Genetic Testing for Neurofibromatosis

Policy # 00502
Original Effective Date: 04/20/2016
Current Effective Date: 07/10/2023

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

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 for neurofibromatosis 1 (NF1) or neurofibromatosis type 2 (NF2) pathogenic variants to be **eligible for coverage**** when a diagnosis of neurofibromatosis is clinically suspected due to signs of disease, but a definitive diagnosis cannot be made without genetic testing.

Based on review of available data, the Company may consider genetic testing for NF1 or NF2 pathogenic variants in at-risk relatives with no signs of disease to be **eligible for coverage**** when a definitive diagnosis cannot be made without genetic testing AND at least one of the following criteria is met:

- A close relative (ie, first-, second-, or third-degree relative) has a known *NF* 1 or NF 2 variant; or
- A close relative has been diagnosed with neurofibromatosis but whose genetic status is unavailable.

When Services Are Considered Investigational

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

Genetic testing for neurofibromatosis for all other situations and when patient selection criteria are not met is considered to be **investigational.***

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Policy Guidelines

Testing Strategy

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 individuals with suspected NF1, testing for *SPRED1* variants is reasonable.

There are a number of cancer types associated with NF, including breast cancer associating with *NF1*. While the National Comprehensive Cancer Network's Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic consensus guidelines (version 1.2023) addresses the risk of breast cancer with *NF1* and has intensified breast cancer screening recommendations, these screening recommendations apply only to individuals with a clinical diagnosis of NF1.[1,] Criteria for a clinical diagnosis are included below.

Definitions

Mutation Scanning

Mutation scanning is a process by which a particular segment of DNA is screened to identify sequence variants. Variant gene regions are then further analyzed (eg, by sequencing) to identify the sequence alteration. Mutation scanning allows for screening of large genes and novel sequence variants.

Schwann Cells

Schwann cells cover the nerve fibers in the peripheral nervous system and form the myelin sheath.

Simplex Disease

Simplex disease is a single occurrence of a disease in a family.

Somatic Mosaicism

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.

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Genetics Nomenclature Update
The Human Genome Variation Society nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. It is being implemented for genetic testing medical evidence review updates starting in 2017 (see Table PG1). The Society's nomenclature is recommended by the Human Variome Project, the Human Genome Organization, and by the Human Genome Variation Society itself.

The American College of Medical Genetics and Genomics and the Association for Molecular Pathology standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations, in addition to 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 PG2 shows the recommended standard terminology- "pathogenic," "likely pathogenic," "uncertain significance," "likely benign," and "benign"- to describe variants identified that cause Mendelian disorders.

Table PG1. Nomenclature to Report on Variants Found in DNA

Previous	Updated	Definition
Mutation	Disease-associated variant	Disease-associated change in the DNA sequence
	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 PG2. 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-AMP: American College of Medical Genetics and Genomics and the Association for Molecular Pathology.

Genetic Counseling

Genetic counseling is primarily aimed at individuals 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

Neurofibromatosis

There are 3 major clinically and genetically distinct forms of neurofibromatosis (NF): NF type 1 (NF1; also known as von Recklinghausen disease), NF type 2 (NF2), and schwannomatosis.

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 1 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 6 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
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.

Individuals 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 individuals with NF1 and non-central nervous system cancers compared to similar individuals 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 of 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 including valvar pulmonic stenosis, 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 genotypic 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.

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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 a de novo *NF1* variant. Penetrance is virtually complete after childhood though expressivity is highly variable.

The variants responsible for NF1 are 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 and 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 a 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 (eg, 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 goals for individuals with NF1 are early detection and treatment of symptomatic complications.

It is recommended that radiotherapy is avoided because radiotherapy in individuals with NF1 may 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, individuals will be missing key features or will have features of the other disorder. However, 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 the treatment of manifestations and prevention of secondary complications. Treatment of manifestations include 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 which rarely progress to visually significant cataracts.

Most individuals with NF2 present with hearing loss, which is usually unilateral at the 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% to 30%) present with an intracranial meningioma, spinal, or cutaneous tumor. The presentation in pediatric populations may differ from adult populations as vestibular schwannomas may account for only 15% to 30% of initial symptoms.

Genetic Testing for Neurofibromatosis

Policy # 00502
Original Effective Date: 04/20/2016
Current Effective Date: 07/10/2023

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.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 individuals 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 (eg, 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 results 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 (ie, 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.

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 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.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

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, NF type 2, and schwannomatosis. The potential benefit of genetic testing for NF type 1 (*NF1*), neurofibromatosis type 2 (*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.

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 NF type 1; for NF type 2, 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 an 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 individuals 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 an improvement in the net health outcome.

Supplemental Information

Practice Guidelines and Position Statements
Guidelines or position statements will be considered for inclusion in ‘Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American Academy of Pediatrics
In 2019, the American Academy of Pediatrics published diagnostic and health supervision guidance for children with neurofibromatosis type 1 (NF1). The guidance makes the following statements related to genetic testing:

"NF1 genetic testing may be performed for purposes of diagnosis or to assist in genetic counseling and family planning. If a child fulfills diagnostic criteria for NF1, molecular genetic confirmation is usually unnecessary. For a young child who presents only with [café-au-lait macules], NF1 genetic testing can confirm a suspected diagnosis before a second feature, such as skinfold freckling, appears. Some families may wish to establish a definitive diagnosis as soon as possible and not wait for this second feature, and genetic testing can usually resolve the issue" and "Knowledge of the NF1 [pathogenic sequence variant] can enable testing of other family members and prenatal diagnostic testing."

The guidance includes the following summary and recommendations about genetic testing:

- can confirm a suspected diagnosis before a clinical diagnosis is possible;
- can differentiate NF1 from Legius syndrome;
- may be helpful in children who present with atypical features;
- usually does not predict future complications; and
- may not detect all cases of NF1; a negative genetic test rules out a diagnosis of NF1 with 95% (but not 100%) sensitivity

National Comprehensive Cancer Network
The National Comprehensive Cancer Network's Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic consensus guidelines (version 1.2023) address the association between pathogenic *NF1* variants and risk of breast cancer. The panel recommends annual screening mammograms for breast cancer beginning at age 30 years (or younger, if indicated according to family history of breast cancer) in individuals with such *NF1* variants, with consideration for screening via breast magnetic resonance imaging (MRI) through age 50 due to excess risk between the ages of 30 and 50, and referral to an NF1 specialist for evaluation and management of other *NF1*-associated cancer risks. The guidelines state that studies show that beginning at age 50 breast cancer risk in women with NF1 may not significantly differ from that of women in the general population; and, therefore, breast MRI screening in individuals with NF1 may be discontinued at 50 years of

age. Note that these screening recommendations apply only to individuals with a clinical diagnosis of NF1.

U.S. Preventive Services Task Force Recommendations
Not applicable.

Medicare National Coverage
There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials
A search of ClinicalTrials.gov in November 2022 did not identify any ongoing or unpublished trials that would likely influence this review.

References

1. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic. Version 1.2023.
2. Friedman JM. Neurofibromatosis 1. In: Adam MP, Everman DB, Mirzaa GM, et al., eds. GeneReviews. Seattle, WA: University of Washington; 1993-2022. Updated April 21, 2022.
3. Uusitalo E, Rantanen M, Kallionpää RA, et al. Distinctive Cancer Associations in Patients With Neurofibromatosis Type 1. J Clin Oncol. Jun 10 2016; 34(17): 1978-86. PMID 26926675
4. Walker L, Thompson D, Easton D, et al. A prospective study of neurofibromatosis type 1 cancer incidence in the UK. Br J Cancer. Jul 17 2006; 95(2): 233-8. PMID 16786042
5. Nishida T, Tsujimoto M, Takahashi T, et al. Gastrointestinal stromal tumors in Japanese patients with neurofibromatosis type I. J Gastroenterol. Jun 2016; 51(6): 571-8. PMID 26511941
6. Stiller CA, Chessells JM, Fitchett M. Neurofibromatosis and childhood leukaemia/lymphoma: a population-based UKCCSG study. Br J Cancer. Nov 1994; 70(5): 969-72. PMID 7947106
7. Niemeyer CM, Arico M, Basso G, et al. Chronic myelomonocytic leukemia in childhood: a retrospective analysis of 110 cases. European Working Group on Myelodysplastic Syndromes in Childhood (EWOG-MDS). Blood. May 15 1997; 89(10): 3534-43. PMID 9160658
8. Neurofibromatosis. Conference statement. National Institutes of Health Consensus Development Conference. Arch Neurol. May 1988; 45(5): 575-8. PMID 3128965

9. Legius E, Messiaen L, Wolkenstein P, et al. Revised diagnostic criteria for neurofibromatosis type 1 and Legius syndrome: an international consensus recommendation. Genet Med. Aug 2021; 23(8): 1506-1513. PMID 34012067
10. Bernier A, Larbrisseau A, Perreault S. Café-au-lait Macules and Neurofibromatosis Type 1: A Review of the Literature. Pediatr Neurol. Jul 2016; 60: 24-29.e1. PMID 27212418
11. Hersh JH. Health supervision for children with neurofibromatosis. Pediatrics. Mar 2008; 121(3): 633-42. PMID 18310216
12. Legius E, Stevenson D. Legius Syndrome. In: Adam MP, Everman DB, Mirzaa GM, et al., eds. GeneReviews. Seattle, WA: University of Washington; 1993-2022. Updated August 6, 2020.
13. Evans DG. Neurofibromatosis 2. In: Adam MP, Everman DB, Mirzaa GM, et al., eds. GeneReviews. Seattle, WA: University of Washington; 1993-2022. Updated March 15, 2018.
14. Evans DG, Sainio M, Baser ME. Neurofibromatosis type 2. J Med Genet. Dec 2000; 37(12): 897-904. PMID 11106352
15. Plotkin SR, Messiaen L, Legius E, et al. Updated diagnostic criteria and nomenclature for neurofibromatosis type 2 and schwannomatosis: An international consensus recommendation. Genet Med. Sep 2022; 24(9): 1967-1977. PMID 35674741
16. Dhamija R, Plotkin S, Asthagiri A, Messiaen L, Babovic-Vuksanovic D. Schwannomatosis. In: Adam MP, Everman DB, Mirzaa GM, et al, eds. GeneReviews. Seattle, WA: University of Washington; 1993-2022. Updated March 8, 2018.
17. van Minkelen R, van Bever Y, Kromosoeto JN, et al. A clinical and genetic overview of 18 years neurofibromatosis type 1 molecular diagnostics in the Netherlands. Clin Genet. Apr 2014; 85(4): 318-27. PMID 23656349
18. Sabbagh A, Pasmant E, Imbard A, et al. NF1 molecular characterization and neurofibromatosis type I genotype-phenotype correlation: the French experience. Hum Mutat. Nov 2013; 34(11): 1510-8. PMID 23913538
19. Valero MC, Martín Y, Hernández-Imaz E, et al. A highly sensitive genetic protocol to detect NF1 mutations. J Mol Diagn. Mar 2011; 13(2): 113-22. PMID 21354044
20. Spurlock G, Bennett E, Chuzhanova N, et al. SPRED1 mutations (Legius syndrome): another clinically useful genotype for dissecting the neurofibromatosis type 1 phenotype. J Med Genet. Jul 2009; 46(7): 431-7. PMID 19443465
21. Zhu L, Zhang Y, Tong H, et al. Clinical and Molecular Characterization of NF1 Patients: Single-Center Experience of 32 Patients From China. Medicine (Baltimore). Mar 2016; 95(10): e3043. PMID 26962827

22. Zhang J, Tong H, Fu X, et al. Molecular Characterization of NF1 and Neurofibromatosis Type 1 Genotype-Phenotype Correlations in a Chinese Population. Sci Rep. Jun 09 2015; 5: 11291. PMID 26056819
23. Bianchessi D, Morosini S, Saletti V, et al. 126 novel mutations in Italian patients with neurofibromatosis type 1. Mol Genet Genomic Med. Nov 2015; 3(6): 513-25. PMID 26740943
24. Calì F, Chiavetta V, Ruggeri G, et al. Mutation spectrum of NF1 gene in Italian patients with neurofibromatosis type 1 using Ion Torrent PGM™ platform. Eur J Med Genet. Feb 2017; 60(2): 93-99. PMID 27838393
25. Giugliano T, Santoro C, Torella A, et al. Clinical and Genetic Findings in Children with Neurofibromatosis Type 1, Legius Syndrome, and Other Related Neurocutaneous Disorders. Genes (Basel). Jul 31 2019; 10(8). PMID 31370276
26. Angelova-Toshkina D, Holzapfel J, Huber S, et al. Neurofibromatosis type 1: A comparison of the 1997 NIH and the 2021 revised diagnostic criteria in 75 children and adolescents. Genet Med. Sep 2022; 24(9): 1978-1985. PMID 35713653
27. Pasmant E, Sabbagh A, Spurlock G, et al. NF1 microdeletions in neurofibromatosis type 1: from genotype to phenotype. Hum Mutat. Jun 2010; 31(6): E1506-18. PMID 20513137
28. Mautner VF, Kluwe L, Friedrich RE, et al. Clinical characterisation of 29 neurofibromatosis type-1 patients with molecularly ascertained 1.4 Mb type-1 NF1 deletions. J Med Genet. Sep 2010; 47(9): 623-30. PMID 20543202
29. Upadhyaya M, Huson SM, Davies M, et al. An absence of cutaneous neurofibromas associated with a 3-bp inframe deletion in exon 17 of the NF1 gene (c.2970-2972 delAAT): evidence of a clinically significant NF1 genotype-phenotype correlation. Am J Hum Genet. Jan 2007; 80(1): 140-51. PMID 17160901
30. Rojnueangnit K, Xie J, Gomes A, et al. High Incidence of Noonan Syndrome Features Including Short Stature and Pulmonic Stenosis in Patients carrying NF1 Missense Mutations Affecting p.Arg1809: Genotype-Phenotype Correlation. Hum Mutat. Nov 2015; 36(11): 1052-63. PMID 26178382
31. Pinna V, Lanari V, Daniele P, et al. p.Arg1809Cys substitution in neurofibromin is associated with a distinctive NF1 phenotype without neurofibromas. Eur J Hum Genet. Aug 2015; 23(8): 1068-71. PMID 25370043
32. Hutter S, Piro RM, Waszak SM, et al. No correlation between NF1 mutation position and risk of optic pathway glioma in 77 unrelated NF1 patients. Hum Genet. May 2016; 135(5): 469-475. PMID 26969325

33. Ko JM, Sohn YB, Jeong SY, et al. Mutation spectrum of NF1 and clinical characteristics in 78 Korean patients with neurofibromatosis type 1. Pediatr Neurol. Jun 2013; 48(6): 447-53. PMID 23668869
34. Pasmant E, Sabbagh A, Hanna N, et al. SPRED1 germline mutations caused a neurofibromatosis type 1 overlapping phenotype. J Med Genet. Jul 2009; 46(7): 425-30. PMID 19366998
35. Messiaen L, Yao S, Brems H, et al. Clinical and mutational spectrum of neurofibromatosis type 1-like syndrome. JAMA. Nov 18 2009; 302(19): 2111-8. PMID 19920235
36. Wallace AJ, Watson CJ, Oward E, et al. Mutation scanning of the NF2 gene: an improved service based on meta-PCR/sequencing, dosage analysis, and loss of heterozygosity analysis. Genet Test. 2004; 8(4): 368-80. PMID 15684865
37. Evans DG, Ramsden RT, Shenton A, et al. Mosaicism in neurofibromatosis type 2: an update of risk based on uni/bilaterality of vestibular schwannoma at presentation and sensitive mutation analysis including multiple ligation-dependent probe amplification. J Med Genet. Jul 2007; 44(7): 424-8. PMID 17307835
38. Evans DG. Neurofibromatosis type 2. In: UpToDate, ed. UpToDate. Waltham, MA: Kluwer Wolters; Updated October 28, 2022.
39. Selvanathan SK, Shenton A, Ferner R, et al. Further genotype--phenotype correlations in neurofibromatosis 2. Clin Genet. Feb 2010; 77(2): 163-70. PMID 19968670
40. Miller DT, Freedenberg D, Schorry E, et al. Health Supervision for Children With Neurofibromatosis Type 1. Pediatrics. May 2019; 143(5). PMID 31010905

Policy History

Original Effective Date: 04/20/2016
Current Effective Date: 07/10/2023

04/07/2016	Medical Policy Committee review
04/20/2016	Medical Policy Implementation Committee approval. New policy.
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
04/06/2017	Medical Policy Committee review
04/19/2017	Medical Policy Implementation Committee approval. No change to coverage.
06/07/2018	Medical Policy Committee review
06/20/2018	Medical Policy Implementation Committee approval. No change to coverage.
06/06/2019	Medical Policy Committee review
06/19/2019	Medical Policy Implementation Committee approval. No change to coverage.

Genetic Testing for Neurofibromatosis

Policy # 00502
Original Effective Date: 04/20/2016
Current Effective Date: 07/10/2023

06/04/2020	Medical Policy Committee review
06/10/2020	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
06/03/2021	Medical Policy Committee review
06/09/2021	Medical Policy Implementation Committee approval. Policy statement edited to clarify that genetic testing refers to testing for pathogenic variants in NF1 and NF2 genes.
06/02/2022	Medical Policy Committee review
06/08/2022	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
06/01/2023	Medical Policy Committee review
06/14/2023	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

Next Scheduled Review Date: 06/2024

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2022 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

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Genetic Testing for Neurofibromatosis

Policy # 00502
Original Effective Date: 04/20/2016
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contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.

CPT is a registered trademark of the American Medical Association.

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	81405, 81406, 81408
HCPCS	No codes
ICD-10 Diagnosis	All related diagnoses

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment,

would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

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.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.