Description of Procedure or Service

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), NF type 2 (NF2), and schwannomatosis. The potential benefit of genetic testing for NF is to confirm the diagnosis in an individual with suspected NF who does not fulfill diagnostic clinical criteria, or to determine future risk of NF in asymptomatic at-risk relatives.

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 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. It is referred to as segmental NF1 when 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 spots occur in nearly all affected individuals and intertriginous freckling occurs in almost 90%. Café-au-lait spots 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**

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
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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 then stabilize throughout adulthood. Plexiform neurofibromas can compress the spinal cord or airway and can transform into malignant peripheral nerve sheath tumors (MPNST). MPNST occur in approximately 10% of affected individuals.

Central Nervous System 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 in adulthood.

While optic pathway gliomas are particularly associated with NF1, other central nervous system (CNS) tumors occur at higher frequency in NF1, including astrocytomas and brainstem gliomas.

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. Vascularopathies 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 usually be made on clinical findings, and genetic testing is rarely needed. The clinical diagnosis of NF1 should be suspected in individuals with the diagnostic criteria for NF1 developed by the National Institute of Health (NIH). The criteria are met when an individual has 2 or more of the following features:

- Six or more café-au-lait macules over 5 mm in greatest diameter in prepubertal individuals and over 15 mm in postpubertal 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)
- A distinctive osseous lesion such as sphenoid dysplasia or tibial pseudarthrosis
- A first degree relative with NF1 as defined by the above criteria.

In adults, the clinical 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. Almost all do by age 8 years of age 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
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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 followed clinically as if they do. A definitive diagnosis of NF1 can be made in most children by 4 years of age using NIH criteria.

**Genetics**
NF1 is caused by dominant loss-of-function mutations 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 mutation. Penetrance is virtually complete after childhood, however, expressivity is highly variable.

The mutations responsible for NF1 are very heterogeneous, and include nonsense and missense single nucleotide changes, single base insertions/deletions, splicing mutations (~30% of cases), whole gene deletions (~5% of cases), intragenic copy number variants, and other structural rearrangements. Several thousand pathogenic NF1 mutations have been identified, however, none are 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 iris, 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 are for regular annual visits to include 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 for individuals with NF1 aims at early detection and symptomatic treatment of complications. It is recommended that radiotherapy be avoided, if possible, because radiotherapy in individuals with NF1 appears to be associated with a high risk of developing MPNST within the field of treatment.

**Legius Syndrome**
There are a few clinical syndromes that may have clinical overlap with NF1, including Proteus syndrome, Noonan syndrome, McCune-Albright syndrome, and LEOPARD syndrome, but in most cases patients will be missing key features or will have features of the alternative disorder. 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 with regard to potential serious NF-related complications.

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.

**Management**
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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 ADHD; physical, speech, and occupational therapy for those with identified developmental delays; and individual education plans for those with learning disorders.

Neurofibromatosis 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 the pediatric population may differ from the adult population, in that, in children, vestibular schwannomas may account for as little as 15% to 30% of initial symptoms.

Diagnosis
The diagnosis of NF2 is usually made on clinical findings. Modified NIH diagnostic clinical criteria are one of the following:

- Bilateral vestibular schwannomas
- A first-degree relative with NF2 AND
  - Unilateral vestibular schwannoma OR
  - Any 2 of: meningioma, schwannoma, glioma, neurofibroma, posterior subcapsular lenticular opacities.

- Multiple meningiomas AND
  - Unilateral vestibular schwannoma OR
  - Any 2 of: schwannoma, glioma, neurofibroma, cataract.

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 be lower because molecular genetic testing 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 establish the extent of the disease, typically using head MRI, hearing evaluation, and ophthalmologic and cutaneous examinations.
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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 examination should be conducted in individuals with NF2.

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 that is defined as multiple schwannomas without the vestibular schwannomas that are diagnostic of NF2. 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. Clinically, schwannomatosis is distinct from NF1 and NF2, although some individuals eventually fulfill diagnostic criteria for NF2. SMARCB1 variants have been shown to cause 30% to 60% of familial schwannomatosis but only a small number of simple disease.

**Regulatory Status:**

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

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

**Policy**

BCBSNC will provide coverage for Genetic Testing for Neurofibromatosis when it is determined to be medically necessary because the medical criteria and guidelines shown below are met.

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

When Genetic Testing for Neurofibromatosis is covered

Genetic testing for neurofibromatosis 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 neurofibromatosis in at-risk relatives with no signs of disease 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 (ie, first-, second-, or third-degree relative) has a known NF mutation; or
- A close relative has been diagnosed with neurofibromatosis but whose genetic status is unavailable

When Genetic Testing for Neurofibromatosis is not covered

Genetic testing for neurofibromatosis for all other situations not meeting the criteria outlined above is considered investigational.

Policy Guidelines

The evidence for genetic testing for NF in individuals who have suspected neurofibromatosis (NF), includes clinical validation studies using a multistep diagnostic protocol, and genotype-phenotype correlation studies. Relevant outcomes are test accuracy and validity, symptoms, morbidity events, and functional outcomes. A multistep variant testing protocol identifies more than 95% of pathogenic variants in NF type 1 (NF1), whereas for NF type 2 (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.

The evidence for genetic testing for NF in individuals who are asymptomatic with a close relative(s) with NF, there is no direct evidence. Relevant outcomes are test accuracy and validity, symptoms, morbidity 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. Published evidence on the clinical utility of genetic testing for NF is lacking, but 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 NF2 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.

Testing Strategy

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

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

Applicable service codes: 81405, 81406, 81408

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

Scientific Background and Reference Sources


Evans DG. Neurofibromatosis type 2. In: UpToDate, ed. UpToDate. Waltham, MA; 2016.


Medical Director review 7/2016


Medical Director review 1/2017

Specialty Matched Consultant Advisory Panel review 7/2017

Medical Director review 7/2017


Medical Director review 1/2018

Policy Implementation/Update Information
Genetic Testing for Neurofibromatosis

4/29/16  New policy developed titled, “Genetic Testing for Neurofibromatosis”. 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. (td)

8/30/16  Specialty Matched Consultant Advisory Panel review 7/2016. Medical Director review 7/2016. (jd)

2/24/17  Updated Description section and added Legius syndrome information. Added Testing Strategy for evaluation of neurofibromatosis type 1 (NF1) to the Policy Guidelines. References updated. (jd)


2/9/18  Description, policy guidelines and references updated. Medical Director review. (jd)

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