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Corporate Medical Policy

Genetic Testing for Neurofibromatosis AHS – M2134

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Origination:	01/01/2019
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Description of Procedure or Service

Neurofibromatoses are a group of three clinically and genetically distinct disorders that cause tumors to form on nerve tissue. Neurofibromatosis type 1 (NF1), is caused by autosomal dominant mutations in the neurofibromin (*NF1*) gene, and characterized by multiple café-au-lait macules and neurofibromas(Korf, 2018). Neurofibromatosis type (NF2) is caused by autosomal dominant mutations in the merlin, also known as schwannomin, (*NF2*) gene, and characterized by multiple tumors of the nervous system including the more common bilateral vestibular schwannomas as well as intracranial and spinal meningiomas, intrinsic ependymomas, and other spine tumors (Evans, 2018b). Schwannomatosis is caused by inactivating mutations in *SMARCB1* and *LZTR*, and is characterized by multiple schwannomas and pain arising in adulthood (Bergner & Yohay, 2018).

******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

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

1. Genetic counseling for genetic testing for neurofibromatosis is considered medically necessary.

2. Genetic testing for neurofibromatosis type 1 is considered medically necessary when the diagnosis is clinically suspected due to signs of disease, but a definitive diagnosis cannot be made without genetic testing. The patient must have one of the following signs of NF1:

   A. Six or more café-au-lait macules over 5 mm in greatest diameter in pre-pubertal individuals and over 15 mm in greatest diameter in post-pubertal individuals
   B. Two or more neurofibromas of any type or one plexiform neurofibroma
   C. Freckling in the axillary or inguinal regions
   D. Optic glioma

E. Two or more Lisch nodules (iris hamartomas)
F. A distinctive osseous lesion such as sphenoid dysplasia or tibial pseudarthrosis
G. A first-degree relative (parent, sib, or offspring) with NF1 as defined by the above criteria

3. Genetic testing for neurofibromatosis in at-risk relatives with no signs of disease is considered medically necessary when a definitive diagnosis cannot be made without genetic testing AND at least ONE of the following criteria is met:

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

4. Prenatal testing for diagnosis of neurofibromatosis is considered medically necessary only if the disease-causing allele of an affected family member has been identified before prenatal testing.

5. Preimplantation genetic diagnosis of neurofibromatosis is considered medically necessary only if the NF1 or NF2 pathogenic variant has been identified in the family.

6. Genetic testing for diagnosis of NF2 is considered medically necessary when the diagnosis is clinically suspected due to signs of disease, but a definitive diagnosis cannot be made without genetic testing. The patient must meet one of the following criteria:

   A. Individuals with a first degree relative with NF2 (ie, affected parent, sibling, or offspring)
   B. Multiple spinal tumors (schwannomas, meningiomas)
   C. Cutaneous schwannomas
   D. Apparently sporadic vestibular schwannoma less than 30 years of age, or spinal tumor or meningioma less than 20 years of age
   E. Unilateral vestibular schwannoma in those less than 20 years of age

When Genetic Testing for Neurofibromatosis is not covered

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

Policy Guidelines

Literature Review

Neurofibromatosis type 1

Neurofibromatosis type 1 is relatively common, affecting approximately 1 in 3,000 individuals (Evans et al., 2010; Lammert, Friedman, Kluwe, & Mautner, 2005). Almost half of these cases are *de novo* mutations, resulting from the unusually high (~1:10,000) mutation rate in the *NF1* tumor suppresser gene primarily in paternally derived chromosomes (Stephens et al., 1992). The GTPase protein product of the *NF1* gene, neurofibromin, is expressed in many tissues, including brain, kidney, spleen, and thymus (Shen, Harper, & Upadhyaya, 1996) leading to a wide spectrum of clinical manifestations. *NF1* typically presents as café-au-lait macules, followed by axillary and/or inguinal freckling, and later Lisch nodules (iris hamartomas), and neurofibromas(Korf, 2018). Ocular, neurologic, musculoskeletal, vascular, cardiac, and malignant manifestations have been reported (Hirbe & Gutmann, 2014).
NF1 mutations are highly penetrant and inherited dominantly, however NF1 is variably expressed resulting in significant clinical variability, not only between unrelated individuals and

among affected individuals within a single family but even within a single person with *NF1* at different times in life (Friedman, 2018). Despite thousands of *NF1* mutations identified, few genotype/phenotype correlations have been observed (Shofty, Constantini, & Ben-Shachar, 2015). Recent reports indicate the growing utility of next generation sequencing to provide solutions for problems like genetic heterogeneity, overlapping clinical manifestations, or the presence of mosaicism, and interactions between *SPRED1* and neurofibromin provide functional insight that will help in the interpretation of pathogenicity of certain missense variants identified in *NF1* and Legius syndrome patients (Fisher et al., 2018).

Clinical Validity and Utility

NF1 is diagnosed clinically using the criteria developed by the National Institutes of Health (NIH, 1988), which are both highly specific and sensitive in all but very young children. Approximately 46% of sporadic *NF1* cases fail to meet the NIH Diagnostic Criteria by 1 year of age. Nearly all (97%; 95% confidence interval: 94-98) *NF1* patients meet the criteria for diagnosis by 8 years old, and all do so by 20 years old (DeBella, Szudek, & Friedman, 2000).

Molecular testing for *NF1* includes sequencing of all of the coding exons as well as deletions/rearrangements due to the large size of the gene and the heterogeneity of mutations. Messiaen et al (2000) reported identification of the causative DNA mutation in 64 of 67 patients with a clinical diagnosis of *NF1*. Korf (2018) states that molecular testing is reported to identify approximately 95 percent of causative mutations. However, a positive *NF1* mutation test does not predict the severity or complications of the disorder (Gutmann et al., 1997).

Molecular genetic testing is indicated for individuals in whom NF1 is suspected but who do not fulfill the NIH diagnostic criteria (Friedman, 2018). Additionally, there is increasing use of genetic testing in the diagnosis of NF1 for patients who meet only these two NIH criteria in addition to those with only one NIH criterion as a positive genetic test may shorten the period of diagnostic uncertainty, allowing the initiation of appropriate screening evaluations (Korf, 2018). Further examples of clinical utility which would justify molecular testing include: a young child with a serious tumor (e.g., optic glioma) in whom establishing a diagnosis of NF1 immediately would affect management, an adult with NF1 if prenatal or preimplantation genetic diagnosis in a current or future pregnancy is anticipated (Friedman, 2018). Lastly, some rare variants of NF1 including spinal NF1 are known to produce a phenotype in which affected individuals may not meet the NIH diagnostic criteria, in which case molecular testing is indicated for at-risk relatives (Burkitt Wright et al., 2013).

A negative *NF1* mutation test in patients with only café-au-lait macules and axillary freckling should be tested for *SPRED1* mutations followed by the four mismatch repair genes as Legius syndrome, constitutional mismatch repair-deficiency (CMMR-D) syndrome, and Noonan syndrome may present with these indications (Korf, 2018).

Neurofibromatosis type 2

Neurofibromatosis type 2 refers to what was originally thought to be a rare subtype of neurofibromatosis type 1, but rather is a distinct entity both genetically and clinically (Evans, 2018b). It is characterized by bilateral vestibular schwannomas with associated symptoms of tinnitus, hearing loss, and balance dysfunction resulting from mutation in the *NF2* gene (Evans, 2018a). Affected individuals may also develop schwannomas of other cranial and peripheral nerves, meningiomas, ependymomas, and, very rarely, astrocytomas. The prevalence is about 1:60,000 with a birth incidence of 1:33,000(Evans et al., 2010). Typical age of onset is 18 to 24 years, with almost all affected individuals developing bilateral schwannomas by the age of 30. Skin tumors and ocular findings seem to be the first manifestations, and have been underrecognized in children (Ruggieri et al., 2005).

The protein encoded by the NF2 gene, merlin or schwannomin, is a cell membrane related tumor suppressor (Rouleau et al., 1993; Trofatter et al., 1993). Inactivation of both alleles is necessary for tumor development. Variable expressivity of *NF2* results in varying size, location, and number of tumors. Despite that fact that these tumors are not malignant, their number and anatomical location contribute significantly to morbidity and mortality with the average age of death being 36 (Baser et al., 2002). However, advances in molecular diagnosis, imaging and treatment of NF2-associated tumors have resulted in the lower mortality (Hexter et al., 2015).

Clinical criteria for NF2 were initially established with those for NF1(NIH, 1988), modified as the Manchester criteria to include molecular diagnostics and increase specificity without affecting sensitivity (Gutmann et al., 1997). Most recently, the identification of *LZTR1* as a cause of schwannomatosis reduces the specificity of these more inclusive criteria and even the presence of bilateral VS is now no longer sufficient to be certain that an individual has NF2 (Smith et al., 2017) resulting in further modification of the Manchester criteria.

Clinical Validity and Utility

Detailed molecular testing is reported to identify mutations in NF2 in 93% of families with multiple members affected by NF2 (Evans, 2018c). Early diagnosis of individuals with NF2 facilitates treatment and reduction of mortality (Hexter et al., 2015), however genetic testing and management is complicated by the well-documented risk of mosaicism (Evans, Raymond, Barwell, & Halliday, 2012).

More so than with NF1, the stronger genotype/phenotype correlations in mutations of NF2(Baser et al., 2004; Baser et al., 2005), high frequency of de novo mutations, and presentation of patients before clinical diagnostic criteria are fulfilled have provided a stronger rationale for the clinical utility of molecular testing than for NF1 (Evans, 2018a).

Molecular testing approaches can differ for NF2 based on the clinical picture. Patients with the distinctive phenotypic and laboratory findings suggestive of NF2 are likely to be diagnosed with gene targeted testing (75%), whereas in those where the diagnosis of NF2 has not been considered or they do not completely meet the diagnostic criteria, especially children are diagnosed after exome sequencing (Evans, 2018a).

A protocol developed in England to address the risks, genetic testing and screening protocol of individuals who are at risk of NF2 given they have features of the disease that fall short of diagnostic criteria or are the first-degree relative of someone with NF2 or suspected NF2. (Evans et al., 2012).

Pathmanaban et al (2017) analyzed the database of the Manchester Centre for Genomic Medicine to determine the frequency of the known heritable meningioma- or schwannoma-predisposing mutations in children and young adults presenting with a solitary meningioma or schwannoma. They found that “A significant proportion of young people with an apparently sporadic solitary meningioma or schwannoma had a causative predisposition mutation. This finding has important clinical implications because of the risk of additional tumors and the possibility of familial disease. Young patients presenting with a solitary meningioma or schwannoma should be referred for genetic testing.”

As many as 25% to 33% of individuals with de novo variants will have somatic variation necessitating molecular testing of tumor tissue (Kluwe et al., 2003).

Castillanos et al (2018) recently demonstrated the clinical utility of a careful dermatological inspection and the correct identification of skin plaques in children for an early diagnosis of NF2. Skin plaques from 7 patients (4 male and 3 female) were analyzed and histologically characterized as plexiform schwannomas. Genetic analysis of primary Schwann cell cultures derived from them allowed the identification of a constitutional and a somatic NF2 mutation.

Genetic testing allowed the early diagnosis of NF2 in a child only exhibiting the presence of skin plaques. Most of the patients with NF2 analyzed had an early presentation of skin plaques and a severe NF2 phenotype.

The biggest single factor that determines NF2 severity is the type of mutation, its position within the gene and the proportion of cells carrying it. A genetic severity score has recently been developed and validated to draw these factors together to enable genotypic data to be routinely factored into clinical and research use (Halliday et al., 2017).

Decreased clinical validity was shown in a study from Evans et al (2015) which found that "~25% of cases of BVS over 50 years and 50% over 70 years of age where no other features of NF2 are present represent a chance occurrence rather than due to an underlying mosaic or constitutional NF2 mutation".

Schwannomatosis

Schwannomatosis is an uncommon form of neurofibromatosis characterized by predisposition to develop multiple schwannomas and, less frequently, meningiomas. Its estimated prevalence is 1:70,000 (Dhamija, Plotkin, Asthagiri, Messiaen, & Babovic-Vuksanovic, 2018), but is thought to be an underestimate(Koontz et al., 2013). Although there is some clinical overlap with NF2, schwannomatosis is caused by the concomitant mutational inactivation of two or more tumor suppressor genes. Germline mutations of either the *SMARCB1* or *LZTR1* tumor suppressor genes have been identified in 86% of familial and 40% of sporadic schwannomatosis patients (Kehrer-Sawatzki, Farschtschi, Mautner, & Cooper, 2017).

The median age of symptom onset is 30 years, with pain being the most common presenting symptom in 57 percent of patients. In others (41 percent), a mass was the presenting symptom(Merker, Esparza, Smith, Stemmer-Rachamimov, & Plotkin, 2012). Other symptoms reported at presentation vary based on the location of the tumors, but can include focal numbness, weakness, and muscle atrophy (Bergner & Yohay, 2018). Peripheral and spinal schwannomas are common in schwannomatosis patients. Severe pain is difficult to treat in these patients and often associated with anxiety and depression (Merker et al., 2012).

Clinical Validity and Utility

Diagnostic criteria for schwannomatosis was first set forth by MacCollin et al (2005), but has been revised with the addition of molecular diagnostic criteria(Plotkin et al., 2013), and most recently combined clinical and molecular criteria (Kehrer-Sawatzki et al., 2017).

Kehrer-Sawatzki et al (2017) also recommended "Comprehensive mutation analysis of all three genes, *LZTR1*, *SMARCB1*, and *NF2*, in patients with schwannomatosis should be performed to identify the complete mutational spectra and the number of mutational hits that affect these genes. This comprehensive testing may help to classify the tumors according to their mutation-profile. The mutation analysis should also include methods, such as next-generation sequencing, which are well suited to detect somatic mosaicism with mutant cells present in low proportions. This approach should identify tumor heterogeneity and help to distinguish between mosaic NF2 and schwannomatosis, since some NF2 patients with somatic mosaicism for an *NF2* gene mutation fulfil the diagnostic criteria for schwannomatosis".

Pathmanaban et al (2017) analyzed the database of the Manchester Centre for Genomic Medicine to determine the frequency of the known heritable meningioma- or schwannoma-predisposing mutations in children and young adults presenting with a solitary meningioma or schwannoma. They found that "A significant proportion of young people with an apparently sporadic solitary meningioma or schwannoma had a causative predisposition mutation. This finding has important clinical implications because of the risk of additional tumors and the possibility of familial

disease. Young patients presenting with a solitary meningioma or schwannoma should be referred for genetic testing."

Applicable Federal Regulations

This test is considered a laboratory developed test (LDT); developed, validated and performed by individual laboratories.

LDTs are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA'88).

As an LDT, the U. S. Food and Drug Administration has not approved or cleared this test; however, FDA clearance or approval is not currently required for clinical use.

Guidelines and Recommendations

Practice Guidelines and Position Statements

American Academy of Pediatrics (AAP)
In 2008, the AAP committee on genetics published guidelines on health supervision in children with NF1 (AAP, 2008). The committee stated that genetic consultation and genetic testing should be considered to expedite a diagnosis when there is uncertainty regarding a definitive diagnosis of NF1. The committee also noted that "molecular testing also may represent an option in those instances when a couple in which one person has NF1 is seeking prenatal diagnosis."

National Society of Genetic Counselors (NSGC)
In 2007, the NSGC published recommendations for the genetic counseling of patients and families undergoing evaluation for NF1 (Radtke et al, 2007). NSGC stated that "testing may be beneficial to individuals meeting only one of the diagnostic criteria or when the diagnosis is unclear." The guidelines noted that "prenatal molecular genetic testing is available for families in which the mutation has been identified in the proband." Given the variability and unpredictable nature of the condition, genetic counseling is critical for a couple considering prenatal testing for NF1. The NSGC also recommended that "pre-implantation genetic diagnosis (PGD) may be available for couples in which the causative NF1 mutation has been identified or if linkage phase has been established."

Billing/Coding/Physician Documentation Information

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 ,96040, S0265

Code Number	PA Required	PA Not Required	Not Covered
81405	X		
81406	X		
81408	X		
96040		X	
S0265		X	

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

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Policy Implementation/Update Information

1/1/2019	BCBSNC will provide coverage for genetic testing for neurofibromatosis when it is determined to be medically necessary because criteria and guidelines are met. Medical Director review 1/1/2019. Policy noticed 1/1/2019 for effective date 4/1/2019. (jd)