MEDICAL POLICY

POLICY TITLE	GENETIC TESTING FOR NEUROFIBROMATOSIS
POLICY NUMBER	MP 2.358

CLINICAL BENEFIT	☐ MINIMIZE SAFETY RISK OR CONCERN. ☐ MINIMIZE HARMFUL OR INEFFECTIVE INTERVENTIONS. ☐ ASSURE APPROPRIATE LEVEL OF CARE. ☐ ASSURE APPROPRIATE DURATION OF SERVICE FOR INTERVENTIONS. ☒ ASSURE THAT RECOMMENDED MEDICAL PREREQUISITES HAVE BEEN MET. ☐ ASSURE APPROPRIATE SITE OF TREATMENT OR SERVICE.
Effective Date:	**10/1/2024**

I. POLICY

Genetic testing for neurofibromatosis type 1 (NF1) or neurofibromatosis type 2-related schwannomatosis (NF2) pathogenic variants may be considered **medically necessary** when the diagnosis is clinically suspected due to signs of disease, but a definitive diagnosis cannot be made without genetic testing.

Genetic testing for NF1 or NF2 pathogenic variants in asymptomatic individuals may be considered **medically necessary** when a definitive diagnosis cannot be made without genetic testing AND at least one of the following criteria is met:

- A close relative (i.e., first-, second-, or third-degree relative) has a known NF variant; or
- A close relative has been diagnosed with neurofibromatosis but whose genetic status is unavailable.

Genetic testing for neurofibromatosis for all other situations not meeting the criteria outlined above is considered **investigational**. There is insufficient evidence to support a conclusion concerning the health outcomes or benefits associated with this procedure.

Policy Guidelines

For evaluation of neurofibromatosis type 1 (NF1), testing for a variety of pathogenic variants of NF1, preferably through a multistep variant detection protocol, is indicated. If no NF1 pathogenic variants are detected in patients with suspected NF1, testing for SPRED1 variants is reasonable.

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.

II. PRODUCT VARIATIONS

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This policy is only applicable to certain programs and products administered by Capital Blue Cross and subject to benefit variations as discussed in Section VI. Please see additional information below.

FEP PPO – Refer to FEP Medical Policy Manual. The FEP Medical Policy manual can be found at: https://www.fepblue.org/benefit-plans/medical-policies-and-utilization-management-guidelines/medical-policies

III. DESCRIPTION/BACKGROUND

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NEUROFIBROMATOSIS

Neurofibromatoses are autosomal dominant genetic disorders associated with tumors of the peripheral and central nervous systems. There are 3 clinically and genetically distinct forms: neurofibromatosis (NF) type 1 (NF1; also known as von Recklinghausen disease), NF type 2-related schwannomatosis (formerly NF type 2) (NF2), and schwannomatosis. The potential benefit of genetic testing for NF1, NF2, or SPRED1 pathogenic variants is to confirm the diagnosis in an individual with suspected NF who does not fulfill clinical diagnostic criteria or to determine future risk of NF in asymptomatic at-risk relatives.

Neurofibromatosis Type 1

NF1 is one of the most common dominantly inherited genetic disorders, with an incidence at birth of 1 in 3000 individuals.

Clinical Characteristics

The clinical manifestations of NF1 show extreme variability, between unrelated individuals, among affected individuals within a single family, and within a single person at different times in life.

NF1 is characterized by multiple café-au-lait spots, axillary and inguinal freckling, multiple cutaneous neurofibromas, and iris Lisch nodules. Segmental NF1 is limited to one area of the body. Many individuals with NF1 only develop cutaneous manifestations of the disease and Lisch nodules.

Cutaneous Manifestations

Café-au-lait macules occur in nearly all affected individuals, and intertriginous freckling occurs in almost 90%. Café-au-lait macules are common in the general population, but when more than six are present, NF1 should be suspected. Café-au-lait spots are often present at birth and increase in number during the first few years of life.

Neurofibromas

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Neurofibromas are benign tumors of Schwann cells that affect virtually any nerve in the body and develop in most people with NF1. They are divided into cutaneous and plexiform types. Cutaneous neurofibromas, which develop in almost all people with NF1, are discrete, soft, sessile, or pedunculated tumors. Discrete cutaneous and subcutaneous neurofibromas are rare before late childhood. They may vary from a few to hundreds or thousands, and the rate of development may vary greatly from year to year. Cutaneous neurofibromas do not carry a risk of malignant transformation but may be a major cosmetic problem in adults.

Plexiform neurofibromas, which occur in about half of individuals with NF1, are more diffuse growths that may be locally invasive. They can be superficial or deep and, therefore, the extent cannot be determined by clinical examination alone; magnetic resonance imaging (MRI) is the method of choice for imaging plexiform neurofibromas. Plexiform neurofibromas represent a major cause of morbidity and disfigurement in individuals with NF1. They tend to develop and grow in childhood and adolescence and stabilize throughout adulthood. Plexiform neurofibromas can compress the spinal cord or airway and can transform into malignant peripheral nerve sheath tumors. Malignant peripheral nerve sheath tumors occur in approximately 10% of affected individuals.

Other Tumors

Optic gliomas, which can lead to blindness, develop in the first 6 years of life. Symptomatic optic gliomas usually present before 6 years of age with loss of visual acuity or proptosis, but they may not become symptomatic until later in childhood or adulthood. While optic pathway gliomas are particularly associated with NF1, other central nervous system tumors occur at higher frequency in NF1, including astrocytomas and brainstem gliomas.

Patients with NF1 have a high lifetime risk of cancer, including solid tumors not described above, with excess risk appearing to manifest prior to age 50 years. Particularly strong links have been identified between pathogenic and likely pathogenic NF1 variants and risks of breast cancer and gastrointestinal stromal tumors, and 5-year overall survival is significantly worse for patients with NF1, and non-central nervous system cancers compared to similar patients without NF1. Additionally, children with NF1 have long been recognized to carry significantly higher risk of juvenile myelomonocytic leukemia than children who do not have NF1.

Other Findings

Other findings in NF1 include:

- Intellectual disability occurs at a frequency about twice that in the general population, and features of autism spectrum disorder occur in up to 30% of children with NF1.
- Musculoskeletal features include dysplasia of the long bones, most often the tibia and fibula, which is almost always unilateral. Generalized osteopenia is more common in people with NF1 and osteoporosis is more common and occurs at a younger age than in the general population.
- Cardiovascular involvement includes the common occurrence of hypertension. Vasculopathies may involve major arteries or arteries of the heart or brain and can have serious or fatal consequences. Cardiac issues include valvar pulmonic stenosis and congenital heart defects, and hypertrophic cardiomyopathy may be especially frequent in

individuals with NF1 whole gene deletions. Adults may develop pulmonary hypertension, often in association with parenchymal lung disease.

- Lisch nodules are innocuous hamartomas of the iris.

Diagnosis

Although the clinical manifestations of NF1 are extremely variable and some are age-dependent, the diagnosis can be made clinically or with the use of combined clinical and genetic findings.

The clinical diagnosis of NF1 should be suspected in individuals with the diagnostic criteria for NF1 developed by the National Institute of Health (NIH) in 1988; these clinical criteria were revised in 2021 by an international expert consensus panel to account for advances in understanding of genotype and phenotypic features of NF1 and mosaic NF1. The criteria are met when an individual has:

- Two or more of the following features for diagnosis of NF1:
    - Is the child of a parent who meets NF1 diagnostic criteria (does not contribute to diagnosis of mosaic NF1; see below);
    - Germline heterozygous *NF1* pathogenic variant with allele fraction of 50%;
    - Six or more café-au-lait macules over 5 mm in greatest diameter in prepubertal individuals and over 15 mm in post pubertal individuals;
    - Two or more neurofibromas of any type or one plexiform neurofibroma;
    - Freckling in the axillary or inguinal regions;
    - Optic glioma;
    - Two or more Lisch nodules (raised, tan-colored hamartomas of the iris) or 2 or more choroidal abnormalities;
    - A distinctive osseous lesion such as sphenoid dysplasia, anterolateral bowing of the tibia, or tibial pseudarthrosis.
- Any of the following features for diagnosis of mosaic NF1:
    - Germline heterozygous *NF1* pathogenic variant with allele fraction significantly less than 50% plus one or more of the criteria for NF1 above (except for being the child of a parent meeting NF1 diagnostic criteria);
    - Identical somatic heterozygous *NF1* pathogenic variant identified in 2 anatomically independent affected tissues;
    - Clearly segmental distribution of café-au-lait macules or cutaneous neurofibromas plus either one or more of the criteria for NF1 above (except for being the child of a parent meeting NF1 diagnostic criteria) or is the parent of a child who meets NF1 diagnostic criteria;
    - Is the parent of a child who meets NF1 diagnostic criteria plus has 2 or more neurofibromas or one plexiform neurofibroma, freckling in the axillary or inguinal region, optic glioma, 2 or more Lisch nodules or 2 or more choroidal abnormalities, or a distinctive osseous lesion.

In adults, the diagnostic criteria are highly specific and sensitive for a diagnosis of NF1.

Approximately half of children with NF1 and no known family history of NF1 meet NIH criteria for the clinical diagnosis by age 1 year. By 8 years of age, most meet NIH criteria because many features of NF1 increase in frequency with age. Children who have inherited NF1 from an affected parent can usually be diagnosed within the first year of life because the diagnosis requires 1 diagnostic clinical feature in addition to a family history of the disease. This feature is usually multiple café-au-lait spots, present in infancy in more than 95% of individuals with NF1.

Young children with multiple café-au-lait spots and no other features of NF1 who do not have a parent with signs of NF1 should be suspected of having NF1 and should be followed clinically as if they do. A definitive diagnosis of NF1 can be made in most children by 4 years of age using the NIH criteria.

Genetics

NF1 is caused by dominant loss-of-function variants in the NF1 gene, which is a tumor suppressor gene located at chromosome 17q11.2 that encodes neurofibromin, a negative regulator of RAS activity. About half of affected individuals have it as a result of a de novo NF1 variant. Penetrance is virtually complete after childhood; however, expressivity is highly variable.

The variants responsible for NF1 are very heterogeneous and include nonsense and missense single nucleotide changes, single base insertions or deletions, splicing variants (~30% of cases), whole gene deletions (~5% of cases), intragenic copy number variants, and other structural rearrangements. Several thousand pathogenic NF1 variants have been identified; however, none is frequent.

Management

Patient management guidelines for NF1 have been developed by the American Academy of Pediatrics, the National Society of Genetic Counselors, and other expert groups.

After an initial diagnosis of NF1, the extent of the disease should be established, with personal medical history and physical examination and particular attention to features of NF1, ophthalmologic evaluation including slit lamp examination of the irides, developmental assessment in children, and other studies as indicated on the basis of clinically apparent signs or symptoms.

Surveillance recommendations for an individual with NF1 focus on regular annual visits for skin examination for new peripheral neurofibromas, signs of plexiform neurofibroma or progression of existing lesions, checks for hypertension, other studies (e.g., MRI) as indicated based on clinically apparent signs or symptoms, and monitoring of abnormalities of the central nervous system, skeletal system, or cardiovascular system by an appropriate specialist. In children, recommendations include annual ophthalmologic examination in early childhood (less frequently in older children and adults) and regular developmental assessment.

Long-term care for individuals with NF1 aims at early detection and treatment of symptomatic complications.

It is recommended that radiotherapy is avoided, if possible because radiotherapy in individuals with NF1 appears to be associated with a high risk of developing a malignant peripheral nerve sheath tumor within the field of treatment.

Legius Syndrome

Clinical Characteristics

A few clinical syndromes may overlap clinically with NF1. In most cases, including Proteus syndrome, Noonan syndrome, McCune-Albright syndrome, and LEOPARD syndrome, patients will be missing key features or will have features of the other disorder. However, the Legius syndrome is a rare autosomal dominant disorder characterized by multiple café-au-lait macules, intertriginous freckling, macrocephaly, lipomas, and potential attention-deficit/hyperactivity disorder. Misdiagnosis of Legius syndrome as NF1 might result in overtreatment and psychological burden on families about potential serious NF-related complications.

Genetics

Legius syndrome is associated with pathogenic loss-of-function variants in the SPRED1 gene on chromosome 15, which is the only known gene associated with Legius syndrome.

Diagnosis

The 2021 revision to the NIH diagnostic criteria for NF1 included new criteria for Legius syndrome and mosaic Legius syndrome. The criteria are met when an individual has:

- Any of the following features for diagnosis of Legius syndrome:
    - Both of the following in an individual who is not the child of a parent diagnosed with Legius syndrome:
        - Six or more café-au-lait macules, with or without axillary or inguinal freckling, and no other features diagnostic of NF1;
        - Germline heterozygous *SPRED1* pathogenic variant with allele fraction of 50%;
    - Either of the above criteria for Legius syndrome in an individual who is the child of a parent diagnosed with Legius syndrome.
- Any of the following features for diagnosis of mosaic Legius syndrome:
    - Germline heterozygous *SPRED1* pathogenic variant with allele fraction significantly less than 50% plus 6 or more café-au-lait macules;
    - Identical somatic heterozygous *SPRED1* pathogenic variant identified in 2 independent affected tissues;
    - Clearly segmental distribution of café-au-lait macules plus is the parent of a child who meets Legius syndrome diagnostic criteria.

Management

Legius syndrome typically follows a benign course and management generally focuses on treatment of manifestations and prevention of secondary complications. Treatment of

manifestations includes behavioral modification and/or pharmacologic therapy for those with attention-deficit/hyperactivity disorder; physical, speech, and occupational therapy for those with identified developmental delays; and individualized education plans for those with learning disorders.

Neurofibromatosis Type 2

NF2 (also known as bilateral acoustic neurofibromatosis and central neurofibromatosis) is estimated to occur in 1 in 33,000 individuals.

Clinical Characteristics

NF2 is characterized by bilateral vestibular schwannomas and associated symptoms of tinnitus, hearing loss, and balance dysfunction. The average age of onset is 18 to 24 years, and almost all affected individuals develop bilateral vestibular schwannomas by age 30 years. Affected individuals may also develop schwannomas of other cranial and peripheral nerves, ependymomas, meningiomas, and, rarely, astrocytomas. The most common ocular finding, which may be the first sign of NF2, is posterior subcapsular lens opacities; they rarely progress to visually significant cataracts.

Most patients with NF2 present with hearing loss, which is usually unilateral at onset. Hearing loss may be accompanied or preceded by tinnitus. Occasionally, features such as dizziness or imbalance are the first symptom. A significant proportion of cases (20%-30%) present with an intracranial meningioma, spinal, or cutaneous tumor. The presentation in pediatric populations may differ from adult populations, in that, in children, vestibular schwannomas may account for only 15% to 30% of initial symptoms.

Diagnosis

The diagnosis of NF2 is usually based on clinical findings and more recently identified molecular findings. Historically, diagnosis of NF2 was based on modified NIH diagnostic criteria. In 2022, revised diagnostic criteria were introduced by an international expert consensus panel to incorporate advances in understanding of genotypic and phenotypic features of NF2, as well as to better delineate between NF2 and schwannomatosis.[15,] The new criteria for NF2 are met when an individual has one of the following:

- Bilateral vestibular schwannomas;
- Identical somatic *NF2* pathogenic variant identified in at least 2 anatomically distinct NF2-related tumors;
- Either 2 major criteria below or 1 major plus 2 minor criteria below:
    - Major criteria:
        - Unilateral vestibular schwannoma;
        - First-degree non-sibling relative with NF2;
        - Two or more meningiomas;
        - Germline *NF2* pathogenic variant (considered mosaic NF2 if variant allele fraction is significantly less than 50%).

- Minor criteria:
  - Single meningioma;
  - Ependymoma or schwannoma (each distinct tumor counts as one minor criterion);
  - Juvenile subcapsular or cortical cataract;
  - Retinal hamartoma;
  - Epiretinal membrane in an individual age <40 years.

Genetics

NF2 is inherited in an autosomal-dominant manner; approximately 50% of individuals have an affected parent, and the other 50% have NF2 as a result of a de novo variant.

Between 25% and 33% of individuals with NF2 caused by a de novo variant have somatic mosaicism. Variant detection rates are lower in simplex cases and in an individual in the first generation of a family to have NF2 because they are more likely to have somatic mosaicism. Somatic mosaicism can make clinical recognition of NF2 difficult and results in lower variant detection rates. Clinical recognition of NF2 in these patients may be more difficult because these individuals may not have bilateral vestibular schwannomas. Variant detection rates may also be lower because molecular genetic test results may be normal in unaffected tissue (e.g., lymphocytes), and molecular testing of tumor tissue may be necessary to establish the presence of somatic mosaicism.

Management

In an individual diagnosed with NF2, it is recommended that an initial evaluation establishes the extent of the disease, typically using cranial MRI, hearing evaluation, and ophthalmologic and cutaneous examinations. Counseling is recommended for insidious problems with balance and underwater disorientation, which can result in drowning. Hearing preservation and augmentation are part of the management of NF2, as is early recognition and management of visual impairment from other manifestations of NF2. Therefore, routine hearing and eye examinations should be conducted. Surveillance measures for affected or at-risk individuals include annual MRI beginning at around age 10 and continuing until at least the fourth decade of life.

Treatment of manifestations includes surgical resection of small vestibular schwannomas, which may often be completely resected with preservation of hearing and facial nerve function. Larger tumors are often managed expectantly with debulking or decompression when brain stem compression, deterioration of hearing, and/or facial nerve dysfunction occur.

Radiotherapy should be avoided, because radiotherapy of NF2-associated tumors, especially in childhood, may induce, accelerate, or transform tumors.

Evaluation of At-Risk Relatives

Early identification of relatives who have inherited the family-specific NF2 variant allows for appropriate screening using MRI for neuroimaging and audiologic evaluation, which result in

earlier detection and improved outcomes. Identification of at-risk relatives who do not have the family-specific NF2 variant eliminates the need for surveillance.

Schwannomatosis

Schwannomatosis is a rare condition characterized by development of multiple schwannomas and, less frequently, meningiomas. Individuals with schwannomatosis may develop intracranial, spinal nerve root, or peripheral nerve tumors. Familial cases are inherited in an autosomal-dominant manner, with highly variable expressivity and incomplete penetrance. The presentation of schwannomatosis exists on a spectrum with NF2, with certain key distinguishing clinical and more recently recognized molecular features. SMARCB1 and LZTR1 variants have been shown to cause most cases of familial schwannomatosis but account for a lesser proportion of simplex disease. Some cases are also characterized by chromosome 22 abnormalities, typically involving the 22q region encompassing SMARCB1, LZTR1, and NF2, without identification of SMARCB1 or LZTR1 pathogenic variants. New diagnostic criteria for molecularly defined subtypes of schwannomatosis not associated with NF2 pathogenic variants (i.e., with germline or somatic pathogenic variants of SMARCB1 or LZTR1, or with loss of heterozygosity of chromosome 22q) were proposed alongside the 2022 NF2 diagnostic criteria, with cases not meeting these definitions categorized as schwannomatosis-not elsewhere classified.

REGULATORY STATUS

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. Lab tests for NF are available under the auspices of the Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

IV. RATIONALE

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Summary of Evidence

For individuals who have suspected NF who receive genetic testing for NF1, NF2, or SPRED1 pathogenic variants, the evidence includes clinical validation studies of a multistep diagnostic protocol and genotype-phenotype correlation studies. Relevant outcomes are test accuracy and validity, symptoms, morbid events, and functional outcomes. A multistep variant testing protocol identifies more than 95% of pathogenic variants in NF1; for NF2, the variant detection rate approaches more than 70% in simplex cases and exceeds 90% for familial cases. 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 a close relative(s) with an NF diagnosis, who receive genetic testing for NF1, NF2, or SPRED1 pathogenic variants, there is no direct evidence. Relevant outcomes are test accuracy and validity, symptoms, morbid events, and functional outcomes. For individuals with a known pathogenic variant in the family, testing of at-

risk relatives will confirm or exclude the variant with high certainty. While direct evidence on the clinical utility of genetic testing for NF is lacking, a definitive diagnosis resulting from genetic testing can direct patient care according to established clinical management guidelines, including referrals to the proper specialists, treatment of manifestations, and surveillance. Testing of at-risk relatives will lead to initiation or avoidance of management and/or surveillance. Early surveillance may be particularly important for patients with NF type 2 because early identification of internal lesions by imaging is expected to improve outcomes. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

V. DEFINITIONS

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SCHWANN CELLS cover the nerve fibers in the peripheral nervous system and form the myelin sheath.

SIMPLEX DISEASE is a single occurrence of a disease in a family.

SOMATIC MOSAICISM is the occurrence of 2 genetically distinct populations of cells within an individual, derived from a postzygotic variant. Unlike inherited variants, somatic mosaic variants may affect only a portion of the body and are not transmitted to progeny.

VI. BENEFIT VARIATIONS

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The existence of this medical policy does not mean that this service is a covered benefit under the member's health benefit plan. Benefit determinations should be based in all cases on the applicable health benefit plan language. Medical policies do not constitute a description of benefits. A member's health benefit plan governs which services are covered, which are excluded, which are subject to benefit limits, and which require preauthorization. There are different benefit plan designs in each product administered by Capital Blue Cross. Members and providers should consult the member's health benefit plan for information or contact Capital Blue Cross for benefit information.

VII. DISCLAIMER

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Capital Blue Cross' medical policies are developed to assist in administering a member's benefits, do not constitute medical advice and are subject to change. Treating providers are solely responsible for medical advice and treatment of members. Members should discuss any medical policy related to their coverage or condition with their provider and consult their benefit information to determine if the service is covered. If there is a discrepancy between this medical policy and a member's benefit information, the benefit information will govern. If a provider or a member has a question concerning the application of this medical policy to a specific member's plan of benefits, please contact Capital Blue Cross' Provider Services or Member Services. Capital Blue Cross considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.

VIII. CODING INFORMATION

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Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

Covered when medically necessary:

Procedure Codes							
81403	81405	81406	81408	81479			

ICD-10-CM Diagnosis Code	Description
Q85.00	Neurofibromatosis, unspecified
Q85.01	Neurofibromatosis, type 1
Q85.02	Neurofibromatosis, type 2
Q85.03	Schwannomatosis
Q85.09	Other neurofibromatosis

IX. REFERENCES

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41. *Blue Cross Blue Shield Association Medical Policy Reference Manual. 2.04.137, Genetic Testing for Neurofibromatosis, February 2024*

X. POLICY HISTORY

TOP

MP 2.358	**05/07/2018 New Policy.** Adopt BCBSA. Genetic testing for neurofibromatosis (NF) may be considered medically necessary in individuals with suspected NF and in at-risk relatives in whom the diagnosis cannot be made without genetic testing.
	03/21/2019 Consensus Review. No changes to policy statement. References updated.
	03/16/2020 Consensus Review. No change to policy statement. References updated. Coding reviewed.
	02/01/2021 Consensus Review. Policy statement edited to clarify the specific genetic testing, otherwise no change to policy statement. Reference and coding reviewed. Background updated.
	02/03/2022 Minor Review. Changed wording of criteria from “at-risk individual” to “asymptomatic member”. Updated FEP and references.
	02/02/2023 Consensus Review. Updated background and references. Added 81403 and 81479 to coding table.
	03/15/2024 Consensus Review. Small editorial refinement to policy statement; intent unchanged. Updated background, rationale, definitions and references. No changes to coding.

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