Corporate Medical Policy

Genetic Testing for Neurofibromatosis and Related Disorders AHS – M2134

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, intracranial 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). Legius syndrome is an NF1-like disorder caused by autosomal dominant mutations in the sprout-related EVH1[enabled/vasodilator-stimulated phosphoprotein homology 1] domain-containing protein 1 (SPRED1) gene, resulting in café-au-lait macules. Constitutional mismatch repair-deficiency syndrome (CMMR-D), caused by mutations in mismatch repair genes, can also result in café-au-lait macules, axillary freckling, and Lisch nodules similar to NF1; however, unlike NF1, CMMR-D can also result in a variety of different malignancies, including glioblastoma and colorectal cancer (Korf, 2018).

Related Policies
Prenatal Screening AHS-G2035

***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 and related disorders when it is determined the medical criteria or reimbursement guidelines 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 and Related Disorders is covered

1. Reimbursement is allowed for genetic counseling for genetic testing for neurofibromatosis, schwannomatosis, Legius Syndrome, and Constitutional Mismatch Repair deficiency (CMMRD).
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 type 1 or type 2 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 (i.e., 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

7. Genetic testing for mutations in *SMARCBL* and LZTR1 in individuals with one or more non-intradermal schwannoma, including those with VS (vestibular schwannoma) negative for NF2 is considered medically necessary.

8. Genetic testing of *SPRED1* for the diagnosis of Legius Syndrome is considered medically necessary for individuals with at least one of the following:

   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. Freckling in the axillary or inguinal regions
   c. Symptoms of NF1, but genetic test results for NF1 were negative

9. Genetic testing for CMMRD (the four mismatch repair genes *MLH1*, *MSH2*, *MSH6*, and *PMS2*) in children and adolescents is considered medically necessary when the following criteria are met:

   a. All of the following are required, AND
   i. The presence of at least two hyperpigmented skin patches (café-au-lait macules)
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ii. No NF1 and SPRED1 germline mutations detected
iii. Absence of diagnostic NF1 sign(s) in both parents, if known

b. At least one of the following is required (either in the family or in the patient)
   i. In the family
      (1) Consanguineous parents
      (2) Genetic diagnosis of Lynch syndrome in one or both of the parental families
      (3) Sibling with diagnostic NF1 sign(s)
      (4) Sibling, living or deceased, with any type of childhood malignancy
      (5) One of the following carcinomas from the Lynch syndrome spectrum in a first- or second-degree relative before the age of 60 years: colorectal cancer, endometrial cancer, ovarian cancer, gastric cancer, small bowel cancer, cancer of the bile duct or gall bladder, pancreatic cancer or urothelial cancer
   ii. In the patient
      (1) Atypical café-au-lait macules (irregular borders and/or pigmentation)
      (2) Hypopigmented skin patches
      (3) One or more pilomatricoma(s)
      (4) Agenesis of the corpus callosum
      (5) Non-therapy-induced cavernoma
      (6) Multiple developmental vascular abnormalities (cerebral venous angiomas) in separate regions of the brain

**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**

**Background**

**Neurofibromatosis type 1**

Neurofibromatosis type 1 is relatively common, affecting approximately 1 in 3,000 individuals (Korf, 2018). Almost half of these cases are *de novo* mutations, resulting from the unusually high (~1:10,000) mutation rate in the *NF1* tumor suppressor 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 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 \textit{NF1} and Legius syndrome patients (Fisher et al., 2018).

Conditions similar to neurofibromatosis type 1 exist. Legius syndrome has similar clinical features to NF1 such as the café-au-lait macules but does not have the neurofibromas or central nervous system tumors. Furthermore, the primary genetic alteration in Legius syndrome is the sprouty-related EVH1 [enabled/vasodilator-stimulated phosphoprotein homology 1 gene (\textit{SPRED1}) compared to \textit{NF1} for neurofibromatosis 1. Another similar condition is constitutional mismatch repair-deficiency syndrome (CMMR-D) which also has similar clinical symptoms but leads to different malignancies compared to neurofibromatosis 1. CMMR-D patients may develop hematologic or colorectal malignancies in addition to the neurofibromas seen in NF1 patients (Korf, 2018).

Clinical Validity and Utility

\textit{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 \textit{NF1} cases fail to meet the NIH Diagnostic Criteria by 1 year of age. Nearly all (97\%; 95\% confidence interval: 94-98) \textit{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 \textit{NF1} includes sequencing of all 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 \textit{NF1}. Korf (2018) states that molecular testing is reported to identify approximately 95 percent of causative mutations. However, a positive \textit{NF1} mutation test does not predict the severity or complications of the disorder (Korf, 2018).

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; moreover, individuals 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 that 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 \textit{NF1} mutation test in patients with only café-au-lait macules and axillary freckling should be tested for \textit{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).

\section*{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 \textit{NF2} gene. Affected individuals may also develop schwannomas of other cranial and peripheral nerves, meningiomas, ependymomas, and, very rarely, astrocytomas. Typical age of onset is 18 to 24 years, with almost all affected individuals developing bilateral schwannomas by the age of 30. (Evans, 2018a). The prevalence is about 1:60,000 with a birth incidence of 1:33,000 (Evans et al., 2010). Skin tumors and ocular findings often are the first manifestations and have been underrecognized in children (Ruggieri et al., 2005).
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The protein encoded by the NF2 gene, merlin or schwannomin, is a cell membrane-related tumor suppressor (Evans, 2018b). Inactivation of both alleles is necessary for tumor development. Variable expressivity of NF2 results in varying size, location, and number of tumors. Despite 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 lower mortality (Hexter et al., 2015).

Clinical criteria for NF2 were initially established with those for NF1 (NIH, 1988), and they were modified as the Manchester criteria to include molecular diagnostics and increase specificity without affecting sensitivity (Evans, 2018b). 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, 2018b). 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 using gene-targeted testing (75%), whereas those where the diagnosis of NF2 has not been considered or had met the diagnostic criteria (such as children) are diagnosed after exome sequencing (Evans, 2018a).

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 (Pathmanaban et al., 2017).”

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.

A genetic severity score has recently been developed to draw these factors together to enable genotypic data to be routinely factored into clinical and research use. This UK NF2 Genetic Severity Score classifies patients into three categories, which are tissue mosaic (1), classic (2), and severe (3). Within each category are subcategories, which consists of the following in increasing severity: presumed tissue
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mosaicism (1A), confirmed tissue mosaicism (1B), mild NF2 (2A), moderate NF2 (2B), and severe NF2 (3). These categories are separated by severity of mutation shown below (Halliday et al., 2017)

<table>
<thead>
<tr>
<th>Genetic Severity</th>
<th>Subcategory</th>
<th>Clinical Characteristics</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (Tissue Mosaic)</td>
<td>1A</td>
<td>Presumed tissue Mosaicism</td>
<td>Meets clinical criteria for sporadic NF2 but not confirmed molecularly with identical NF2 mutations detected in two separate tissue samples.</td>
</tr>
<tr>
<td></td>
<td>1B</td>
<td>Confirmed tissue mosaicism</td>
<td>Mosaic NF2 confirmed molecularly with identical NF2 mutations detected in two or more separate tissue samples</td>
</tr>
<tr>
<td>2 (Classic)</td>
<td>2A</td>
<td>Mild NF2</td>
<td>Full or mosaic NF2 mutation identified in blood excluding those found in group 2B or 3: missense mutations; in-frame deletions and duplications; deletions involving the promoter region or exon 1; splice site mutations in exons 8–15; truncating mutations of exon 1; mosaicism in blood for mutations other than truncating mutations in exons 2–13 Inherited NF2 but no NF2, SMARCB1 or LZTR1 mutation identified in blood</td>
</tr>
<tr>
<td></td>
<td>2B</td>
<td>Moderate NF2</td>
<td>Full or mosaic NF2 mutation identified in blood including: splicing mutation involving exons 1–7; large deletion not including the promoter or exon 1; truncating mutations in exons 14–15; mosaic in blood for a truncating mutation in exons 2–13</td>
</tr>
<tr>
<td>3 (Severe)</td>
<td>3</td>
<td>Severe NF2</td>
<td>Full NF2 truncating mutation exons 2–13</td>
</tr>
</tbody>
</table>

Halliday et al evaluated the validity of this score in 142 patients (63 in group 1, 35 in group 2, and 19 in group 3 with no mutation identified) More severe symptoms such as intracranial meningiomas, BVS, and spinal schwannomas, were more likely to be found in group 3 compared to group 1. For example, BVS and intracranial meningiomas were found in 100% and 94.7% of group 3 patients respectively, compared to 54% and 59% in group 1. Spinal meningiomas were found in 36.8% of group 3 patients compared to 15.3% of group 1, and schwannomas were found in 94.7% of group 3 patients compared to 48.3% of group 1. The authors concluded that “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 (Halliday et al., 2017).”

Evans et al investigated the clinical validity of the primary development of NF2, the bilateral vestibular schwannoma (BVS). The authors observed that out of a database of over 1200 patients, approximately 25% of them over 50 developed a BVS without any other clinical features of NF2. Over 50% of the patients over 70 developed a BVS as well. This lack of other clinical features in addition to the BVS led the authors to suggest that these developments of a BVS were due to chance rather than an NF2 mutation (Evans et al., 2015).
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 underestimated (Koontz et al., 2013). Although there is 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). LZTR1 encodes leucin-zipper-like transcriptional regulator 1 and SMARCB1 (also known as INI1) encodes a subunit of the SWI/SNF chromatin remodeling complex, and both act as tumor suppressors. Biallelic inactivation of these tumor suppressor genes leads to schwannomatosis (Radhika Dhamija, 2018).

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 they 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). More recently combined clinical and molecular criteria from Kehrer-Sawatzki et al, have been proposed (Kehrer-Sawatzki et al., 2017).

“A combined molecular and clinical diagnosis may be made with ≥ 2 tumors with 22q LOH and different somatic NF2 mutations AND ≥ 2 pathologically confirmed schwannomas or meningiomas

OR

Germline SMARCB1 or LZTR1 pathogenic mutation AND one pathologically confirmed schwannoma or meningioma”

“A strictly clinical diagnosis may be made with ≥ 2 nonintradermal schwannomas, one pathologically confirmed and no bilateral vestibular schwannoma by high quality MRI (some mosaic NF2 patients will be included in this diagnosis at a young age and some schwannomatosis patients may have unilateral vestibular schwannomas or meningiomas)

OR

one pathologically confirmed schwannoma or intracranial meningioma AND an affected first degree relative.

Exclusion criteria for schwannomatosis are as follows:

- Germline pathogenic NF2 mutation
- First degree relative with NF2
- Fulfillment of diagnostic criteria for NF2
- If schwannomas occur exclusively in a region of previous radiation therapy (Kehrer-Sawatzki et al., 2017)
Kehrer-Sawatzki et al (2017) also recommended, “Comprehensive mutation analysis of all three genes, \textit{LZTR1}, \textit{SMARCB1}, and \textit{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 \textit{NF2} gene mutation fulfil the diagnostic criteria for schwannomatosis (Kehrer-Sawatzki et al., 2017).”

Hutter et al evaluated the proportion of schwannomatosis cases that come from mutations aside from the germline variants in \textit{SMARCB1} and \textit{LZTR1}. The authors performed whole exome sequencing on 23 patients with sporadic schwannomatosis (without \textit{SMARCB1} mutations) and found only 5 \textit{LZTR1} or \textit{NF2} mutations. However, since the authors noted the reported frequency of \textit{SMARCB1} mutations to be only 10\% in sporadic schwannomatosis patients, they concluded that approximately 65\% (or at least the “majority”) of sporadic schwannomatosis mutations are caused by an unknown gene (Hutter et al., 2014).

Louvrier and colleagues performed targeted next generation sequencing to investigate genetic differences between \textit{NF2}, schwannomatosis, and meningiomatosis. The authors sequenced 196 patients (79 with \textit{NF2}, 40 with schwannomatosis, 12 with meningiomatosis, and 65 with no clearly established diagnosis) for \textit{NF2}, \textit{SMARCB1}, \textit{LZTR1}, \textit{SMARCE1}, and \textit{SUFU}. The \textit{NF2} and schwannomatosis results were as follows: “An \textit{NF2} variant was found in 41 of 79 \textit{NF2} patients (52\%). \textit{SMARCB1} or \textit{LZTR1} variants were identified in 5/40 (12.5\%) and 13/40 (32\%) patients in the schwannomatosis cohort. Potentially pathogenic variants were found in 12/65 (18.5\%) patients with no clearly established diagnosis. A \textit{LZTR1} variant was identified in 16/47 (34\%) \textit{NF2}/\textit{SMARCB1}-negative schwannomatosis patients (Louvrier et al., 2018).”

Guidelines and Recommendations

\textbf{American Academy of Pediatrics (AAP)}

In 2008, the AAP committee on genetics published guidelines on health supervision in children with \textit{NF1} (Hersh, 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 \textit{NF1}. The committee also noted that “molecular testing also may represent an option in those instances when a couple in which one person has \textit{NF1} is seeking prenatal diagnosis.”

This guideline was reaffirmed in 2017.

\textbf{National Society of Genetic Counselors (NSGC)}

In 2007, the NSGC published recommendations for the genetic counseling of patients and families undergoing evaluation for \textit{NF1} (Radtke, Sebold, Allison, Haidle, & Schneider, 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 \textit{NF1}. The NSGC also recommended that “pre-implantation genetic diagnosis (PGD) may be available for couples in which the causative \textit{NF1} mutation has been identified or if linkage phase has been established.”

\textbf{American College of Medical Genetics and Genomics (ACMG)}

In their guidelines detailing the care of adults with \textit{NF1}, the ACMG noted that “In most cases, the diagnosis can be easily made based on a history, physical exam, and pedigree review and no additional imaging or \textit{NF1} genetic testing is needed”. Furthermore, the ACMG stated that genetic testing can
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quickly establish a diagnosis for children thereby relieving anxiety, but this is not as significant an issue for adults (ACMG, 2018).

However, in the ACMG’s guidelines for reporting of secondary findings in exome or genome sequencing, mutations in the NF2 gene were recommended for return (ACMG, 2016).

**Neurofibromatosis Association of the United Kingdom (NFA, 2007)**

The NFA recommends against routine genetic testing for NF1 (NFA, 2007).

**2016 American Association for Cancer Research (AACR) Childhood Cancer Predisposition Workshop**

The following recommendations were created based on expert review of the literature and discussion brought to this workshop.

**NF1**

- “A child who meets one or more clinical criterion should now have NF1 molecular genetic testing (sequencing and deletion/duplication analysis) offered to confirm if NF1 is the correct diagnosis.” Genetic testing is especially recommended in children fulfilling only pigmentary features of the criteria.

The clinical diagnostic criteria are as follows:

- Six or more CAL macules, the greatest diameter of which is more than 5 mm in prepubertal patients and more than 15 mm in postpubertal patients
- Two or more neurofibromas of any type, or one plexiform neurofibroma
- Axillary or inguinal freckling
- Optic glioma
- Two or more Lisch nodules
- A distinctive osseous lesion such as sphenoid dysplasia or pseudarthrosis
- A first-degree relative with NF1 according to the preceding criteria

The guidelines note that according to the NIH, two or more of these criteria must be present. This is in contrast to their own guidelines’ statement of only requiring one clinical criterion.

The guidelines summarize their genetic testing recommendations as follows:

- “Children considered at risk of NF1 especially with 6+ CAL macules or diagnosed with NIH criteria should ideally have genetic testing of the NF1 gene with an RNA-based approach and testing of SPRED1 if pigmentary features only”.
- “Those testing negative should be considered for a panel of genes including GNAS, MLH1, MSH2, MSH6, NF2, PMS2, PTPN11, SOS1, and SPRED1 (if not already tested)” (D. Gareth R. Evans et al., 2017).

**NF2**

- “All children presenting with either clear diagnostic criteria for NF2, including combined retinal hamartomas, or those with an NF2 tumor (any schwannoma/meningioma) presenting in childhood should undergo genetic testing of NF2, ideally in both blood and tumor if available in sporadic cases.”

**Schwannomatosis**

- “Test for mutations in SMARCB1 and LZTR1 in children and young adults with one or more non-intradermal schwannoma, including those with VS (vestibular schwannoma) negative for NF2” (D. G. R. Evans et al., 2017).
European consortium ‘Care for CMMRD’ (C4CMMRD, 2014)

The C4CMMRD recommends further testing for patients reaching three points on the clinical scoring scale. “Further testing” generally follows the protocols for Lynch syndrome, which involves analysis of microsatellite instability or immunohistochemistry staining of the main mismatch repair proteins (MLH1, MSH2, MSH6 and PMS2). The clinical scoring scale is as follows (Wimmer et al., 2014):

Malignancies/premalignancies: one is mandatory; if more than one is present in the patient, add the points.
- Carcinoma from the LS spectrum* at age <25 years 3 points
- Multiple bowel adenomas at age <25 years and absence of APC/MUTYH mutation(s) or a single high-grade dysplasia adenoma at age <25 years 3 points
- WHO grade III or IV glioma at age <25 years 2 points
- NHL (non-Hodgkin's lymphoma) of T-cell lineage or sPNET (supratentorial primitive neuroectodermal tumour) at age <18 years 2 points
- Any malignancy at age <18 years 1 point

Additional features: optional; if more than one of the following is present, add the points
- Clinical sign of NF1 and/or ≥2 hyperpigmented and/or hypopigmented skin alterations Ø>1 cm in the patient 2 points
- Diagnosis of LS in a first-degree or second-degree relative 2 points
- Carcinoma from LS spectrum* before the age of 60 in first-degree, second-degree, and third-degree relative 1 point
- A sibling with carcinoma from the LS spectrum*, high-grade glioma, sPNET or NHL 2 points
- A sibling with any type of childhood malignancy 1 point
- Multiple pilomatrixomas in the patient 2 points
- One pilomatrixoma in the patient 1 point
- Agenesis of the corpus callosum or non-therapy-induced cavernoma in the patient 1 point
- Consanguineous parents 1 point
- Deficiency/reduced levels of IgG2/4 and/or IgA 1 point

*Colorectal, endometrial, small bowel, ureter, renal pelvis, biliary tract, stomach, bladder carcinoma (Wimmer et al., 2014).

The consortium in 2018 issued the selection strategy for CMMRD testing as follows:

Prerequisites for testing are...
- “Suspicion of NF1 due to the presence of at least one diagnostic NF1 feature, including at least two hyperpigmented skin patches reminiscent of CALMs [café-au-lait macules]
- No NF1 and SPRED1 germline mutations detected using comprehensive and highly sensitive mutation analysis protocols.
- Absence of diagnostic NF1 sign(s) in both parents
- Additional features, at least one (either in the family or in the patient) is required
  - In the family
    - Consanguineous parents.
    - Genetic diagnosis of Lynch syndrome in one or both of the parental families.
    - Sibling with diagnostic NF1 sign(s).
    - A (deceased) sibling§ with any type of childhood malignancy.
    - One of the following carcinomas from the Lynch syndrome spectrum: colorectal cancer, endometrial cancer, ovarian cancer, gastric cancer, small bowel cancer, cancer of the bile duct or gall bladder, pancreatic
cancer or urothelial cancer before the age of 60 years in first-degree or second-degree relative.

- In the patient
  - Atypical CALMs (irregular borders and/or pigmentation).
  - Hypopigmented skin patches.
  - One or more pilomatricoma(s) in the patient.
  - Agenesis of the corpus callosum.
  - Non-therapy-induced cavernoma.
  - Multiple developmental vascular abnormalities (also known as cerebral venous angiomas) in separate regions of the brain.

This can be expanded to second-degree and third-degree relatives in populations with a high prevalence of founder mutations (Suerink et al., 2019).

**National Comprehensive Cancer Network (NCCN)**

Within the Lynch Syndrome guidelines, the NCCN states, “For patients of reproductive age, advise about the risk of a rare recessive syndrome called constitutional MMR deficiency (CMMRD) syndrome…if both partners are a carrier of a mutation/s in the same MMR gene or EPCAM (for example, if both partners carry a mutation in the PMS2 gene, then their future offspring will be at risk of having CMMRD syndrome) (NCCN, 2018).”

**Applicable Federal Regulations**

No FDA-approved tests for neurofibromatosis or schwannomatosis were found as of April 4, 2019. Additionally, many labs have developed specific tests that they must validate and perform in house. These laboratory-developed tests (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.

**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, 81292, 81293, 81294, 81295, 81296, 81297, 81298, 81299, 81300, 81301, 81317, 81318, 81319, 81479*

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**

*For policy titled: Genetic Testing for Neurofibromatosis:*


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Genetic Testing for Neurofibromatosis and Related Disorders AHS – M2134


Genetic Testing for Neurofibromatosis and Related Disorders AHS – M2134


Genetic Testing for Neurofibromatosis and Related Disorders AHS – M2134


For policy titled: Genetic Testing for Neurofibromatosis and Related Disorders:


Genetic Testing for Neurofibromatosis and Related Disorders AHS – M2134


NFA. (2007). Guidelines for the diagnosis and management of individuals with neurofibromatosis 1. Retrieved from [https://img.bmj.com/content/jmedgenet/44/2/81.full.pdf](https://img.bmj.com/content/jmedgenet/44/2/81.full.pdf).


Specialty Matched Consultant Advisory Panel review 7/2019

Medical Director review 7/2019

**Policy Implementation/Update Information**

**For policy titled: Genetic Testing for Neurofibromatosis:**

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)


**For policy titled: Genetic Testing for Neurofibromatosis and Related Disorders:**

9/10/19    Reviewed by Avalon 2nd Quarter 2019 CAB with title change. Description updated, and Related Policies added to this section. Policy statement updated with the addition of “and related disorders” to coincide with title change. The following revisions were made to the When Covered section: item 1: added “schwannomatosis, Legius Syndrome, and Constitutional Mismatch Repair deficiency (CMMRD)”, and added items 7, 8, and 9. Policy guidelines extensively revised. The following codes were added to the Billing/Coding section: 81292, 81293, 81294, 81295, 81296, 81297, 81298, 81299, 81300, 81301, 81317, 81318, 81319, 81479, and the following codes were removed along with the code table: 96040, S0265. References updated. Medical Director review 8/2019. (jd)

10/29/19    Wording in the Policy, When Covered, and/or Not Covered section(s) changed from Medical Necessity to Reimbursement language, where needed.

Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment.

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and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.