cell cycle affliction, senescence and cellular apoptosis (Dziewulska, Nycz, Rajczewska-Oleszkiewicz, Bojakowski, & Sulejczak, 2018).

Individual symptoms, onset, and disease severity span a wide spectrum (Wang, 2018). Thus, descriptions of hereditary multi-infarct dementia, chronic familial vascular encephalopathy, and familial subcortical dementia, originally thought to be separate disorders, represent early reports of this condition (Dichgans, 2019). CADASIL usually presents with one or more of the following: dementia, psychiatric disturbances, migraine, and recurrent strokes (Chabriat et al., 2009; Dichgans et al., 1998; M.Wang, 2018). Rarer symptoms include lumbago, humpback, and Parkinson syndrome (Cao et al., 2019; Lim, Millar, & Zaman, 2019). Migraine with aura occurs in 55% of CADASIL cases and is often the initial manifestation of the disease (Di Donato et al., 2017). Subcortical ischemic attacks begin at a mean age of 47 years and present as lacunar syndromes (Adib-Samii, Brice, Martin, & Markus, 2010; Dichgans et al., 1998). Accumulation of lacunae, which impact executive performance and function independence, strongly correlate to clinical severity (Ling et al., 2017). Cognitive impairment associated with CADASIL is progressive; a profile of frontal lobe dysfunction, declarative memory impairment suggestive of a retrieval deficit, and relatively preserved language is often evident with this disease (Harris & Filley, 2001). A concurrent stepwise deterioration due to recurrent strokes is also common (Rutten & Lesnik Oberstein, 2016). Mood disturbances are reported in approximately 30% of individuals (Adib-Samii et al., 2010; Dichgans et al., 1998). Further, apathy, which may be independent of depression, is reported in 40% of individuals (Reyes et al., 2009).

Genetic linking of the disorder to chromosome 19 was first recognized in 1993, and the identification of the *NOTCH3* gene from the CADASIL mapped region was later discovered in 1996 (Ping & Zhao, 2018). While CADASIL was originally diagnosed via neuroimaging techniques, such as magnetic resonance imaging (MRI), the identification of the distinctive missense mutations in *NOTCH3* has allowed genetic testing to debut as the current gold standard for CADASIL diagnostics (Rutten & Lesnik Oberstein, 2016). However, MRI testing for the detection of cerebral white matter changes in the brain is still used to assist in CADASIL diagnoses; most often, MRI imaging is used as a diagnostic measure before symptoms present (Ferrante et al., 2019).
Missense mutations in the *NOTCH3* gene typically lead to the gain or loss of a cysteine, therefore resulting in an unpaired number of cysteine residues in one of 34 highly conserved epidermal growth factor-like repeat (EGFr) domains (Joutel et al., 1996; Papakonstantinou et al., 2019; Rutten et al., 2014). This leads to an increased multimerization tendency of mutant NOTCH3 (Duering et al., 2011), toxic accumulation of the protein and extracellular matrix in disulfide cross-linked detergent-insoluble aggregates (Monet-Lepretre et al., 2013), altered neurovascular coupling (Huneau et al., 2018), and ultimately reduced cerebral blood flow, recurrent stroke, and vascular dementia (Rutten et al., 2016). However, certain *NOTCH3* mutations do not present with a cysteine change; this type of non-cysteine mutation can cause a great loss of structure in the NOTCH3 protein (Papakonstantinou et al., 2019).

More than 200 *NOTCH3* mutations have been reported since its original discovery in the development of CADASIL syndrome in 1996; some of these mutations result in a phenotypic change while some present as a silent mutation. A few prevalent *NOTCH3* variants include the 34 identified in EGFr. EGFr 1–6 pathogenic variants are more common in the CADASIL population than EGFr 7–34 pathogenic variants; unfortunately, patients with EGFr 1–6 variants tend to present with more severe symptoms and phenotypes (Papakonstantinou et al., 2019; Rutten et al., 2018). These severe symptoms include stroke onset an average of 12 years earlier and overall lower survival rates (Papakonstantinou et al., 2019).

The prevalence of the disease has been estimated to be at 0.8 to 5 per 100,000 individuals (Moreton, Razvi, Davidson, & Muir, 2014; Narayan, Gorman, Kalaria, Ford, & Chinnery, 2012; Razvi, Davidson, Bone, & Muir, 2005); however, many suspect that these numbers are underestimates. A more recent investigation of the frequency of the characteristic missense CADASIL mutations in a public database found a total prevalence of 3.4/1000 (Rutten et al., 2016).

Analytical Validity

There are no established diagnostic criteria for CADASIL. The phenotype is highly variable, and although imaging may be suggestive, no characteristic is pathognomonic; genetic testing remains the gold standard for diagnosis (Rutten & Lesnik Oberstein, 2016; Wang, 2018). As a heterozygous pathogenic variant in the NOTCH3 protein coding gene is well established as a main reason for CADASIL development, a CADASIL diagnosis is generally delivered based on molecular genetic testing or electron microscopy and immunohistochemistry results. Molecular genetic testing approaches may include both gene-targeted testing and in-depth genomic testing, such as exome sequencing and genome sequencing (Hack et al., 2019; Papakonstantinou et al., 2019).

Immunohistochemistry combined with electron microscopy of skin biopsy can be useful when molecular testing is not definitive (Rutten & Lesnik Oberstein, 2016). Immunohistochemistry assay of a skin biopsy sample for the accumulation of NOTCH3 protein in the walls of small blood vessels (Joutel et al., 2001) has an estimated sensitivity and specificity at 85-90% and 95-100%, respectively (Lesnik Oberstein et al., 2003). Detection of granular osmiophilic material deposits (GOM) containing the ectodomain of the *NOTCH3* gene by electron microscopy (del Rio-Espinola et al., 2009; Muqtadar & Testai, 2012) had a sensitivity of 45% and a specificity of 100% (Brulin, Godfraind, Leteurtre, & Ruchoux, 2002; Malandrini et al., 2007; Markus et al., 2002).

MRI is useful to demonstrate radiologic features of CADASIL, including recent lunar infarctions and white matter hyperintensities. Computed tomography (CT) scans are less sensitive than MRI in this regard (Dichgans, 2019). MRI may also provide prognostic information. Brain lesions in CADASIL patients tend to precede symptoms by 10 to 15 years; however, a normal MRI in the fourth decade of life should not automatically rule out CADASIL syndrome even though most patients exhibit an abnormal MRI by age 35 (Samoes et al., 2016). White matter hyperintensities on MRI can be visualized in those aged 21 years and older, and lesion volume correlates with the level of disability and three-year clinical course of CADASIL (Jouvent et al., 2016). Isolated T2 hyperintensities involving the temporal poles can differentiate CADASIL from chronic microvascular ischemia due to hypertension with a sensitivity and specificity of 95% and 80%, respectively (O'Sullivan et al., 2001). Cerebral microbleeds visible on T2 weighted MRI images detected in 36% of patients with CADASIL were independently associated with an increased risk of incident ischemic stroke and may be a marker for a subgroup of patients with CADASIL who have a more severe or advanced form of the disease (Puy et al., 2017).

Clinical Validity and Utility

One study has reported that the sequence analysis of *NOTCH3* is 95-100% sensitive and 100% specific to establish the diagnosis of CADASIL (Dotti et al., 2005; Peters et al., 2005; Tikka et al., 2009; Yin et al., 2015). A preliminary scale was proposed to screen for patients who should undergo *NOTCH3* gene analysis with a sensitivity of 96.7% and a specificity of 74.2% (Pescini et al., 2012). Another study of Russian patients with clinically suspected CADASIL concluded that careful assessment of genealogical, clinical, and neuroimaging data in patients with lacunar stroke can help select patients with a high probability of finding mutations on genetic screening (Abramycheva et al., 2015). In the absence of clinical features suggestive of CADASIL, screening of patients with lacunar stroke, leukoarosis, and migraine have low yield (de Vries, Frants, Ferrari, & van den Maagdenberg, 2009; Dong et al., 2003).

As individual symptoms and disease severity span a wide spectrum, it must be noted that symptom onset alone cannot warrant a CADASIL syndrome diagnosis. Researchers previously screened 123 patients who exhibited two common CADASIL symptoms: lacunar stroke and transient ischemic attack. These participants were genetically tested for CADASIL; it was determined that only 12.5% had a *NOTCH3* mutation, showing that common CADASIL symptoms are shared with many other disorders (Bersano et al., 2018). This highlights the importance of genetic testing as a diagnostic measure. Further, three features were found to be significantly associated with a CADASIL diagnosis: “A family history of stroke, the presence of dementia and external capsule lesions on MRI” (Bersano et al., 2018).

CADASIL was first diagnosed by visualizing granular osmiophilic material (GOM) in the tunica media of small arteries through light microscopy. Although GOM deposit is the pathological hallmark of CADASIL, *NOTCH3* genetic sequencing is the confirmative diagnostic tool. While most genetic tests use Sanger sequencing methods to target specific *NOTCH3* exons, next-generation sequencing (NGS) and whole exome sequencing (WES) have proven to deliver greater efficacy. One study has reported that NGS and WES have increased sensitivity to detect low frequency variants of *NOTCH3* mutations compared to Sanger sequencing. Through Sanger sequencing, 10.8% of tests were able to identify *NOTCH3* mutations compared to 15.8% of tests identifying mutations through next-generation sequencing. With NGS, the results were in concordance with Sanger sequencing, but it extended the capacity to detect mutations and previously unreported variants. As diagnostic sequencing techniques continue to advance, NGS and WES may play an important role in identifying other genes involved with CADASIL (Dunn et al., 2020).

Predictive Testing of At-Risk Family Members

For an asymptomatic individual, knowledge of mutation status will generally not lead to any management changes that can prevent or delay the onset of the disorder. Avoiding tobacco use may be a factor that delays onset of disease, but this is a general recommendation that is not altered by genetic testing. Goldman (2015) has suggested that asymptomatic family members follow the guidelines for presymptomatic testing for Huntington disease (HDSA, 2016).

CADASIL genetic testing may assist decision making in areas such as employment choices and reproductive decision making. However, the impact of these decisions on health outcomes is uncertain. Further, the testing of asymptomatic at-risk individuals with nonspecific or equivocal symptoms is not useful in predicting age of onset, severity, type of symptoms, or rate of progression in asymptomatic individuals (Rutten & Lesnik Oberstein, 2016). Initial data from Reyes, Kurtz, Herve, Tournier-Lasserve, and Chabriat (2012) show that predictive testing is rarely requested and has a high dropout rate.

Di Donato et al. (2017) state that the MRI of an unaffected family member could have a similar impact to a genetic test because MRIs are able to accurately predict CADASIL disease development before symptoms present. Therefore, the potential implications of MRI testing should be shared before this type of testing is completed.

Guidelines and Recommendations

American Heart Association and American Stroke Association (Powers et al., 2019; Smith et al., 2017)

The American Heart Association and American Stroke Association do not provide any recommendations on rare genetic causes of cerebral small vessel disease, such as CADASIL, but they do provide suggestions on when rare genetic causes could be suspected. They suggest that the diagnosis could be made on the basis of testing for mutations in the *NOTCH3* gene (Powers et al., 2019; Smith et al., 2017).

European Federation of Neurological Societies (Burgunder et al., 2010)

The European Federation of Neurological Societies guideline on the molecular diagnosis of channelopathies, epilepsies, migraine, stroke, and dementias notes that most *NOTCH3* mutations occur within exons 3 and 4 and suggests direct sequencing of these 2 exons if clinical suspicion is high (Burgunder et al., 2010).

U.S. Preventive Services Task Force (USPSTF, 2020)

As of 9/04/2020, the USPSTF has not published guidelines for the genetic testing of CADASIL patients.

European Academy of Neurology (EAN) (Mancuso et al., 2020)

The European Academy of Neurology (EAN) released guidelines for monogenic cerebral small-vessel disease (cSVD), including diagnosis and management of CADASIL. EAN suggests that the first line diagnosis for CADASIL should be genetic testing, but diagnosis can also be established by skin biopsy with electron microscopy revealing granular osmiophilic material (GOM). Most *NOTCH3* variants causing CADASIL are due to a loss or gain of a cysteine in the EGFR repeats. Some non-cysteine changing variants have been reported, but most of these non-cysteine changing variants do not lead to a diseased state. If genetic testing reveals a non-cysteine changing variant, electron microscopy to visualize GOM is a useful tool to confirm CADASIL diagnosis. If the *NOTCH3* variant is of unknown significance, CADASIL diagnosis can be established with skin biopsy via electron microscopy or immunohistochemistry of the NOTCH3 extracellular domain. The guideline recommends "considering" a CADASIL diagnosis in any patient with "unexplained symmetrical periventricular WMHs [white matter hyperintensities] and a positive family history of migraine with aura, stroke, mood disorders or dementia". The guideline also notes that CADASIL cannot be ruled out in the presence of "common cerebrovascular risk factors and extensive WMHs" or in "the absence of a medical or family history of migraine with aura". The guideline remarks that "although most patients have a family history, if the clinical and imaging phenotype is consistent with CADASIL the diagnosis should be considered" (Mancuso et al., 2020).

Overall, the EAN remarks that "CADASIL can only be definitively confirmed by genetic testing, revealing a *NOTCH3* mutation altering the number of cysteines in one of the 34 EGFr domains of the NOTCH3 protein" (Mancuso et al., 2020).

Applicable Federal Regulations

No U.S. Food and Drug Administration-cleared tests were found with the keyword "NOTCH3" as of 09/23/2020; a total of 24 U.S. Food and Drug Administration-cleared tests were found with the keyword "genotyping." Additionally, many labs have developed specific tests that they must validate and perform in house. *NOTCH3* sequencing is therefore a laboratory developed test (LDT). These LDTs are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA '88). As an LDT, the U. S. Food and Drug Administration has not approved or cleared this test; however, FDA clearance or approval is not currently required for clinical use.

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable service codes: 81406

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources

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Specialty Matched Consultant Advisory Panel review 3/2020

Medical Director review 3/2020

Specialty Matched Consultant Advisory Panel review 3/2021

Medical Director review 3/2021

Policy Implementation/Update Information

1/1/2019 BCBSNC will provide coverage for genetic testing of CADASIL syndrome when it is determined to be medically necessary because the criteria and guidelines are met. Medical Director review 1/1/2019. Policy noticed 1/1/2019 for effective date 4/1/2019. (jd)

4/1/2019 Description section, policy guidelines and references updated. Medical Director review 4/2019. (jd)

2/11/20 Annual review by Avalon 4th Quarter CAB 2019. CPT code G0452 and code table removed from the Billing/Coding section. No change to policy intent. Medical Director review 12/2019. (jd)

3/31/20 Specialty Matched Consultant Advisory Panel review 3/2020. Medical Director review 3/2020. (jd)

2/9/21 Annual review by Avalon 4th Quarter CAB 2020. Minor revisions; no change to policy intent. Medical Director review 1/2021. (jd)

3/31/21 Specialty Matched Consultant Advisory Panel review 3/2021. Medical Director review 3/2021. (jd)