Genetic Testing for Neurofibromatosis

Policy # 00502
Original Effective Date: 04/20/2016
Current Effective Date: 04/19/2017

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 May Be 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 (NF) to be eligible for coverage when the diagnosis 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 neurofibromatosis 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 mutation; 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 when patient selection criteria are not met is considered to be investigational.*

Background/Overview
There are 3 major clinically and genetically distinct forms of 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 (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 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 usually 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 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 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, 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.
Genetic Testing for Neurofibromatosis

Policy # 00502
Original Effective Date: 04/20/2016
Current Effective Date: 04/19/2017

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 (eg, MRI) as indicated based on clinically apparent signs or symptoms, and monitoring of abnormalities of the CNS, 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 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
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, Legius syndrome is a rare autosomal-dominant disorder characterized but multiple café-au-lait macules, intertriginous freckling, macrocephaly, lipomas, and potential attention-deficit/hyperactivity disorder.

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

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. 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,
Genetic Testing for Neurofibromatosis

Policy # 00502
Original Effective Date: 04/20/2016
Current Effective Date: 04/19/2017

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 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.
Genetic Testing for Neurofibromatosis

Policy # 00502
Original Effective Date: 04/20/2016
Current Effective Date: 04/19/2017

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.

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 defined as multiple schwannomas without 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 simplex disease.

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 (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. FDA has chosen not to require any regulatory review of this test.

Centers for Medicare and Medicaid Services (CMS)

There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.
Genetic Testing for Neurofibromatosis

Rationale/Source
Schwannomatosis is rare and far less well-described than neurofibromatosis type 1 (NF1) and neurofibromatosis type 2 (NF2); therefore, this review will focus on NF1 and NF2.

CLINICAL CONTEXT AND TEST PURPOSE
The purpose of genetic testing in patients who have suspected NF is to inform a decision to pursue additional surveillance for comorbid conditions as recommended by well-defined management guidelines, if a definitive diagnosis can be made.

The following PICOTS were used to select literature to inform this review.

Patients
The relevant populations of interest are individuals with suspected NF1 or NF2, based on clinical symptoms or because of a family member with a diagnosis of NF1 or NF2.

Intervention
Interventions of interest include are genetic tests for NF1, NF2, and SPRED1 variants.

Comparator
Currently, clinical decision making about NF1 and NF2 is being made through clinical consensus diagnostic criteria.

Outcomes
The general outcomes of interest are test accuracy and validity, symptoms, change in disease status, morbid events, and functional outcomes. Beneficial outcomes resulting from a true test result include the potential for earlier initiation of screening for comorbidities. Harmful outcomes resulting from a false-positive test result include the potential for unneeded additional tests, while false-negative tests could lead to a delay in care.

Time
The duration of follow-up is years for the non-test-related outcomes.

Setting
These tests would typically be ordered by a specialist. Genetic counseling is an important component of care delivery.

Validation of the clinical use of any genetic test focuses on 3 main principles: (1) analytic validity, which refers to the technical accuracy of a test in detecting a variant that is present or in excluding a variant that is absent; (2) clinical validity, which refers to the diagnostic performance of a test (sensitivity, specificity, positive and negative predictive values) in detecting clinical disease; and (3) clinical utility (ie, how the results of the diagnostic test will be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes).
ANALYTIC VALIDITY
Several major laboratories have reported high analytic validity for NF1 and NF2 genetic testing, although published studies on the analytic validity of testing for NF1 and NF2 are lacking.

According to 1 major laboratory’s website, the analytic validity of bidirectional sequencing of the entire NF1 coding region, intron-exon boundaries, multiplex ligation-dependent probe amplification (MLPA) to detect large NF1 locus, and intragenic deletions or duplications is 99%.

CLINICAL VALIDITY
Neurofibromatosis Type 1
Detecting variants in the NF1 gene is challenging because of the gene’s large size, the lack of variant hotspots, and the wide variety of possible lesions.

A multistep variant testing protocol has identified more than 95% of NF1 pathogenic variants in individuals who fulfill the National Institutes of Health (NIH) diagnostic criteria. The protocol involves sequencing of both mRNA (cDNA) and genomic DNA, and testing for whole NF1 deletions (eg, by MLPA) because whole gene deletions cannot be detected by sequencing. Due to the wide variety and rarity of individual pathogenic variants in NF1, sequencing of cDNA increases the detection rate of variants from approximately 61% with genomic DNA sequence analysis alone to greater than 95% with sequencing for both cDNA and genomic DNA and testing for whole gene deletions. This latter method is known as the multistep variant detection protocol. Sensitivity rates of more than 95% for detecting a variant using the multistep protocol have been reported.

Sabbagh et al (2013) reported a comprehensive analysis of constitutional NF1 variants in unrelated, well-phenotyped index cases with typical clinical features of NF1 who enrolled in a French clinical research program. The 565 families in this study (N=1697 individuals) were enrolled between 2002 and 2005; 1083 fulfilled NIH diagnostic criteria for NF1. A comprehensive NF1 variant screening (sequencing of both cDNA and genomic DNA, as well as large deletion testing by MLPA) was performed in 565 individuals, one from each family, who had a sporadic variant or who represented the familial index case. A NF1 variant was identified in 546, a variant detection rate of 97%. A total of 507 alterations were identified at the cDNA and genomic DNA levels. Among these 507 alterations, 487 were identified using only the genomic DNA sequencing approach and 505 were identified using the single cDNA sequencing approach. MLPA detected 12 deletions or duplications that would not have been detected by sequencing. No variant was detected in 19 (3.4%) patients, 2 of whom had a SPRED1 variant, which is frequently confused with NF; the remainder may have been due to an unknown variant of the NF1 locus.

Valero et al (2011) developed a method for detecting NF1 variants by combining an RNA-based cDNA-polymerase chain reaction variant detection method and denaturing high-performance liquid chromatography with MLPA. Their protocol was validated in a cohort of 56 patients with NF1 (46 sporadic cases, 10 familial cases) who fulfilled NIH diagnostic criteria. A variant was identified in 53 cases (95% sensitivity), involving 47 different variants, of which 23 were novel. After validation, the authors implemented the protocol as a routine test and subsequently reported the spectrum of NF1 variants identified in 93 patients from a cohort of 105. The spectrum included a wide variety of variants (nonsense, small deletions
Genetic Testing for Neurofibromatosis

Policy # 00502
Original Effective Date: 04/20/2016
Current Effective Date: 04/19/2017

or insertions/duplications, splice defects, complete gene deletions, missense, single exon deletions and duplications, and a multi-exon deletion), confirming the heterogeneity of the \( NF1 \) gene variants that can cause NF1.

Additional studies have described the testing yield in smaller populations; they are summarized in Table 1.

### Table 1: Diagnostic Performance of Genetic Testing for Suspected NF1

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Population</th>
<th>Test Description</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zhu et al (2016)</td>
<td>32</td>
<td>NF1 patients (plus 120 population match controls)</td>
<td>PCR sequencing of ( NF1 ) gene, followed by MLPA</td>
<td>93.8% (30/32) patients had ( NF1 ) variant detected</td>
</tr>
<tr>
<td>Zhang et al (2015)</td>
<td>109</td>
<td>Patients with NF1-like phenotypes</td>
<td>Sanger sequencing, MLPA, and cDNA of ( NF1 ), in sequence; followed by Sanger sequencing and MLPA of ( SPRED1 ) if all others negative (n=14)</td>
<td>( NF1 ) variant detected in: 89% (89/100) of NF1 probands; 93% (70/75) of patients who met NIH criteria for NF1</td>
</tr>
<tr>
<td>Bianchessi et al (2015)</td>
<td>293</td>
<td>Patients meeting NIH NF1 criteria</td>
<td>MLPA, aCGH, DHPLC, and Sanger sequencing, in sequence, of ( NF1 )</td>
<td>70% had ( NF1 ) variant detected</td>
</tr>
<tr>
<td></td>
<td>150</td>
<td>Patients with NF1-like symptoms without meeting NIH criteria</td>
<td>MLPA, aCGH, DHPLC, and Sanger sequencing, in sequence, of ( NF1 )</td>
<td>22% had ( NF1 ) variant detected</td>
</tr>
<tr>
<td></td>
<td>61</td>
<td>Patients meeting NIH criteria</td>
<td>MLPA followed by RNA sequencing of ( NF1 )</td>
<td>87% had ( NF1 ) variant detected</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>Patients with NF1-like symptoms without meeting NIH criteria</td>
<td>MLPA followed by RNA sequencing of ( NF1 )</td>
<td>33.3% had ( NF1 ) variant detected</td>
</tr>
<tr>
<td>Spurlock et al (2009)</td>
<td>85</td>
<td>Patients with NF1-like phenotypes (mild), with negative ( NF1 ) testing</td>
<td>PCR sequencing of ( SPRED1 )</td>
<td>6 ( SPRED1 ) variants detected</td>
</tr>
</tbody>
</table>

aCGH: array comparative genomic hybridization; DHPLC: denaturing high pressure liquid chromatography; MLPA: multiplex ligation–dependent probe amplification; NF1: neurofibromatosis type 1; NIH: National Institutes of Health; PCR: polymerase chain reaction.

**Legius Syndrome**

In 2009, Pasmant et al described a cohort of 61 index cases meeting the NIH clinical diagnosis of NF1 but without a \( NF1 \) variant detectable who were screened for germline loss-of-function variants in the \( SPRED1 \) gene, located on 15q13.2. \( SPRED1 \) variants were detected in 5% of patients with NF1 features, which were characterized by café-au-lait macules and axillary and groin freckling but not neurofibromas and Lisch nodules. The authors characterized a new syndrome (Legius syndrome) based on the presence of a heterozygous \( SPRED1 \) variant.
Also in 2009, Messiaen et al described a separate cohort of 22 NF1 variant-negative probands who met NIH clinical criteria for NF1 with a SPRED1 loss-of-function variant who participated in genotype-phenotype testing with their families. Forty patients were found to be SPRED1 variant-positive, 20 (50%, 95% CI 34% to 66%) met NIH clinical criteria for NF1, although none had cutaneous or plexiform neurofibromas, typical NF osseous lesions, or symptomatic optic pathway gliomas. The authors also reported on an anonymous cohort of 1318 samples received at a university genomics laboratory for NF1 genetic testing from 2003 to 2007 with a phenotypic checklist of NF-related symptoms filled out by the referring physician. In the anonymous cohort, 26 pathogenic SPRED1 variants in 33 probands were identified. Of 1086 patients fulfilling NIH criteria for a clinical diagnosis of NF1, a SPRED1 variant was identified in 21 (1.9%; 95% CI, 1.2% to 2.9%).

Genotype-Phenotype Correlations
NF1 is characterized by extreme clinical variability between unrelated individuals, among affected individuals within a single family, and even within a single person with NF1 at different times in life. Two clear correlations have been observed between certain NF1 alleles and consistent clinical phenotypes:

1. A deletion of the entire NF1 gene is associated with large numbers and early appearance of cutaneous neurofibromas, more frequent and severe cognitive abnormalities, somatic overgrowth, large hands and feet, and dysmorphic facial features.
2. A 3-base pair inframe deletion of exon 17 is associated with typical pigmentary features of NF1, but no cutaneous or surface plexiform neurofibromas.

In addition, missense variants of NF1 p.Arg1809 have been associated typical NF1 findings of multiple café-au-lait macules and axillary freckling but reduced frequency of NF1-associated benign or malignant tumors. In 1 cohort of 136 patients, 26.2% of patients had features of Noonan syndrome (ie, short stature, pulmonic stenosis) present in excess.

In the Sabbagh et al (2013) study (described above), authors evaluated genotype-phenotype correlations for a subset of patients. This subset included 439 patients harboring a truncating (n=368), inframe splicing (n=36), or missense (n=35) NF1 variant to assess the contribution of intragenic NF1 variants (vs large gene deletions) to the variable expressivity of NF1. Their findings suggested a tendency for truncating variants to be associated with a greater incidence of Lisch nodules and a larger number of café-au-lait spots compared with missense variants.

However, other studies (eg, Zhu et al [2016], shown in Table 1; Hutter et al [2016]; Ko et al [2013]) reported no associations between variant type and phenotype.

Neurofibromatosis Type 2
At least 200 different NF2 variants have been described, most of which are point variants. Large deletions of NF2 represent 10% to 15% of NF2 variants. When variant scanning is combined with deletion/duplication analysis of single exons, the variant detection rate approaches 72% in simplex cases and exceeds 92% for familial cases. Other studies have reported lower variant detection rates, which likely reflects the inclusion of more mildly affected individuals with somatic mosaicism.
Genotype-Phenotype Correlations

Intrafamilial variability is much lower than interfamilial variability, and the phenotypic expression and natural history of the disease are similar within families with multiple members with NF2.

Frameshift or nonsense variants cause truncated protein expression, which has been associated with more severe manifestations of NF2. Missense or inframe deletions have been associated with milder manifestations of the disease. Large deletions of \textit{NF2} have been associated with a mild phenotype.

Selvanathan et al (2010) reported on genotype-phenotype correlations in 268 patients with an \textit{NF2} variant. Variants that resulted in a truncated protein were associated with statistically significant younger age at diagnosis, higher prevalence and proportion of meningiomas, spinal tumors and tumors of cranial nerves other than VIII, vestibular schwannomas at a younger age, and more cutaneous tumors. Variants found in the later part of the gene, especially exons 14 and 15, were associated with milder disease and fewer meningiomas.

CLINICAL UTILITY

The clinical utility of genetic testing for NF depends on how the results can be used to improve patient management. No direct evidence was identified reporting on outcomes for genetic testing of individuals with suspected NF or at-risk relatives with a proband with NF. In the absence of direct evidence, a chain of evidence based on clinical validity may be used to demonstrate clinical utility, if all of the links in the chain are strong.

Clinical Utility for Individuals with Suspected NF

In many cases of suspected NF1, the diagnosis can be made clinically based on the NIH criteria, which are both highly sensitive and specific, except in young children. However, there are suspected cases in children and adults who do not meet the NIH diagnostic criteria. Given the well-established clinical management criteria, these patients benefit from genetic testing to confirm the diagnosis and to direct clinical management according to accepted guideline recommendations.

For NF2, affected individuals may have little in the way of external manifestations and the onset of symptoms may be due to tumors other than vestibular schwannomas, particularly in children. Early identification of patients with NF2 can lead to earlier intervention and improved outcomes, and direct clinical management according to accepted guideline recommendations.

Clinical Utility for At-Risk Relatives

Similar to the case for suspected NF1, it is most often the case that a clinical diagnosis can be made in an at-risk relative of a proband because one of the NIH criterion for diagnosis is having a first-degree relative with NF1 and, therefore, only 1 other clinical sign is necessary to confirm diagnosis. Cases in at-risk relatives who do not fulfill the NIH diagnostic criteria may benefit from genetic testing to direct clinical management according to accepted guideline recommendations.

Testing for NF2 may be useful to identify at-risk relatives of patients with an established diagnosis of NF2, allowing for appropriate surveillance, earlier detection, and treatment of disease manifestations, and
Genetic Testing for Neurofibromatosis

Policy # 00502
Original Effective Date: 04/20/2016
Current Effective Date: 04/19/2017

avoiding unnecessary surveillance in an individual who does not have the family-specific variant. Unlike NF1, the age of symptom onset for NF2 is relatively uniform within families. Therefore, it is usually not necessary to offer testing or surveillance to asymptomatic parents of a proband. However, testing of at-risk asymptomatic individuals younger than 18 years of age may help avoid unnecessary procedures in a child who has not inherited the variant.

SUMMARY OF EVIDENCE
For individuals who have suspected NF or who are asymptomatic with a close relative(s) with an NF diagnosis who receive genetic testing for NF, the evidence includes clinical validation studies of a multistep diagnostic protocol and genotype-phenotype correlation studies. Relevant outcomes are test accuracy and validity, symptoms, change in disease status, morbid events, and functional outcomes. Several major laboratories have reported high analytic validity for neurofibromatosis type 1 (NF1) and neurofibromatosis type 2 (NF2) genetic testing, although published studies are lacking. 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. For individuals with a known pathogenic variant in the family, testing of at-risk relatives will confirm or exclude the variant with high certainty. Direct evidence on the clinical utility of genetic testing for NF is lacking, but a definitive diagnosis 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.

References
Genetic Testing for Neurofibromatosis

Policy # 00502
Original Effective Date: 04/20/2016
Current Effective Date: 04/19/2017


Policy History
Original Effective Date: 04/20/2016
Current Effective Date: 04/19/2017
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.
Next Scheduled Review Date: 04/2018

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 2016 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.

The responsibility for the content of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines is with Blue Cross and Blue Shield of Louisiana and no endorsement by the AMA is intended or should be implied. The AMA disclaims responsibility for any consequences or liability attributable or related to any use, nonuse or interpretation of information contained in Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines. Fee schedules, relative value units, conversion factors and/or related components are not assigned by the AMA, are not part of CPT, and the AMA is not recommending their use. The AMA does not directly or indirectly practice medicine or dispense medical services. The AMA assumes no liability for data contained or not contained herein. Any use of CPT outside of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines should refer to the most current Current
Genetic Testing for Neurofibromatosis

Policy # 00502
Original Effective Date: 04/20/2016
Current Effective Date: 04/19/2017

Procedural Terminology which 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:

<table>
<thead>
<tr>
<th>Code Type</th>
<th>Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT</td>
<td>81405, 81406, 81408</td>
</tr>
<tr>
<td>HCPCS</td>
<td>No codes</td>
</tr>
<tr>
<td>ICD-10 Diagnosis</td>
<td>Q85.00-Q85.09</td>
</tr>
</tbody>
</table>

*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 the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated 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: 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.