Genetic Testing: CADASIL Disease

MEDICAL POLICY NUMBER: 238

Effective Date: 11/1/2023

Last Review Date: 8/2023

Next Annual Review: 8/2024

INSTRUCTIONS FOR USE: Company Medical Policies serve as guidance for the administration of plan benefits. Medical policies do not constitute medical advice nor a guarantee of coverage. Company Medical Policies are reviewed annually and are based upon published, peer-reviewed scientific evidence and evidence-based clinical practice guidelines that are available as of the last policy update. The Company reserves the right to determine the application of medical policies and make revisions to medical policies at any time. The scope and availability of all plan benefits are determined in accordance with the applicable coverage agreement. Any conflict or variance between the terms of the coverage agreement and Company Medical Policy will be resolved in favor of the coverage agreement. Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case. In cases where medical necessity is not established by policy for specific treatment modalities, evidence not previously considered regarding the efficacy of the modality that is presented shall be given consideration to determine if the policy represents current standards of care.

SCOPE: Providence Health Plan, Providence Health Assurance, and Providence Plan Partners as applicable (referred to individually as “Company” and collectively as “Companies”).

PLAN PRODUCT AND BENEFIT APPLICATION

☒ **Commercial** ☒ **Medicaid/OHP*** ☐ **Medicare****

*Medicaid/OHP Members

Oregon: Services requested for Oregon Health Plan (OHP) members follow the OHP Prioritized List and Oregon Administrative Rules (OARs) as the primary resource for coverage determinations. Medical policy criteria below may be applied when there are no criteria available in the OARs and the OHP Prioritized List.

**Medicare Members

This *Company* policy may be applied to Medicare Plan members only when directed by a separate *Medicare* policy. Note that investigational services are considered **"not medically necessary"** for Medicare members.

COVERAGE CRITERIA

Genetic Testing: Symptomatic Individuals

I. Genetic testing for *NOTCH3* variants may be considered **medically necessary** to confirm the diagnosis of cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) in a symptomatic individual when **all** of the following (A.-F.) criteria are met:

   A. Genetic Counseling general criteria have been met (Genetic Counseling Policy); **and**
   B. The patient has a family history of stroke and/or vascular dementia; **and**
   C. Documented presence of white matter hyperintensity lesions in the brain by neuroimaging; **and**
   D. The patient is experiencing **at least one** of the following (1.-4.) clinical signs:
      1. Subcortical ischemic events; **and/or**
      2. Cognitive impairment; **and/or**
      3. Migraine with aura; **and/or**
      4. Psychiatric disturbances (e.g., mood disturbances; apathy); **and**

II. Genetic testing for CADASIL is considered **not medically necessary** in all other situations, including but not limited to when criteria I. above are not met, or when testing for genes other than *NOTCH3*.

Genetic Testing: Asymptomatic Individuals

III. Genetic testing for *NOTCH3* variants in asymptomatic adults (18 years of age or older) may be considered **medically necessary** when both of the following are met:

A. Genetic Counseling general criteria have been met; **and**
B. A first- or second-degree adult relative has documented confirmation of a *NOTCH3* pathogenic variant **and** a confirmed diagnosis of CADASIL. (See Policy Guidelines below for definition of first- and second-degree relative)

IV. Genetic testing for CADASIL is considered **not medically necessary** in asymptomatic individuals if they are under the age of 18 years.

V. Repeat testing of the same germline genetic content, for the same genetic information, is considered **not medically necessary.**

Link to Evidence Summary

POLICY CROSS REFERENCES

- Genetic Counseling, MP316
- Genetic Testing: Reproductive Planning and Prenatal Testing, MP78

The full Company portfolio of current Medical Policies is available online and can be accessed here.

POLICY GUIDELINES

*First-degree relatives are parents, siblings, and children. Second-degree relatives are grandparents, aunts, uncles, nieces, nephews, grandchildren, and half-siblings (siblings with one shared biological parent).

Although CADASIL is inherited in an autosomal dominant manner, clinical presentation can vary within a family. As a result, affected members within a family may be misdiagnosed or underdiagnosed due to late-onset and variability in clinical presentation. Therefore, an extended family pedigree should be assessed and confirmation of a CADASIL diagnosis in either a first- or second-degree relative is indicated.[1]

DOCUMENTATION REQUIREMENTS

In order to determine the clinical utility of a genetic test, the following documentation must be provided at the time of the request. Failure to submit complete documentation may affect the outcome of the review.

- Specific gene, trade or proprietary name of the test, or if a custom-built test, include every gene(s) and/or component of the test
- Name of laboratory where the testing is being conducted or was conducted
- Clinical notes to include the following:
  - Documentation of genetic counseling as required in the policy criteria below which includes how test results will impact clinical decision making

- Reason (indication) for performing test, including the suspected condition
- Existing signs and/or symptoms related to reason for current test request
- Prior test/laboratory results related to reason for current test request
- Family history, if applicable
- How results from current test request will impact clinical decision making

- All relevant CPT/HCPCS codes billed

BACKGROUND

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a rare, inherited brain disorder that causes mid-adult onset migraine headaches and multiple, recurrent ischemic strokes. The prevalence is thought to be between 2-4/100,000. Although CADASIL is considered an adult-onset disease, with the mean age of onset typically in the third or fourth decade of life, symptoms such as migraine with aura have been documented in patients as early as six years of age.[2,3]

CADASIL is inherited in an autosomal dominant manner.[4] However, a family history consistent with autosomal dominant inheritance supports the diagnosis but is not required, as affected family members may have been misdiagnosed due to varying clinical presentation within families and inaccurate reporting of negative family history. In addition, clinical presentation of the disease varies within and between families. More than 95% of individuals with CADASIL have pathogenic mutations in the *NOTCH3* gene on chromosome 19 and *de novo* pathogenic mutations appear to be rare.[1]

The pathologic hallmarks of CADASIL are electron-dense granules in the media of arterioles as detected by electron microscopy, and increased expression of the Notch3 protein in the arterial wall detected by immunostaining, both which can be evaluated in a skin biopsy. The combined analysis by electron microscopy and immunohistochemistry, when interpreted by an experienced neuropathologist, usually allows for a conclusive CADASIL diagnosis. However, the sensitivity of the electron microscopy is variable. Of note, there are currently no generally accepted diagnostic criteria for CADASIL.[1]

Unfortunately, genetic testing does not detect all patients with CADASIL and up to 4 percent of patients may not be identified. As a result, skin biopsy is indicated if genetic testing is negative (or unavailable) when there is a high index of clinical suspicion for diagnosis of CADASIL.[5]

Brain imaging abnormalities are also common signs of CADASIL, which may be detected in asymptomatic and symptomatic individuals. [1] These abnormalities evolve as the disease progresses. Characteristic abnormalities can be detected by MRI as early as the 20s, but are not considered to be diagnostic.[6]

CLINICAL EVIDENCE AND LITERATURE REVIEW

EVIDENCE REVIEW

Since the analytical and clinical validity of testing for *NOTCH3* pathogenic variants for the diagnosis of CADASIL have been established, the evidence review below, conducted through August 2023, will focus on the clinical utility of testing. In the present context, clinical utility was evaluated in the following situations:

- Confirmation of a diagnosis in a symptomatic individual
- Identification of asymptomatic at-risk family members

Confirmation of a CADASIL Diagnosis in a Symptomatic Individual

No studies were identified that reported on how confirmation of a CADASIL diagnosis by way of a positive result for NOTCH3 mutation testing led to changes in medical management or improved outcomes for symptomatic patients. However, the value of genetic testing for NOTCH3 diagnostic variant effectually ends the diagnostic odyssey for these patients and prevents patients from having to undergo further testing.

Recently, groups in Japan and Italy published updated diagnostic criteria based on evaluation of the frequencies of clinical features in large case/control studies that included patients with genetically confirmed CADASIL.

In 2017, Mizuta et al. reported that the presence of white matter lesions was the feature given the strongest weight in the new criteria, based on the frequency among 102 CADASIL confirmed Japanese patients.[7] In this study, a definite diagnosis included a positive NOTCH3 result, presence of white matter lesions, and exclusion of leukodystrophy.

In 2018, Bersano et al. recruited 128 patients to evaluate clinical and neuroimaging features important in the diagnosis of CADASIL.[8] This study found that a family history of stroke, the presence of dementia and external capsule lesions on MRI were the only features significantly associated with the diagnosis of CADASIL. Both of these recent studies reported that using updated criteria including presence of specific lesions in the brain and a more flexible requirement for family history increased the yield for genetic testing.

In 2018 ECRIgene completed a clinical evidence assessment for NOTCH3 testing to diagnose or assess risk for CADASIL.[4] The review included nine case-control studies, seven prospective cohort studies, eight retrospective cohort studies, fifteen case series, seventeen case studies and single-family studies, and nine narrative reviews. The report concluded that despite the lack of a cure, NOTCH3 testing may inform reproductive and medical decision making about treatments to delay symptom onset and manage stroke risk. ECRI listed the evidence bar is evidence is somewhat favorable.

Identification of Asymptomatic At-Risk Family Members

The 2018 ECRIgene clinical evidence assessment also reviewed testing in asymptomatic patients with a family history of CADASIL.[4] The report concluded that in asymptomatic patients with a family history of CADASIL, NOTCH3 testing can identify those who will develop the disorder. These patients would experience the same benefits listed previously. ECRI listed the evidence bar is evidence is somewhat favorable.

In 2012, Reyes et al. published the results of a study that investigated the characteristics, motivations and long-term outcome of testing of asymptomatic subjects at risk of CADASIL.[9] This series on genetic screening examined sociodemographic, motivational, and psychological variables of health individuals at risk for CADASIL who enrolled over a seven-year period. Although only 33 subjects requested genetic testing for CADASIL risk, the authors reported a high dropout rate (63% after the initial assessment). Of

the 11 subjects who the six-month study period, six were carriers of the mutation and were still asymptomatic after a mean follow-up of 19 months. No negative events were reported; all reported a high overall quality of life, and two carriers gave birth to their first child. Although a very small sample, this study provided some evidence of clinical utility of presymptomatic genetic testing for CADASIL and suggests that resulting knowledge of risk for this disorder does not produce detrimental effects on overall quality of life.

CLINICAL PRACTICE GUIDELINES

American College of Radiology (ACR)

The 2015 ACR evidence-based appropriateness criteria on dementia and movement disorders have no imaging recommendations at this time for CADASIL. The ACR panel stated that certain structural MRI changes in these patients may help to suggest the diagnosis, but, "diagnosis is confirmed by skin biopsy or detection of a pathogenic NOTCH3 mutation on direct sequencing."[10]

European Federation of Neurological Sciences (EFNS)

Although not U.S. based, in 2010, the EFNS completed a well-conducted, evidence-based guideline on the molecular diagnosis of channelopathies, epilepsies, migraine, stroke, and dementia.[11] The guideline a high recommendation for direct sequencing of exons 3 and 4 as a first step if clinical suspicion of CADASIL. The guideline also stated, "the diagnosis may *also be supported* by skin biopsy showing typical osmiophilic granula" by electron microscopy. [11] This recommendation was given a Level B rating, indicating that the genetic testing as being, "probably useful/predictive" and was based on evidence comprised of, "at least one convincing class II study or overwhelming class III evidence".

EVIDENCE SUMMARY

Despite insufficient evidence of clinical utility for the genetic testing of NOTCH3 for CADASIL, testing for pathogenic mutations can help diagnose CADASIL, which may inform reproductive and medical decision making about treatments to delay symptom onset and manage stroke risk. Despite the fact the CADASIL is considered an adult-onset disease, testing in this situation is appropriate for patients of all ages, children under the age of 18 years may present with symptoms. Lastly, genetic testing of NOTCH3 to confirm a diagnosis of CADASIL in this situation is supported by current clinical practice guidelines.

Despite insufficient evidence of clinical utility for the genetic testing of NOTCH3 for CADASIL, testing for NOTCH3 mutations in at-risk adults with a family history of CADASIL and a known pathogenic mutation can help individuals make reproductive planning decisions and avoid unnecessary diagnostic testing.

Genetic testing for CADASIL is considered not medically necessary and not covered in asymptomatic individuals if they are under the age of 18 years. Testing of asymptomatic children for adult-onset disorders is recommended against by major medical associations.

There is insufficient evidence that genetic testing for CADASIL alters decision-making or directs management in individuals that do not meet the medical necessity criteria outlined above. In addition, there is a lack of support from clinical practice guidelines for genetic testing for CADASIL in populations other than symptomatic patients that meet the medical necessity criteria outlined above.

BILLING GUIDELINES AND CODING

CODES*		
CPT	81406	Molecular pathology procedure, Level 7 (eg, analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons, cytogenomic array analysis for neoplasia) – when used for "Notch 3 (NOTCH3) targeted sequence analysis. Notch 3 (NOTCH3) targeted sequence analysis of exons 1-23."
HCPCS	None	

***Coding Notes:**

- The above code list is provided as a courtesy and may not be all-inclusive. Inclusion or omission of a code from this policy neither implies nor guarantees reimbursement or coverage. Some codes may not require routine review for medical necessity, but they are subject to provider contracts, as well as member benefits, eligibility and potential utilization audit.
- All unlisted codes are reviewed for medical necessity, correct coding, and pricing at the claim level. If an unlisted code is submitted for non-covered services addressed in this policy then it will be **denied as not covered**. If an unlisted code is submitted for potentially covered services addressed in this policy, to avoid post-service denial, **prior authorization is recommended**.
- **See the non-covered and prior authorization lists on the Company Medical Policy, Reimbursement Policy, Pharmacy Policy and Provider Information website for additional information.**
- HCPCS/CPT code(s) may be subject to National Correct Coding Initiative (NCCI) procedure-to-procedure (PTP) bundling edits and daily maximum edits known as "medically unlikely edits" (MUEs) published by the Centers for Medicare and Medicaid Services (CMS). This policy does not take precedence over NCCI edits or MUEs. Please refer to the CMS website for coding guidelines and applicable code combinations.

REFERENCES

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11. Burgunder JM, Finsterer J, Szolnoki Z, et al. EFNS guidelines on the molecular diagnosis of channelopathies, epilepsies, migraine, stroke, and dementias. *European journal of neurology.* 2010;17(5):641-648.

POLICY REVISION HISTORY

DATE	REVISION SUMMARY
2/2023	Converted to new policy template.
11/2023	Annual update. Added criterion V. regarding repeat testing.