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Genetic Testing for Neurofibromatosis and Related Disorders

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I. Policy Description

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 is characterized by multiple café-au-lait macules and neurofibromas (Korf et al., 2024). Neurofibromatosis type (NF2) is caused by autosomal dominant mutations in the merlin, also known as schwannomin, (NF2) gene, and is 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, 2023b).

Schwannomatosis is caused by inactivating mutations in SMARCB1 and LZTR and is characterized by multiple schwannomas and pain arising in adulthood (Bergner & Yohay, 2024).

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 et al., 2024).

II. Indications and/or Limitations of Coverage

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request. Specifications pertaining to Medicare and Medicaid can be found in the "Applicable State and Federal Regulations" section of this policy document.

1) Prior to genetic testing for neurofibromatosis, *NF2-, SMARCB1-,* or *LZTR1*-related schwannomatosis, Legius Syndrome, **or** constitutional mismatch repair deficiency (CMMRD), genetic counseling **IS REQUIRED.**
2) For individuals who are clinically suspected of having neurofibromatosis type 1 (NF1), but for whom a definitive diagnosis cannot be made without genetic testing, genetic testing for *NF1* mutations **MEETS COVERAGE CRITERIA** when **one** of the following signs of NF1 is present:
   a) *Individual has six or more café-au-lait macules (over 5 mm in greatest diameter in pre-pubertal individuals; over 15 mm in greatest diameter in post-pubertal individuals).*
   b) *Individual has two or more neurofibromas of any type or one plexiform neurofibroma.*
   c) *Individual has freckling in the axillary or inguinal regions.*
   d) *Individual has optic glioma.*
   e) *Individual has two or more Lisch nodules (iris hamartomas).*
   f) *Individual has a distinctive osseous lesion, such as sphenoid dysplasia, anterolateral bowing of the tibia, or pseudarthrosis of the long bone.*
   g) *Individual has a first-degree relative (see Note 1) with NF1 as defined by the above criteria.*
3) For asymptomatic individuals who have a close blood relative (see Note 1) with a deleterious *NF1* or *NF2* gene mutation, the following testing **MEETS COVERAGE CRITERIA**:
   a) *Testing restricted to the known familial mutation.*
   b) *Comprehensive genetic testing when the specific familial mutation is unknown (i.e., family member is unavailable for testing or testing results are unavailable).*
4) For individuals who have a clinical diagnosis of neurofibromatosis and who are planning to conceive, preconception screening for *NF1* or *NF2* gene mutations, when the individual has not previously received genetic screening for a pathogenic mutation, **MEETS COVERAGE CRITERIA.**
5) For individuals who are clinically suspected of having *NF2*-related schwannomatosis, but for whom a definitive diagnosis and classification cannot be made without genetic testing, genetic testing for *NF2* gene mutations **MEETS COVERAGE CRITERIA** when **one** of the following signs of *NF2*-related schwannomatosis is present:
   a) *Individual has bilateral vestibular schwannomas (VS)*
   b) *Individual has either two major or one major and two minor criteria:*
      i) *Major criteria:*
         (a) *Unilateral VS*
         (b) *First-degree relative (see Note 1) other than a sibling) with NF2-related schwannomatosis*
         (c) *Two or more meningiomas (note that a single meningioma qualifies as minor criteria)*
      ii) *Minor criteria:*
         (a) Can count >1 of a type (e.g., 2 distinct schwannomas would count as 2 minor criteria): Ependymoma, schwannoma (note that if the major criterion is unilateral VS, at least 1 schwannoma must be dermal in location)

(b) Can count only once (e.g., bilateral cortical cataracts count as a single minor criterion): Juvenile subcapsular or cortical cataract, retinal hamartoma, epiretinal membrane in a person aged <40 years, meningioma (because multiple meningiomas qualify as a major criteria).

6) For individuals who are negative for *NF2* mutations **and** who have one or more pathologically confirmed schwannoma or hybrid nerve sheath tumor, genetic testing for mutations in *SMARCB1* and *LZTR1* **MEETS COVERAGE CRITERIA**.
7) For individuals who are clinically suspected of having Legius Syndrome, genetic testing of *SPRED1* **MEETS COVERAGE CRITERIA** when **one** of the following conditions is met:
   a) *The individual has six or more café-au-lait macules (over 5 mm in greatest diameter in pre-pubertal individuals; over 15 mm in greatest diameter in post-pubertal individuals).*
   b) *The individual has freckling in the axillary or inguinal regions.*
   c) *The individual has symptoms of NF1, but genetic test results for NF1 were negative.*
8) For individuals 25 years and younger who have at least two hyperpigmented skin patches (café-au-lait macules), who have tested negative for *NF1* and *SPRED1* mutations, **and** for whom neither parent has diagnostic signs of NF1 (if known), genetic testing for CMMRD (*MLH1, MSH2, MSH6,* and *PMS2*) **MEETS COVERAGE CRITERIA** when **one** of the following risk factors is present:
   a) Risk factors in the patient include:
      i) Atypical café-au-lait macules (irregular borders and/or pigmentation).
      ii) Hypopigmented skin patches.
      iii) One or more pilomatricoma(s).
      iv) Agenesis of the corpus callosum.
      v) Non-therapy-induced cavernoma.
      vi) Multiple developmental vascular abnormalities (cerebral venous angiomas) in separate regions of the brain.
   b) Familial risk factors include:
      i) Consanguineous parents.
      ii) A genetic diagnosis of Lynch syndrome in one or both of the parental families.
      iii) A sibling with diagnostic NF1 sign(s).
      iv) A sibling, living or deceased, with any type of childhood malignancy.
      v) A first- or second-degree relative (see Note 1) diagnosed before the age of 60 years with 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.

The following does not meet coverage criteria due to a lack of available published scientific literature confirming that the test(s) is/are required and beneficial for the diagnosis and treatment of an individual's illness.

9) For all other situations not meeting the criteria outlined above, genetic testing for neurofibromatosis **DOES NOT MEET COVERAGE CRITERIA**

NOTES:

Note 1: Close blood relatives include 1st-degree relatives (e.g., parents, siblings, and children), 2nd-degree relatives (e.g., grandparents, aunts, uncles, nieces, nephews, grandchildren, and half-siblings), and 3rd-degree relatives (great-grandparents, great-aunts, great-uncles, great-grandchildren, and first cousins), all of whom are on the same side of the family.

Note 2: For 2 or more gene tests being run on the same platform, please refer to AHS-R2162 Reimbursement Policy.

III. Table of Terminology

Term	Definition
AACR	American Association for Cancer Research
AAP	American Academy of Pediatrics
ACMG	American College of Medical Genetics and Genomics
BVS	Bilateral vestibular schwannoma
C4CMMRD	Care for constitutional mismatch repair deficiency
CALM	Café au lait macule
CLIA ’88	Clinical Laboratory Improvement Amendments Of 1988
CMMRD	Constitutional mismatch repair deficiency
CMS	Centers for Medicare and Medicaid Services
EANO	European Association of Neuro-Oncology
EVH1	*Enabled/vasodilator-stimulated phosphoprotein homology 1*
FDA	Food and Drug Administration
LDT	Laboratory-developed test
LZTR1	*Leucin-zipper-like transcriptional regulator 1*
MMR	Measles, mumps, and rubella
MRI	Magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
NF1	Neurofibromatosis type 1
NF2	Neurofibromatosis type 2
NGS	Next-generation sequencing
NSD	Noonan spectrum disorders
SMARCB1	*SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily B, member 1*
SPRED1	*Sprout-Related EVH1 Domain-Containing Protein 1*
sVS	Sporadic vestibular schwannoma

VS	Vestibular schwannoma

IV. Scientific Background

Neurofibromatosis type 1

Neurofibromatosis type 1 is relatively common, affecting approximately one in 3,000 individuals (Korf et al., 2024). 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 et al., 2024). 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, 2023). Despite thousands of *NF1* mutations identified, few genotype/phenotype correlations have been observed (Shofty et al., 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).

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 one year of age. Nearly all (97%; 95% confidence interval: 94-98) NF1 patients meet the criteria for diagnosis by eight years old, and all do so by 20 years old (DeBella et al., 2000).

Molecular testing for 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. reported identification of the causative DNA mutation in 64 of 67 patients with a clinical diagnosis of NF1. Korf et al. (2024) 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 (Korf et al., 2024).

Molecular genetic testing is indicated for individuals in whom NF1 is suspected but who do not fulfill the NIH diagnostic criteria (Friedman, 2023). 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 et al., 2024). 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, 2023).

Prenatal testing is available through direct mutation testing of fetal DNA taken from CVS or from amniocentesis to diagnose *NF1* pathogenic variants in the fetus. An additional option is assessing DNA markers in families with two or more affected individuals; however, many partners do not perform a prenatal assessment because of "the inability to determine disease severity" in the fetus (Ferner et al., 2007). Because the time for prenatal diagnosis is limited, it is common for families to detect pathogenic *NF1* alleles through linkage analysis as a more "rapid and useful" method for diagnosis (Terzi et al., 2009). Additionally, detection of pathogenic *NF1* mutations can be complex and challenging because of wide phenotypic variability and an absence of genotype-phenotype correlation (Terzi et al., 2009).

Preimplantation genetic diagnosis is also available to assist individuals who want to avoid a later termination of a pregnancy. Preimplantation genetic diagnosis occurs using cells removed from an embryo (available at the approximately 3-day mark of embryo development). This helps individuals determine which embryos do not carry the NF1 mutation in order to transfer unaffected embryos for implantation. Additionally, NF1 experts recommend that all NF1 pathogenic mutation affected individuals should receive genetic counseling prior to conception (Ferner et al., 2007).

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 this case, molecular testing is indicated for at-risk relatives (Burkitt-Wright et al., 2013).

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, 2023b). It is characterized by bilateral vestibular schwannomas with associated symptoms of tinnitus, hearing loss, and balance dysfunction resulting from mutation in the *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, 2023b). 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).

The protein encoded by the *NF2* gene, merlin or schwannomin, is a cell membrane-related tumor suppressor (Evans, 2023b). 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, 2023b). 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.

Detailed molecular testing is reported to identify mutations in NF2 in 93% of families with multiple members affected by NF2 (Evans, 2023b). 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 et al., 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.*

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, 2023a).

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 et al., 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 et al., 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, 2023).

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 et al., 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, 2024). 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).

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, *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" (Kehrer-Sawatzki et al., 2017).

Legius Syndrome

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 (*SPRED1*) compared to *NF1* for neurofibromatosis 1.

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 et al., 2024).

CMMR-D

Constitutional mismatch repair-deficiency syndrome (CMMR-D) has similar clinical symptoms to neurofibromatosis 1 but leads to different malignancies. Hematologic malignancies develop in infancy to early childhood, brain tumors (such as glioblastoma) may present in mid-childhood, and colorectal cancer may show up in adolescence or young adulthood (Korf et al., 2024). CMMR-D is a childhood cancer predisposition syndrome that is caused by biallelic pathogenic variants in one of four mismatch repair genes (Hizuka et al., 2021). Individuals with this syndrome may develop hematologic or colorectal malignancies in addition to the neurofibromas seen in NF1 patients (Korf et al., 2024).

One important characteristic of CMMR-D is that it is typically diagnosed in childhood. The Federal Food, Drug, and Cosmetic Act (FD&C Act) defines pediatric patients as persons aged 21 or younger at the time of their diagnosis or treatment and the *Bright Futures* guidelines from the American Academy of Pediatrics identify adolescence as 11 to 21 years of age, dividing the group into early (ages 11–14 years), middle (ages 15–17 years), and late (ages 18–21 years). CMMR-D is most often diagnosed before the age of 18. One collaborative review from the European consortium established the ages of first diagnosis as ranging from 0.4 to 39 years. However, the "vast majority" of patients are diagnosed with a first malignancy before the age of 18 (82% diagnosed before age 18) (Wimmer et al., 2014).

Clinical Utility and Validity

Neurofibromatosis type 1

Giugliano et al. (2019) investigated the clinical and genotypic associations in children with pigmentary features characteristic of a neurocutaneous condition, such as neurofibromatosis type 1. A group of 281 patients were included, with 150 definitively diagnosed with NF1, 95 presenting with only pigmentary features such as café au lait macules (CALMs), and 36 presenting with a clinical suspicion of another "RASopathy" (a condition caused by mutations in the MAPK pathway) or other neurocutaneous disorder. The authors identified the causative pathogenic variant in 239 of 281 cases (leaving 42 undiagnosed). Of the patients diagnosed with NF1, mutations were detected in 98% of cases (147/150) but in patients with only pigmentary features, the detection rate fell to 69.5% (66/95), with *SPRED1* accounting for eight of those cases. In patients presenting with a separate neurocutaneous condition, mutation detection rate was found to be 72.2% (26/36), with pathogenic variants found in 10 genes such as PTPN11. The authors recognized the difficulty of diagnosing these neurocutaneous and concluded that a "combined NGS-based approach can assist clinicians in the diagnosis of NF1 as well as other neurocutaneous disorders and overlapping conditions" (Giugliano et al., 2019).

Castellanos et al. (2020) developed a custom next-generation sequencing (NGS) panel for testing patients with "a clinical suspicion of a RASopathy (n = 48) and children presenting multiple CALMs [café-au-lait macules] (n = 102)". The authors stated that phenotypic overlaps may exist in children if multiple CALMs are the only clinical symptom present and that genetic testing may differentiate between conditions. Of the 48 patients with clinical suspicion of a RASopathy, 21 were found to harbor a pathogenic mutation (with *NF1* mutations comprising five of 48 cases). Of the patients with multiple

CALMs, both *NF1* and *SPRED1* pathogenic mutations were identified. Overall, the authors concluded that "an NGS panel strategy for the genetic testing of these two phenotype-defined groups outperforms previous strategies" (Castellanos et al., 2020).

Witkowski et al. (2020) studied the benefits of adding *NF1* and *SPRED1* sequencing to the Noonan spectrum/ RASopathy NGS panel. Noonan spectrum disorders (NSD) are a group of disorders caused by problems in the MAPK pathway. NSD's are due to gain of function, while NF1 is caused by a loss of function. The study included 28 patients with a negative NSD panel that underwent *NF1* and *SPRED1* sequencing, and a validation panel analyzed 14 RASopathy associated genes in 505 patients. In total, 21% of the 28 patients had disease-causing *NF1/SPRED1* variants. In the validation cohort, only 2% of the patients were found to have disease-causing variants in the *NF1/SPRED1* genes. Adding *NF1* and *SPRED1* to the panel increased the diagnostic yield from 23.5% to 25.7%. The authors concluded that "adding the *NF1* and *SPRED1* genes to Noonan spectrum disorder/RASopathy NGS gene panels modestly increases clinical diagnoses" (Witkowski et al., 2020).

In a retrospective study, Elmas (2022) studied the use of artificial intelligence, Face2Gene, to diagnosis neurofibromatosis type 1. Fourteen patients underwent Face2Gene analysis. As a result, the most detected mutation type was nonsense mutation (42.8%) and suggested NF1 diagnosis for 10 of the 14 patients. The authors concluded that Face2Gene will be used a lot in the routines of medical doctors in the next 10 years (Elmas, 2022).

Neurofibromatosis type 2

Evans et al. (2015) 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).

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).

Castellanos 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 seven patients (four male and three 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 authors remarked that "Dermatological identification of skin plaque schwannomas in children would facilitate the early

diagnosis and treatment of patients with NF2 before development of severe adverse effects" (Castellanos et al., 2018).

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 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).

Genetic Severity	Sub-category	Clinical Characteristics	Definition
1 (Tissue Mosaic)	1A	Presumed tissue mosaicism	Meets clinical criteria for sporadic NF2 but not confirmed molecularly with identical NF2 mutations detected in two separate tissue samples
	1B	Confirmed tissue mosaicism	Mosaic NF2 confirmed molecularly with identical NF2 mutations detected in two or more separate tissue samples
2 (Classic)	2A	Mild NF2	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
	2B	Moderate NF2	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
3 (Severe)	3	Severe NF2	Full *NF2* truncating mutation exons 2–13

Halliday et al. (2017) evaluated the validity of this score in 142 patients (63 in group 1, 35 in group 2, and 19 in group 3 with three 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).

Lu et al. (2019) examined the efficacy and safety of bevacizumab for vestibular schwannomas (VS) in neurofibromatosis type 2. The authors included eight articles including 161 patients and 196 VS. The authors identified radiographic response in 41% of cases (termed "partial regression"), no change in 47% of cases, and tumor progression of 7% of cases. Bevacizumab treatment also resulted in hearing improvement in 20% of cases, stability in 69% of cases, and further hearing loss in 6% of cases. Bevacizumab toxicity was observed in 17% of cases, and surgical intervention was needed in 11% of cases. Overall, the authors concluded that bevacizumab may "arrest" tumor progression and hearing loss in NF2 patients presenting with VS lesions but recommended judicious use of bevacizumab due to serious adverse events (Lu et al., 2019).

Schwannomatosis

Hutter et al. (2014) evaluated the proportion of schwannomatosis cases that come from mutations aside from the germline variants in *SMARCB1* and *LZTR1*. The authors performed whole exome sequencing on 23 patients with sporadic schwannomatosis (without *SMARCB1* mutations) and found only five *LZTR1* or *NF2* mutations. However, since the authors noted the reported frequency of *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 et al. (2018) performed targeted next generation sequencing (NGS) to investigate genetic differences between NF2, schwannomatosis, and meningiomatosis. The authors sequenced 196 patients (79 with NF2, 40 with schwannomatosis, 12 with meningiomatosis, and 65 with no clearly established diagnosis) for *NF2, SMARCB1, LZTR1, SMARCE1*, and *SUFU*. The NF2 and schwannomatosis results were as follows: "An NF2 variant was found in 41 of 79 NF2 patients (52%). *SMARCB1* or *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 *LZTR1* variant was identified in 16/47 (34%) NF2/SMARCB1-negative schwannomatosis patients." The authors concluded that targeted NGS was a suitable strategy for identifying NFS mosaicism in blood and for investigation of these tumors (Louvrier et al., 2018).

Sadler et al. (2021) studied which germline pathogenic variants are associated with sporadic vestibular schwannoma (sVS) through genetic analysis of sVS cases of *NF2, LZTR1* and *SMARCB1* genes. NF2 variants were confirmed in 2% of the patients, *LZTR1* was found in 3% of the patients, and there were no pathogenic *SMARCB1* variants identified in this cohort. Therefore, the authors concluded that "loss of *NF2* function is a common event in sVS tumours and may represent a targetable common pathway in VS tumourigenesis. Earlier identification of patients with these syndromes can facilitate more accurate familial risk prediction and prognosis" (Sadler et al., 2021).

Piotrowski et al. (2022) studied the use of targeted massively parallel sequencing to diagnose multiple schwannomas. Thirty-five patients were enrolled in the study and massive parallel sequencing of *LZTR1, SMARCB1*, and *NF2* genomic loci was conducted. The study verified whether any other *LZTR1/SMARCB1/NF2* pathogenic variants could be found in 16 cases carrying a *SMARCB1* constitutional

variant in the 3'-untranslated region. "The 3'-UTR variants c.*17C>T and c.*82C>T showed pathogenicity. Two novel deep intronic *SMARCB1* variants, c.500+883T>G and c.500+887G>A were identified in two individuals. Further resequencing of chromosome 22q in individuals negative for PVs in the *SMARCB1/LZTR1/NF2* demonstrated five potential schwannomatosis-predisposing candidate genes (*MYO18B, NEFH, SGSM1, SGSM3*, and *SBF1*)." The authors conclude that noncoding *SMARCB1/LZTR1* variants are a molecular cause of schwannomatosis, hence it is essential to include them into the molecular diagnostic panel (Piotrowski et al., 2022).

V. Guidelines and Recommendations

American Academy of Pediatrics (AAP)

In 2008, the AAP committee on genetics published guidelines on health supervision in children with 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 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."

This guideline was reaffirmed in 2017.

A Clinical Report from the AAP comments on the role of genetic testing for Neurofibromatosis Type 1. They state that genetic testing:

- "can confirm a suspected diagnosis before a clinical diagnosis is possible;"
- "can differentiate NF1 from Legius syndrome;"
- "may be helpful in children who present with atypical features;"
- "usually does not predict future complications; and"
- "may not detect all cases of NF1; a negative genetic test rules out a diagnosis of NF1 with 95% (but not 100%) sensitivity" (Miller et al., 2019).

American College of Medical Genetics and Genomics (ACMG)

In their guidelines detailing the care of adults with 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 NF1 genetic testing is needed". Furthermore, the ACMG stated that genetic testing can quickly establish a diagnosis for children thereby relieving anxiety, but this is not as significant an issue for adults (Stewart et al., 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 as secondary findings related to cancer phenotypes for both pathogenic and likely pathogenic variants (Miller et al., 2021).

European Association of Neuro-Oncology (EANO)

This EANO guideline on "diagnosis and treatment of vestibular schwannoma" comments on neurofibromatosis type 2, stating that NF2 "should be considered when an individual presents with a unilateral vestibular or other sporadic schwannoma at <30 years or meningioma at <25 years. Germline pathogenic variants can be identified in 1-10% of cases. NF2 should also be considered in older patients with two NF2 related tumors (Goldbrunner et al., 2020).

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 five mm in prepubertal patients and more than 15 mm in post-pubertal 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 contrasts with 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)" (Evans, Salvador, Chang, Erez, Voss, Schneider, 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" (Evans, Salvador, Chang, Erez, Voss, Druker, et al., 2017).

European Consortium 'Care for CMMRD'

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 (K. 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 pilomatricomas in the patient 2 points
- One pilomatricoma 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 (K. Wimmer et al., 2014).

The consortium in 2018 issued the selection strategy for CMMR-D 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 CMMRD syndrome… If both partners are a carrier of a pathogenic variant(s) in the same MMR gene, then their future offspring will be at risk of having CMMRD syndrome" (NCCN, 2023).

International consensus group recommendation on neurofibromatosis type 1

An international consensus group revised diagnostic criteria for neurofibromatosis type 1 as well as sought to establish diagnostic criteria for Legius syndrome (Legius et al., 2021). The group involved global experts, advocacy groups, and patient input in a multistep process to establish criteria.

Diagnostic criteria for neurofibromatosis type 1:

> "A: The diagnostic criteria for NF1 are met in an individual who does not have a parent diagnosed with NF1 if two or more of the following are present:
>
> - Six or more café-au-lait macules over 5 mm in greatest diameter in prepubertal individuals and over 15 mm in greatest diameter in postpubertal individuals
> - Freckling in the axillary or inguinal region
> - Two or more neurofibromas of any type or one plexiform neurofibroma
> - Optic pathway glioma
> - Two or more iris Lisch nodules identified by slit lamp examination or two or more choroidal abnormalities (CAs)—defined as bright, patchy nodules imaged by optical coherence tomography (OCT)/near-infrared reflectance (NIR) imaging
> - A distinctive osseous lesion such as sphenoid dysplasia, anterolateral bowing of the tibia, or pseudarthrosis of a long bone
> - A heterozygous pathogenic *NF1* variant with a variant allele fraction of 50% in apparently normal tissue such as white blood cells.
>
> B: A child of a parent who meets the diagnostic criteria specified in A merits a diagnosis of NF1 if one or more of the criteria in A are present" (Legius et al., 2021).

Diagnostic criteria for Legius syndrome:

> "A: The diagnostic criteria for Legius syndrome are met in an individual who does not have a parent diagnosed with Legius syndrome if the following CRITERIA are present:
>
> - Six or more café-au-lait macules bilaterally distributed and no other *NF1*-related diagnostic criteria except for axillary or inguinal freckling
> - A heterozygous pathogenic variant in *SPRED1* with a variant allele fraction of 50% in apparently normal tissue such as white blood cells
>
> B: A child of a parent who meets the diagnostic criteria specified in A merits a diagnosis of Legius syndrome if one or more of the criteria in A are present" (Legius et al., 2021).

"The diagnostic criteria for mosaic NF1 are met in an individual if any of the following is present:

1. A pathogenic heterozygous *NF1* variant with a variant allele fraction of significantly less than 50% in apparently normal tissue such as white blood cells AND one other NF1 diagnostic criterion (except a parent fulfilling diagnostic criteria for NF1)
2. An identical pathogenic heterozygous *NF1* variant in two anatomically independent affected tissues (in the absence of a pathogenic *NF1* variant in unaffected tissue)
3. A clearly segmental distribution of café-au-lait macules or cutaneous neurofibromas AND
   a. Another NF1 diagnostic criterion (except a parent fulfilling diagnostic criteria for *NF1*)
   or
   b. Child fulfilling diagnostic criteria for NF1
4. Only one NF1 diagnostic criterion from the following list: freckling in the axillary and inguinal region, optic pathway glioma, two or more Lisch nodules or two or more choroidal abnormalities, distinctive osseous lesion typical for NF1, two or more neurofibromas or one plexiform neurofibroma AND a child fulfilling the criteria for NF1"(Legius et al., 2021).

"The diagnostic criteria for mosaic Legius syndrome are met in an individual if any of the following is present:

1. A heterozygous pathogenic *SPRED1* variant with a variant allele fraction of significantly less than 50% in apparently normal tissue such as white blood cells AND six or more café-au-lait macules
2. An identical pathogenic heterozygous *SPRED1* variant in two independent affected tissues (in the absence of a pathogenic *SPRED1* variant in unaffected tissue)
3. A clearly segmental distribution of café-au-lait macules AND a child fulfilling the criteria for Legius syndrome" (Legius et al., 2021).

International consensus group recommendation on neurofibromatosis type 2 and schwannomatosis

The international consensus group also provided new recommendations on the nomenclature of NF2 and schwannomatosis. Traditionally, NF2 and SWN were identified based on primarily clinical features; however, the group's consensus is that the "phenotype of these diseases spans a continuum without absolute delineation of subtypes phenotypically" leading to the need for an umbrella (Plotkin et al., 2022). The group chose the term "schwannomatosis" (i.e. as the umbrella term) to showcase the overlapping clinical phenotype of related conditions. Additionally, the group recommended that the type of SWN be further classified based on the gene that harbors a PV (identified through molecular analysis). According to this nomenclature, NF2 would be renamed "NF2-related schwannomatosis" and SWN would fall as either "SMARCB1-related schwannomatosis," "LZTR1-related schwannomatosis," or "22q-related schwannomatosis," depending on the location of the inherited pathogenic. For patients who have clinical features of NF2/SWN but have not had molecular analysis, the group recommends "schwannomatosis-not otherwise specified" as the type categorization or "schwannomatosis-not elsewhere classified" for patients in whom molecular analysis did not successfully detect a PV variant (Plotkin et al., 2022).

Updated diagnostic criteria for NF2-related schwannomatosis:

"A diagnosis of NF2-related schwannomatosis (previously termed neurofibromatosis 2, NF2) can be made when an individual has one of the following:

1. Bilateral vestibular schwannomas (VS)
2. An identical *NF2* pathogenic variant in at least 2 anatomically distinct NF2-related tumors (schwannoma, meningioma, and/or ependymoma). (Note: if the variant allele fraction (VAF) in unaffected tissues such as blood is clearly <50%, the diagnosis is mosaic NF2-related schwannomatosis)
3. Either 2 major or 1 major and 2 minor criteria as described in the following:

Major criteria:

- Unilateral VS
- First-degree relative other than sibling with NF2-related schwannomatosis
- 2 or more meningiomas (Note: single meningioma qualifies as minor criteria).
- *NF2* pathogenic variant in an unaffected tissue such as blood (Note: if the VAF is clearly <50%, the diagnosis is mosaic NF2-related schwannomatosis)"

Minor criteria:

Can count >1 of a type (e.g., 2 distinct schwannomas would count as 2 minor criteria)

- Ependymoma, meningioma (Note: multiple meningiomas qualify as a major criteria), schwannoma (Note: if the major criterion is unilateral VS, at least 1 schwannoma must be dermal in location)

Can count only once (e.g., bilateral cortical cataracts count as a single minor criterion)

- Juvenile subcapsular or cortical cataract, retinal hamartoma, epiretinal membrane in a person aged <40 years, meningioma" (Plotkin et al., 2022).

"Pattern of genetic changes in unaffected and tumor tissue in *NF2*-related schwannomatosis"

Gene locus	Unaffected Tissue	Tumor 1	Tumor 2	Comment
NF2				
Allele 1	PV1	PV1	PV1	Shared *NF2* pathogenic variant
Allele 2	WT	LOH or *NF2* or PV2	LOH or *NF2* or PV3	Tumor-specific partial loss of 22q in trans position or a different *NF2* somatic second PV in every anatomically unrelated tumor"(Plotkin et al., 2022)

Diagnostic criteria for *SMARCB1*- and *LZTR1*-related schwannomatosis

"A diagnosis of *SMARCB1*- or *LZTR1*-related schwannomatosis can be made when an individual meets 1 of the following criteria:

- At least 1 pathologically confirmed schwannoma or hybrid nerve sheath tumor and a *SMARCB1* (or *LZTR1*) pathogenic variant in an unaffected tissue such as blood
- A shared *SMARCB1* or *LZTR1* pathogenic variant in 2 schwannomas or hybrid nerve sheath tumors" (Plotkin et al., 2022).

"Pattern of genetic changes in unaffected and tumor tissue in *SMARCB1*- and *LZTR1*-related schwannomatosis"

Gene locus	Unaffected Tissue	Tumor 1	Tumor 2	Comment
SMARCB1/LZTR1				
Allele 1	PV1	PV1	PV1	Shared *SMARCB1* or *LZTR1* pathogenic variant
Allele 2	WT	LOH	LOH	Tumor-specific partial loss of 22q in trans position, LOH typically entails deletion of 22q region encompassing *LZTR1/SMARCB1/NF2*"(Plotkin et al., 2022).

Gene locus	Unaffected Tissue	Tumor 1	Tumor 2	Comment
NF2				
Allele 1	WT	PV2	PV3	Tumor-specific pathogenic *NF2* variant in cis to pathogenic *SMARCB1* variant
Allele 2	WT	LOH	LOH	Tumor-specific partial loss of 22q in trans position, LOH typically entails deletion of 22q region encompassing *LZTR1/SMARCB1/NF2*"(Plotkin et al., 2022).

Diagnostic criteria for 22q-related schwannomatosis

"A diagnosis of 22q-related schwannomatosis can be made when an individual does not meet criteria for *NF2*-related schwannomatosis, *SMARCB1*-related schwannomatosis, or *LTZR1*-related schwannomatosis, does not have a germline *DGCR8* pathogenic variant, and has both of the following molecular features:

- LOH of the same chromosome 22q markers in 2 anatomically distinct schwannomas or hybrid nerve sheath tumors and
- A different *NF2* pathogenic variant in each tumor, which cannot be detected in unaffected tissue" (Plotkin et al., 2022).

"Pattern of genetic changes in unaffected and tumor tissue in 22q-related schwannomatosis"

Gene locus	Unaffected Tissue	Tumor 1	Tumor 2	Comment
SMARCB1/ LZTR1				
Allele 1	WT	None found	None found	No shared pathogenic *LZTR1* or *SMARCB1* variant
Allele 2	WT	LOH	LOH	Tumor-specific partial loss of the same chromosome 22q, LOH typically entails deletion of 22q region encompassing *LZTR1/SMARCB1/NF2*"(Plotkin et al., 2022)"

Gene locus	Unaffected Tissue	Tumor 1	Tumor 2	Comment
NF2				
Allele 1	WT	PV1	PV2	Tumor-specific pathogenic *NF2* variant trans to the 22q deletion
Allele 2	WT	LOH	LOH	Tumor-specific partial loss of the same chromosome 22q, LOH typically entails deletion of 22q region encompassing *LZTR1/SMARCB1/NF2*"(Plotkin et al., 2022)"

VI. Applicable State and Federal Regulations

DISCLAIMER: If there is a conflict between this Policy and any relevant, applicable government policy for a particular member [e.g., Local Coverage Determinations (LCDs) or National Coverage Determinations (NCDs) for Medicare and/or state coverage for Medicaid], then the government policy will be used to make the determination. For the most up-to-date Medicare policies and coverage, please visit the Medicare search website. For the most up-to-date Medicaid policies and coverage, visit the applicable state Medicaid website.

Food and Drug Administration (FDA)

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). LDTs are

not approved or cleared by the U. S. Food and Drug Administration; however, FDA clearance or approval is not currently required for clinical use.

VII. Important Reminder

The purpose of this Medical Policy is to provide a guide to coverage. This Medical Policy is not intended to dictate to providers how to practice medicine. Nothing in this Medical Policy is intended to discourage or prohibit providing other medical advice or treatment deemed appropriate by the treating physician.

Benefit determinations are subject to applicable member contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

This Medical Policy has been developed through consideration of the medical necessity criteria under Hawaii's Patients' Bill of Rights and Responsibilities Act (Hawaii Revised Statutes §432E-1.4) or for QUEST members, under Hawaii Administrative Rules (HAR 1700.1-42), generally accepted standards of medical practice and review of medical literature and government approval status.

HMSA has determined that services not covered under this Medical Policy will not be medically necessary under Hawaii law in most cases. If a treating physician disagrees with HMSA's determination as to medical necessity in a given case, the physician may request that HMSA reconsider the application of the medical necessity criteria to the case at issue in light of any supporting documentation.

Genetic testing is covered for level 1 or 2A recommendations of the National Comprehensive Cancer Network (NCCN and in accordance with Hawaii's Patients' Bill of Rights and Responsibilities Act (Hawaii Revised Statutes §432E-1.4) or for QUEST members, the Hawaii Administrative Rules (HAR 1700.1-42).

VIII. Evidence-based Scientific References

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IX. Policy History

Action Date	Action
June 01, 2023	Policy created
December 03, 2024	Policy approved by Medical Directors
December 20, 2024	Policy approved at UMC
February 01, 2025	Policy effective date following notification period