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Updates in the Management of Central and Peripheral Nervous System Tumors among Patients with Neurofibromatosis Type 1 and Neurofibromatosis Type 2

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Short Title: Updates in NF-Related Tumors

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Abstract
Background: Neurofibromatosis type 1 and neurofibromatosis type 2 are unrelated, distinct genetic disorders characterized by the development of central and peripheral nervous system tumors.
Summary: Neurofibromatosis type 1 is the most common inherited tumor predisposition syndrome with a lifelong increased risk of benign and malignant tumor development, such as glioma and nerve sheath tumors. Neurofibromatosis type 2 classically presents with bilateral vestibular schwannoma, yet is also associated with non-vestibular schwannoma, meningioma, and ependymoma. Historically, the number of effective therapies for neurofibromatosis-related neoplasms has been limited.
Key Message: In the past decade there have been significant advances in the development of precision-based therapies for NF-associated tumors with an increased emphasis on functional outcomes in addition to tumor response. Continued scientific discovery and advancement of targeted therapies for NF-associated neoplasms are necessary to continue to improve outcomes for patients with NF.

Introduction
Neurofibromatosis type 1 and neurofibromatosis type 2 are genetic disorders characterized by the development of tumors of the central and peripheral nervous system. Neurofibromatosis type 1 (NF1), formerly known as von Recklinghausen's disease, is one of the most common inherited genetic syndromes, affecting 1 in 3000 people worldwide without predilection for sex or race.[1] Neurofibromatosis type 2 (NF2) has an incidence of approximately 1 in 30,000 people and classically presents with bilateral vestibular schwannomas by the age of 30 years. While treatment of NF-associated neoplasms has historically been limited to surgical interventions, in the past decade there

have been significant advances in the management of NF-associated tumors including novel precision-based therapies with an increased emphasis on functional outcomes in addition to tumor response.

Neurofibromatosis Type 1

Neurofibromatosis type 1 is an autosomal dominant cancer predisposition syndrome with a wide range of neoplastic and non-neoplastic manifestations. Approximately half of patients with NF1 inherit a pathogenic *NF1* mutation from either parent, while the other half of cases arise *de novo* from germline mutations. There is significant diversity in pathogenic mutations, with more than 2,800 pathogenic variants described.[2] The *NF1* gene is located on chromosome 17q11 and encodes for the tumor suppressor protein neurofibromin. Neurofibromin has a role in many signaling pathways, including as a negative regulator of the RAS/mitogen activated protein kinase pathway. While neurofibromin is ubiquitously expressed, the highest level of expression occurs within the nervous system. Tumors typically develop in the setting of bi-allelic inactivation of the *NF1* gene due to a second somatic mutation, resulting in loss of neurofibromin expression, unregulated cell proliferation and tumorigenesis.

The diagnosis of NF1 may be made from clinical criteria or with the identification of a pathogenic germline *NF1* mutation in the setting of the clinical features of NF1. The diagnostic criteria for NF1 were originally defined in 1987 and revised in 2021 (Table 1).[3] Patients with NF1 typically present by 8 years of age with penetrance approaching 100% by the third decade of life. Importantly, genotype-phenotype correlations are limited, and even amongst affected family members with identical pathogenic mutations, there can be wide variability in disease phenotype.[2] The manifestations of NF1 are broad and not limited to tumor development. Patients with NF1 commonly present with cutaneous findings such as multiple café au lait macules, skinfold freckling, and cutaneous neurofibromas. They may also develop skeletal abnormalities such as scoliosis, macrocephaly, dysplasia of the sphenoid wing or long bones, pseudoarthrosis, and/or short stature. Ophthalmologic manifestations can include Lisch nodules and choroidal abnormalities, neither of which impact visual acuity or cause visual disturbances. There is an increased risk of hypertension and vasculopathy, with a prevalence of cerebral arteriopathy between 2.5-6%.[4] Patients may also present with non-neoplastic neurologic complications, such as epilepsy, hydrocephalus, autism spectrum disorder, learning disabilities, and abnormalities on brain magnetic resonance imaging (MRI) known as focal areas of signal intensity (FASI). FASI (formerly known as unidentified bright objects [UBOs] or spongiform change) are hyperintense areas on T2-weighted MRI that occur in up to 90% of pediatric patients with NF1.[5] Although sometimes challenging to distinguish from low grade glioma, FASI typically lack contract enhancement and do not cause mass effect. Importantly, FASI do not appear to correlate with tumor development or focal neurologic deficits and do not require routine imaging surveillance.[6]

Diagnosis and Management of Tumors Associated with Neurofibromatosis Type 1

Low Grade Glioma

Patients with NF1 are at increased risk for the development of glioma both within and external to the optic pathway. NF1-associated low grade glioma (NF1-LGG) occur in an estimated 20% of children, presenting most frequently within the optic pathway, followed by the brainstem.[7, 8] These tumors are typically not biopsied at radiologic diagnosis, as most demonstrate indolent behavior and pathologic confirmation is not a determinant of current approaches to management.

Given that surgical biopsy is rarely performed for NF1-LGG in children, until recently there was a paucity of information about the genomic drivers of NF1-LGG. A multi-institutional study integrating molecular and clinical information demonstrated that most pediatric NF1-LGG harbored bi-allelic *NF1* inactivation and were classified as pilocytic astrocytoma (PA).[9] Specifically, tumors arising in the optic pathway or hypothalamus were overwhelming classified as PA and unlikely to harbor addition mutations beyond bi-allelic *NF1* inactivation. In contrast, tumors defined as non-PA were more likely to harbor additional mutations; however, only 11% of the entire cohort demonstrated additional alterations, such as *FGFR1* and *PIK3CA* mutations.[9] No alterations of *TP53*, *CDKN2A*, or *ATRX* were identified in the tumors confirmed to be low grade by methylation profile. In a separate study that included 32 patients with NF1 (10 pediatric) and low-grade glioma by histology, 6 patients (3 pediatric) had *CDKN2A* +/- *ATRX* alterations; however, these tumors did not undergo methylation profiling to determine if they were truly low-grade.[10] These findings support the current practice that biopsy is not indicated in the management of typically appearing NF1-LGG in children, as the likelihood of identifying an unexpected (i.e., non-*NF1*) actionable mutation is

low. However, given the small percentage of tumors with additional alterations, it may be reasonable to consider surgical biopsy for tumors unresponsive to chemotherapy, with atypical features on MRI, or located outside the optic pathway and hypothalamus.

Up to 20% of patients with NF1 will develop a glioma of the optic pathway (NF1-OPG), with a median age of diagnosis between 2 to 5 years (Fig. 1.)[1, 11]. While NF1-OPG are typically indolent, up to half of children may require at least one treatment regimen for their tumor. The primary indications for treatment are ophthalmologic and include a decline in visual acuity or worsening visual fields. Importantly, radiologic progression and visual acuity do not always correlate, therefore the initiation of chemotherapy may not be indicated with radiologic progression alone.[12] Furthermore, a subset of tumors exhibit spontaneous regression, suggesting that some children may only require monitoring with serial imaging and ophthalmological evaluations.[13] When treatment is indicated, chemotherapy is considered the standard of care. Despite treatment with frontline chemotherapy, approximately one-third of children will demonstrate continued visual acuity decline, with up to 40% of children requiring additional treatment regimens for relapsed or refractory disease within 5 years of initial therapy.[11, 14] Clinical features that may increase the risk of treatment-refractory disease include young age, tumor involvement posterior to the chiasm, and abnormalities of the optic disc, such as edema or pallor, at initiation of therapy.

Surgical intervention is typically contraindicated in OPG, due to the infiltrative nature of these tumors and risk of damage to the visual pathway. As both biopsy and debulking of NF1-OPG can negatively impact vision, the potential benefits of surgical intervention must outweigh the risks. Surgery may be considered for unilateral tumor confined to the optic nerve with complete loss of vision and associated disfiguring and painful proptosis, or partial debulking for significant mass effect on adjacent brain structures. Additionally, radiation therapy is avoided due to the increased risk of radiation-induced secondary malignancies and vasculopathy such as cerebral arteriopathy and moyamoya syndrome.[15, 16]

An estimated 5-10% of children with NF1 will develop a LGG outside of the optic pathway; however, the prevalence is likely higher given the standard practice to defer imaging screening in asymptomatic patients.[17] Similar to OPG, many of the non-optic pathway LGG remain asymptomatic and do not require therapy. Non-optic pathway gliomas occur most frequently in the brainstem, followed by the basal ganglia and cerebellum.[7, 18] The mean age of diagnosis of brainstem glioma in children with NF1 is 7 years.[19] Brainstem glioma can lead to obstructive hydrocephalus and cranial nerve palsies requiring either cerebrospinal fluid (CSF) diversion, chemotherapy, and/or debulking surgery. In children requiring CSF diversion and/or treatment for their brainstem glioma, overall survival is approximately 85%.[19] For tumors arising outside of the optic pathway or brainstem, much less is known regarding the natural history and risk factors for progression; large-scale prospective studies will be required to address these knowledge gaps.

Diffuse astrocytoma represent a subset of glioma in patients with NF1. Diffuse astrocytoma typically develop in adulthood but can occur infrequently in children with NF1, and may be low or high grade histology (WHO II-VI) [20] Diffuse astrocytoma are more likely to be progressive and have atypical features on MRI; thus, their behavior and management can be distinct from typical NF1-LGG and is often guided by histologic grade and/or molecular findings.

When indicated, initial therapy for NF1-LGG within or extrinsic to the optic pathway is typically a carboplatin-based chemotherapy regimen. The standard frontline regimen of carboplatin with vincristine is associated with a 5-year progression free survival (PFS) of 69% and is generally well-tolerated in children.[21] Second-line chemotherapy regimens include vinblastine and bevacizumab.[22, 23] While vinblastine has historically been considered an effective second line for NF1-LGG, a clinical trial is ongoing to determine the efficacy of the addition of the anti-angiogenic agent bevacizumab to vinblastine compared with vinblastine alone in chemotherapy-naïve pediatric subjects with unresectable or progressive low grade glioma (NCT02840409). Importantly, the approach to chemotherapeutic management of NF1-LGG differs from that of sporadic LGG; select agents, such as alkylators, are avoided due to the theoretical increased risk of secondary malignancies in patients with NF1.[24]

Genetically engineered mouse models of *nf1* optic glioma have allowed for preclinical drug investigations and the identification of promising therapies for the treatment of NF1-LGG, including inhibitors of mitogen-activated kinase kinase (MEK), the mechanistic target of rapamycin (mTOR), and phosphatidylinositol-3 kinase (PI3K).[25, 26] Selumetinib, a potent and orally available MEK inhibitor, subsequently demonstrated activity in early phase clinical trials for recurrent or progressive LGG.[27] In a prospective phase 2 study of selumetinib for recurrent NF1-LGG, 10 of 25 subjects (40%) achieved a partial response with a 2-year PFS of 96%.[28] Among 10 subjects with serial

quantitative visual assessments receiving selumetinib, no subjects experienced worsening of vision acuity (VA) while on therapy, two (20%) subjects demonstrated improvement, and 8 (80%) had stable VA. The most common attributable toxicities included rash, creatine phosphokinase elevations, and diarrhea. Based on these results, a randomized trial conducted by the Children's Oncology Group (NCT03871257) is ongoing to determine if selumetinib is an equivalent option to carboplatin/vincristine in children and young adults with NF1-LGG.

Activation of mTOR, a downstream target of the PI3K/Akt pathway, leads to dysregulated cell growth, proliferation, and angiogenesis in preclinical models of NF1-LGG. In a phase 2 clinical trial of everolimus for patients with progressive NF1-LGG, 68% of subjects demonstrated either stable disease or response, with a 2-year PFS of approximately 70%.[29] On a per subject analysis of visual outcomes, 3 of 14 subjects had improved vision, 9 had stable vision, and 2 of 14 had worsening of vision.[30] Further emphasizing the importance of the evaluation of both functional and radiographic outcomes in patients with NF1-OPG is the discordance observed between imaging response and visual outcomes, as 2 subjects with radiographically stable disease had improved vision at the end of therapy.

Targeting the pathways impacted by loss of neurofibromin has not always proved successful in the clinical setting. In a phase 2 study of sorafenib, a multi-target small molecular tyrosine kinase inhibitor (including RAF), treatment of children with NF1-LGG resulted in unexpected and accelerated tumor growth with a median time to progression of 2.8 months.[31] In addition, as with all novel therapies, the long-term benefits and durability of these new agents are unknown; thus, ongoing assessment of outcomes, such as toxicity and relapse, in comparison to standard of care therapy are necessary.

Studies of novel therapies for the treatment of recurrent NF1-LGG include a phase 2 trial of polyinosinic-polycytidylic acid stabilized with poly-L-lysine and carboxymethylcellulose (poly-ICLC; NCT04544007). Poly-ICLC is a synthetic double-stranded RNA molecule with direct antineoplastic and immune enhancing effects. In a small phase 2 study, 50% of subjects (5/10) with LGG demonstrated response with low toxicity, supporting the expansion to a larger phase 2 trial in subjects with NF1-LGG.[32] Additional studies include a phase 2 study of trametinib with hydroxychloroquine for progressive NF1-LGG (NCT04201457).

Finally, in the past decade, there has been an important shift in the evaluation of treatment outcomes of low-grade glioma in NF1. Oncologists and NF1 clinicians alike have recognized that clinical outcomes, such as function and quality of life, in addition to radiographic response and progression free survival, are essential in the evaluation of efficacy for NF1-LGG.[33] Therefore, there has been an important change in both the treatment paradigm and assessment of response, with primary clinical trial outcome measures assessing not only tumor response but also changes in patient-reported and functional outcomes. For example, in the ongoing phase 3 clinical trial of selumetinib versus carboplatin/vincristine for NF1-LGG, the primary outcome measures include both event free survival and number of patients with improvement in visual acuity, with secondary measures assessing radiographic tumor response, change in motor function, and quality of life.

High Grade Glioma

Patients with NF1 are at increased risk for the development of high-grade gliomas (NF1-HGG) (Fig. 2.) compared to the general population. In contrast to the infrequent occurrence of other mutations in NF1-LGG, NF1-HGG demonstrate recurrent mutations in the *TP53*, *EGFR*, *ATRX*, and *CDKN2A* genes, yet lack the *IDH1* and *histone H3* mutations commonly observed in non-NF1 associated HGG.[10] In a comprehensive analysis of molecular alterations in NF1-glioma, inactivating mutations of *ATRX* co-occurring with loss of *CDKN2A/CDKN2B* and/or *TP53* were observed in 58% of NF1-HGG.

High-grade astrocytoma with piloid features (HGAP) is a newly recognized tumor type in the 2021 WHO classification of tumors of the central nervous system and occurs in patients with and without NF1. HGAP is characterized by alterations in *CDKN2A* and/or *ATRX* despite a histologic appearance of pilocytic astrocytoma and is defined by a specific methylation profile.[34] These molecular alterations appear to confer a more aggressive phenotype driven by the complex pattern of mutations, rather than histology alone. As such, *ATRX* and *CDKN2A* alterations within NF1-glioma are clinically relevant and testing is advised for all biopsied NF1-glioma, as their presence predicts poorer clinical outcomes.[10]

Currently, the epidemiology, optimal treatment, and prognosis of patients with NF1-HGG is unknown. A lack of large-scale studies is the major limitation in the understanding of the management and outcomes of patients with NF1-

HGG. Across case reports, the median age of patients with NF1 diagnosed with glioblastoma appears younger than sporadic glioblastoma; however, the significance of this in terms of outcomes is unclear.[35] While pediatric patients with NF1 appear at increased risk for the development of glioblastoma, a small cohort study of 5 patients reported their survival may be prolonged compared to sporadic glioblastoma despite comparable therapeutic approach (median overall survival of 9.25 years compared to 1.08 years).[36] Surgical resection and radiation are the mainstays of therapy for children and adults with NF1-HGG; however, there is variability in approach to treatment across institutions and the benefits of chemotherapy are undetermined. There is ongoing interest in the potential use of combinations of novel molecular agents such as MEK inhibitors with CDK4/6 inhibitors for the treatment of NF1-associated high-grade gliomas; however, prospective clinical trials have yet to be implemented.

Plexiform Neurofibroma

Plexiform neurofibromas (PN) are benign peripheral nerve sheath tumors occurring in nearly half of patients with NF1 and are thought to be congenital. Although PN may not be apparent at birth, they are typically recognized in early childhood. They involve multiple nerve fascicles, are often vascular, and are multicellular tumors comprised of Schwann cells, perineural cells, fibroblasts and collagen.[37] The burden of symptoms due to PN is broad, and these tumors may be asymptomatic, cause significant morbidity due to pain, disfigurement, and functional impairments, or become life-threatening if they compress the airway or other vital structures (Fig. 3.). Younger age is typically associated with more rapid tumor growth; however, the growth of PN varies between patients and even between a patient's multiple tumors.[38] There is anecdotal concern that PN growth rate accelerates during periods of hormonal excess, such as puberty; however, studies do not support this belief.[39]

The gold standard diagnostic imaging modality for PN is MRI with short tau inversion recovery (STIR) sequences, a fat suppression technique which provides optimal visualization of PN. Screening imaging is not currently recommended for diagnosis and should be prompted by concerns identified on history or physical examination. Biopsy is not required to confirm the diagnosis of PN and is not necessary unless malignant transformation is suspected based on clinical or imaging findings. Currently, there is no standard of care for frequency of surveillance imaging to monitor for tumor growth once diagnosed.

Most PN do not require intervention and can be observed by physical examination and/or imaging following initial diagnosis. Treatment is considered for tumors causing significant morbidity (such as pain, functional impairment, or severe disfigurement), or for ongoing progression with impending morbidity. The decision to treat should be guided by symptoms rather than tumor size, as small tumors may cause significant morbidity while large PN may be relatively asymptomatic. If treatment is indicated, the selection of medical versus surgical intervention should be guided by a multi-disciplinary team of clinicians and surgeons with expertise in NF1. Historically, treatment options for PN were limited to surgical resection or debulking with the main goals of resection to reduce disfigurement, pain, and tumor bulk. However, due to the infiltrative nature of these tumors, complete excision of tumor is only accomplished in approximately 15% of cases.[40] Further, attempts at resection are often associated with risks of worsening of pain and functional impairment due to nerve damage. Like other NF1-associated tumors, radiation therapy is avoided given the risk of developing a subsequent neoplasm within the radiation field.[16]

There have been significant advances in the medical management of PN in the past decade. In a phase 2 clinical trial of the MEK inhibitor selumetinib for children with NF1 and inoperable symptomatic PN, 68% of participants demonstrated an objective partial response, in addition to objective improvements in function and quality of life.[41] Selumetinib was subsequently approved by the Food and Drug Administration in 2020 for the treatment of symptomatic, inoperable PN in children with NF1. Other MEK inhibitors have also demonstrated efficacy in recent or ongoing clinical trials for children or adults with PN.[42, 43] In a phase 2 trial of mirdametinib, 42% of subjects (8/19) achieved a partial response of the target PN by 12 cycles of therapy, and 10 (53%) had stable disease. In addition, as was observed for the study of selumetinib, treatment with mirdametinib resulted in significant and durable decreases in pain ratings.[42] Despite the success of these agents, there are still outstanding questions regarding the duration and durability of treatment as well as the long-term toxicities.

In addition to the MEK inhibitors, cabozantinib, a multi-receptor tyrosine kinase inhibitor, demonstrated efficacy in a clinical trial for adolescents and adults with PN.[37] Ongoing studies are evaluating cabozantinib for the treatment of PN in children (NCT02101736). Further, as MEK inhibitors and cabozantinib demonstrate the greatest efficacy to date,

a trial of the combination of cabozantinib and selumetinib for adolescents and adults with PN is upcoming through the NF Clinical Trials Consortium.

PN may undergo transformation to atypical neurofibroma (AN), atypical neurofibromatous neoplasm of uncertain biological potential (ANNUBP), or malignant peripheral nerve sheath tumor (MPNST). Rapid growth of a PN or worsening pain may be an indication of malignant transformation and should prompt further evaluation. AN are defined by nuclear atypia, increased mitotic indices, and/or loss of the classic neurofibroma architecture on histopathologic examination. ANNUBP represent a subset of AN, and are specifically characterized by at least two of the following features: cytological atypia, hypercellularity, loss of neurofibroma architecture, and an increased mitotic index (>1/50 but <3/10 mitotic figures per high power field).[44] Molecularly, AN/ANNUBP have been characterized by loss of *CDKN2A/B.*[45] [46] It is hypothesized that AN/ANNUBP are pre-malignant with a higher risk for progression to MPNST as compared to classic PN[47]; although the true incidence of malignant transformation is unknown.[45] While the appropriate management of AN/ANNUBP is not yet known, many suggest surgical resection if possible because of concern for further transformation. A phase 1/2 study of the cyclin-dependent kinase (CDK) 4/6 inhibitor abemaciclib is ongoing to determine tolerability and tumor response rate in patients with atypical PN and NF1 (NCT04750928).

Malignant Peripheral Nerve Sheath Tumor

MPNST are aggressive soft tissue tumors that occur in up to 13% of patients with NF1, typically arising due to malignant transformation of a pre-existing PN.[48] MPNST remains the leading cause of early death with 5-year overall survival estimates between 20-50%. [37] Fluorodeoxyglucose (FDG) positron emission tomography (PET) is an imaging modality with high diagnostic accuracy for the detection of MPNST (72-94% specificity), as MPNST are likely to be FDG-avid with increased semi-quantitative values such as standard uptake value (SUV).[49] However, there is the risk of false positive results, as AN/ANNUBP frequently have increased uptake of FDG on PET and benign PN can have varied FDG uptake. Thus, biopsy may be needed to confirm the histology in tumors with high FDG uptake. Further, differences in machinery and software can impact the quantitative analysis of markers (i.e., SUV), thereby limiting comparability between imaging centers. Advanced MRI techniques such as diffusion weighted and dynamic contrast enhanced sequences for the detection of MPNST have been evaluated at a small number of institutions and are promising.[44, 50] Anatomic imaging features associated with poor prognosis include tumor size greater than 5 cm, deep location, and metastatic disease.[51] MPNST most commonly metastasizes to the lung, brain, and bone. Upon histologic diagnosis of MPNST, CT chest should be obtained in addition to full body PET.

Though pathologic confirmation is required for the diagnosis of MPNST, the detection of MPNST within a PN can be challenging given the risk of sampling error and tumor heterogeneity. Despite the lack of a single immunohistochemical test to define malignancy in this spectrum of nerve sheath tumors, molecular analysis, in addition to histologic evaluation, may support the diagnosis of atypical PN versus MPNST. Molecular analyses of MPNST in both mouse models and patients demonstrate recurrent copy number alterations in p16/*CDKN2A*, *TP53*, *EGFR,* and polycomb repressor complex components *SUZ12* and *EED* and gains of chromosome 8q, in addition to *NF1* loss.[52-55] *SUZ12* has been identified to have an essential role in the malignant transformation of PN to MPNST, as inactivating mutations of *SUZ12* are exclusively identified in MPNST and not PN. Moreover, MPNST mouse models with germline inactivating mutations in *Nf1*, *Suz12* and *Tp53* cause a marked reduction in latency of MPNST onset compared to *Nf1*-*Tp53* mutant mice.[52, 54] While loss of *CDKN2A* is frequently observed in MPNST, it can also be detected in atypical PN; thus while it is a potential indicator of early malignant change, it is insufficient to diagnose a malignant lesion. Further, mutations in the polycomb repressor complex components induce a loss of trimethylation at lysine 27 of histone 3 (H3K27me3); thus, a lack of immunohistological staining for H3K27me3 has been used to distinguish MPNSTs from histologic mimetics.[56] Given the aforementioned findings, peripheral nerve tumors in patients with NF1 expressing alterations in any of these genes should heighten the suspicion for the diagnosis of MPNST.

Given the limitations of pathologic sampling and the impact of early diagnosis on prognosis, analysis of circulating tumor DNA (ctDNA) is a potential promising mechanism for both diagnosis and disease surveillance in MPNST. In other sarcomas, such as rhabdomyosarcoma, ctDNA concentrations have shown to reliably correlate with both the initiation of chemotherapy and subsequent progression or relapse.[57] Recent studies have advanced the understanding of ctDNA for MPNST. In a cross-sectional analysis of subjects with either PN or MPNST, circulating free

DNA (cfDNA) from patients with MPNST demonstrated shorter fragmentation profiles compared to patients with PN. cfDNA from patients with MPNST also demonstrated copy number alterations associated with malignant transformation, allowing reliable and accurate discrimination of MPNST from PN.[58] Thus, while surgical biopsy is currently the gold standard for diagnosis, serial ctDNA surveillance for prevalent copy number variations of MPNST ("liquid biopsy") may represent a future diagnostic strategy potentially allowing for earlier diagnosis, intervention and ultimately improved outcomes.

Gross total surgical resection with wide negative margins is the gold standard intervention for MPNST, as tumors with an incomplete resection have worse outcomes.[48] The benefits of chemotherapy for MPNST remain undetermined, as these tumors have historically demonstrated poor to intermediate sensitivity to classic chemotherapy agents. In the prospective trial of upfront chemotherapy for unresectable or metastatic MPNST (SARC006), only 17% (5/29) of subjects with NF1-associated MPNST demonstrated an objective response.[59] However, in spite of suboptimal response rates, adjuvant conventional chemotherapies, such as doxorubicin-based regimens, are often used in an attempt to reduce tumor burden prior to surgical resection and for the treatment of potential undetected micro-metastases.[60] Despite debate over the role of adjuvant radiation therapy for MPNST, radiation is commonly utilized prior to surgical resection or for MPNST with high-risk features such as incomplete resection.

Preclinical drug screening studies in genetically engineered MPNST mouse models have yet to identify effective precision-based therapies for MPNST. Despite promising preclinical findings, no responses were observed in a recent phase 2 study of ganetespib (small molecule inhibitor of Hsp90) and sirolimus (mTOR inhibitor).[61, 62] In addition, a phase 2 study of everolimus (mTOR) and bevacizumab (SARC016) demonstrated a clinical benefit rate of 12% (3/25) and was not considered an active therapy in MPNST.[63] There have been additional studies of targeted agents based on promising preclinical data with similarly disappointing therapeutic outcomes, including erlotinib (EGFR) and imatinib (c-KIT, PDGFR, VEGFR).[64] Additional, novel targeted therapies for MPNST based on preclinical mouse models are presently under evaluation in clinical trials, including a combination of selumetinib (MEK inhibitor) and sirolimus (mTOR inhibitor; NCT03433183). Immunotherapies have also been explored or are under investigation, including a phase 2 study of nivolumab and ipilimumab (NCT02834013) and a phase 1 trial of EGFR-specific chimeric antigen receptor T cells (NCT03618381). In summary, given the lack of effective therapies for MPNST, all efforts should be made to diagnose promptly and achieve gross total resection with wide negative margins.

Neurofibromatosis Type 2/*NF2*-Related Schwannomatosis

Neurofibromatosis type 2 is a tumor predisposition syndrome characterized by the development of bilateral vestibular schwannomas. Given the overlapping clinical features between patients with NF2 and schwannomatosis, revised nomenclature was recently introduced with "*NF2*-related schwannomatosis (*NF2*-SWN)" replacing neurofibromatosis type 2.[65] In addition, expert consensus provided updated clinical and genetic diagnostic criteria for *NF2*-SWN (see Table 2). The revised criteria incorporate molecular information in addition to clinical features. *NF2*-related SWN is caused by an autosomal dominant loss of function mutation in the *NF2* gene, located on chromosome 22q12. Mutations in *NF2* result in loss of production of the tumor suppressor protein merlin, that functions in multiple signaling pathways including the phosphoinositol-3 kinase (PI3K)/Akt/mTOR and Raf/MEK/ERK. Approximately half of cases result from inherited pathogenic mutations, with the remaining occurring *de novo*. *NF2*-related SWN typically presents in adulthood, however nearly 18% of patients are diagnosed at less than 15 years of age, with earlier presentation associated with poorer prognosis.[66, 67] Genotype-phenotype associations have been described in *NF2*-related SWN, with truncating (frameshift or nonsense) mutations typically causing more severe phenotypes.[68]

Diagnosis and Management of Tumors Associated with *NF2*-Related Schwannomatosis

Vestibular Schwannoma

Schwannomas are slow-growing, benign tumors composed of neoplastic Schwann cells. The most common tumor in patients with *NF2*-related SWN is the vestibular schwannoma (VS), which arises from the vestibular branches of the vestibulocochlear nerve (Fig. 4.). Over 95% of people with *NF2*-related SWN develop VS; most patients present with hearing loss and tinnitus, and profound hearing loss is a significant complication. Patients may also develop cranial nerve palsies in the setting of brainstem compression due to mass effect. MRI is the preferred diagnostic modality: VS

typically appear isointense on T1-weighted and heterogeneously intense on T2-weighted images and are enhancing on post-gadolinium T1 sequences.[69]

The management of VS may include observation, surgery, radiation, and/or chemotherapy such as bevacizumab. Surgical intervention is usually considered in the setting of tumor progression in a patient with prior loss of hearing or brainstem compression, or as a hearing preservation surgery. However, in both pediatric and adult populations, there is no consensus or evidence-based guidelines for surgical intervention, as functional deficits such as hearing loss do not consistently correlate with tumor burden. In general, tumors less than 3 centimeters in size in adult patients may be monitored for radiographic growth and/or change in hearing. The risks of surgical resection include further hearing loss or deafness, tinnitus or exacerbation of existing symptoms, and facial nerve damage; therefore, the benefits and risks of surgery must be considered while incorporating factors such as patient age, hearing status, neurologic status, and size of tumor. Surgical intervention is typically indicated for VS if the patient develops obstructive hydrocephalus or brainstem dysfunction due to mass effect, regardless of tumor size.[70] To date, recommendations for surgical intervention based on tumor size have not been proposed for pediatric patients. Unfortunately, surgical outcomes of NF2-associated VS are inferior to those of sporadic VS. Prior studies incorporating imaging, pathologic, and molecular findings suggest that NF2-associated VS represent a collision of multiple, distinct tumors forming a larger, polyclonal, multilobulated mass.[71] It is hypothesized that this complex tumor conglomeration increases the risk of surgical morbidity, resulting in poorer outcomes in patients with *NF2*-VS. Further, stereotactic radiosurgery is commonly used for sporadic vestibular schwannomas; however, use is less frequent in NF2-associated tumors. Despite achieving high tumor control, radiation-based surgical therapies are associated with poor hearing outcomes and cranial nerve injuries.[72] In addition, as with other tumor predisposition syndromes, radiation therapy carries significant risks in patients with *NF2*-related SWN, such as secondary malignancies, vascular complications, and ipsilateral hearing loss; thus, utilization of radiation therapy in children with *NF2*-related SWN should be deferred if feasible.[73]

Effective systemic chemotherapies for VS are lacking. Bevacizumab is a non-FDA approved therapy for VS which has resulted in a reduction of tumor volume in 32-43% and hearing improvement in 36-45% of patients with *NF2*-related SWN.[74-76] Hearing improvement and objective tumor response appear to be less common in children than adults across multiple studies, yet despite these findings, pediatric patients may experience some clinical benefit from bevacizumab, such as improvement in tinnitus, quality of life measures, and stabilization of disease.[74, 76]

Prior clinical trials exploring the use of lapatinib, sorafenib, and everolimus for VS have not demonstrated significant improvements in hearing. Lapatinib, an inhibitor of EGFR and Erb2, was explored as a potential agent due to the expression of both EGFR and Erb2 in VS. In a single institution phase 2 trial of lapatinib for adults and pediatric patients with progressive NF2-VS, only 23.5% of subjects (4/17) demonstrated tumor response and 30% (4/13) had improvement in hearing.[77] These outcomes are considered inferior to bevacizumab; however, combination studies of lapatinib and bevacizumab may be investigated in the future. Studies of other targeted medical therapies are ongoing, with several studies evaluating focal adhesion kinase 1 inhibitors based on promising efficacy in preclinical models, [78, 79] including a Neurofibromatosis Clinical Trials Consortium study of crizotinib (NCT04283669) and a multi-institutional trial of brigatinib (NCT04374305). In addition, based on preclinical data demonstrating decreased schwannoma growth in NF2 transgenic mice with MEK inhibition, a phase 2 trial of selumetinib for progressive NF2 tumors is ongoing (NCT03095248).[80]

Non-Vestibular Schwannoma

Non-vestibular schwannomas are common in *NF2*-related SWN and can arise from the cranial nerves and peripheral nerves and nerve roots. Observation is the initial preferred management of these tumors. If schwannoma are progressive or symptomatic, surgery is the primary therapeutic approach, with avoidance of radiation due to risk of secondary malignancy. As with VS, there is a lack of effective systemic therapies, with a relative paucity of actively enrolling or upcoming clinical trials when compared to NF1-associated tumors.[81] Platform-basket trial designs with designated arms for non-vestibular schwannoma, such as the current study of brigatinib (NCT04374305), will likely facilitate a more rapid assessment of novel treatments for NF2-associated tumors.

Meningioma

Meningiomas arise from the meninges surrounding the brain and spinal cord and are the second most common tumor occurring in patients with *NF2*-related SWN. Intracranial meningiomas occur in over half of adults with NF2, with spinal meningiomas diagnosed in up to 20% of patients. Meningiomas are typically slow growing, low-grade tumors; however, they can also be higher grade and more aggressive lesions. The clinical presentation ranges from asymptomatic to neurologic deficits such as cranial nerve dysfunction, headaches, or seizure.[42] The primary intervention for symptomatic or growing intracranial meningioma is surgical resection. Asymptomatic meningioma may be observed, however the appearance of peri-tumoral edema on imaging may suggest a more aggressive tumor and should prompt expedited surgical evaluation. The optimal timing of resection for spinal meningioma is unknown; however, intervention prior to the onset symptoms may be considered to prevent irreversible neurologic deficits. As with VS, effective medical therapies for meningioma are limited. Anti-angiogenic agents such as bevacizumab have demonstrated variable and limited activity in small and non-randomized studies.[82] In a recent study of AZD2014 (NCT02831257), a dual mTORC1/mTORC2 inhibitor, there was significant withdrawal of subjects (67%) prior to completion of protocol therapy due to intolerable toxicities, thereby limiting the use of this agent. In the study of lapatinib for NF2-VS, there was a subset of patients who also had a meningioma. In these subjects, there was no imaging response of the meningioma to lapatinib. In fact, many of the meningiomas continued to progress while on therapy, with 2 subjects requiring interruption of therapy for surgical resection of progressive meningioma. Ongoing prospective studies of medical therapies for NF2-associated meningioma include basket trials of brigatinib (NCT04374305) and selumetinib (NCT03095248), as well a study evaluating the efficacy and safety of a pan-histone deacetylase inhibitor (REC 2282) for *NF2*-mutated meningioma (NCT05130866).[83] Radiation therapy is typically used only for atypical, anaplastic, or multiply recurrent meningioma due to the risk of secondary malignancy.[70]

Ependymoma

Ependymomas arise from neoplastic ependymal cells of the ventricles and spinal cord. Up to half of patients with *NF2*-related SWN will be diagnosed with spinal or intracranial ependymoma, with most tumors occurring along the cervical spinal cord or cervico-medullary junction. While less common, most intracranial ependymomas in NF2 are classic histology (WHO grade II) and may present at a younger age than spinal ependymoma.[84] The standard of care for intracranial ependymoma in pediatric patients is best possible resection followed by radiation therapy. There is an ongoing Children's Oncology Group study evaluating maintenance chemotherapy after radiation, but it is unclear yet whether this approach will improve outcomes for all or a subset of patients. It is also unknown if the results of this study will apply to the population of patients with NF2-associated ependymoma.

NF2-related spinal ependymoma may be myxopapillary, subependymal (WHO grade I) or classic histology (WHO grade II), can have large cystic components, and typically exhibit an indolent growth pattern. The management of NF2-associated spinal ependymomas has historically been conservative with radiographic surveillance due to risk of surgical morbidity.[85] Spinal ependymomas ultimately result in symptoms in approximately 30% of patients, and symptomatic tumors or those with progressive growth should be considered for excision.[86] Medical therapies for spinal ependymoma are also lacking. Bevacizumab has been reported to be a potential treatment for patients with spinal ependymoma, particularly those with cystic tumors. Small studies have reported improvement in clinical symptoms such as ataxia and sensory deficits and reduction in the cystic component of tumor; however, objective reduction in tumor burden has not been consistently observed.[87, 88] Radiation therapy is typically reserved for recurrent, progressive tumors not amenable to resection.

In summary, there have been significant advances in the management of neurofibromatosis associated tumors in the last 30 years, with an acceleration in the development and identification of effective therapies in the past decade. With ongoing advancements in preclinical models of NF-associated tumors and larger, collaborative clinical trials through the NF Clinical Trials Consortium, there exists an even greater opportunity to discover highly effective and tolerable therapies for nervous system tumors associated with neurofibromatosis type 1 and *NF2*-related schwannomatosis.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Chelsea Kotch drafted and wrote the manuscript. Stephanie N Brosius, Thomas De Raedt, and Michael J Fisher revised the manuscript critically for intellectual content. All authors have given final approval of the version to be published.

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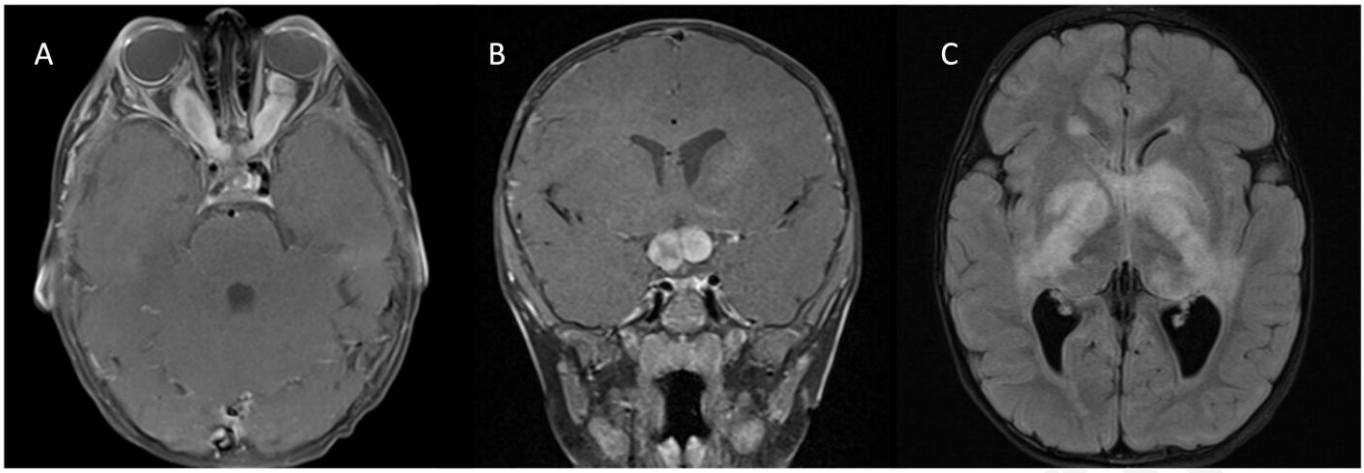
Figure Legends

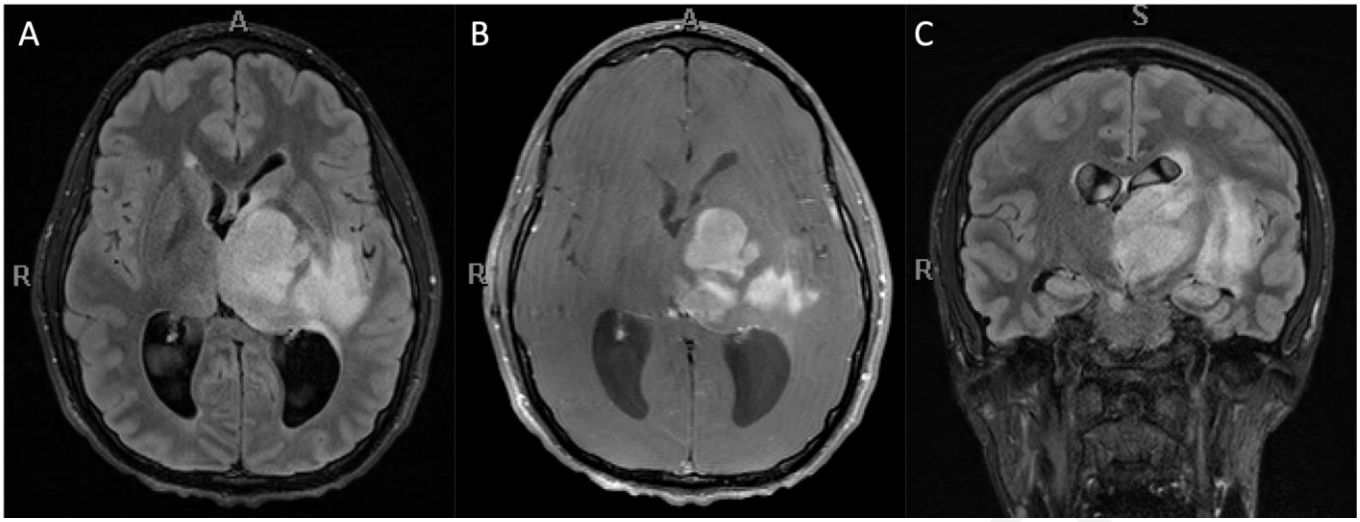
Fig. 1. Bilateral optic pathway glioma in a pediatric patient with neurofibromatosis type 1. Involvement of optic nerves is visualized on axial T1 post-gadolinium (A), chiasm/hypothalamus on coronal T1 post-gadolinium with fat suppression (B) and optic tract/radiations on axial T2 fluid attenuated inversion recovery (C) magnetic resonance sequences.

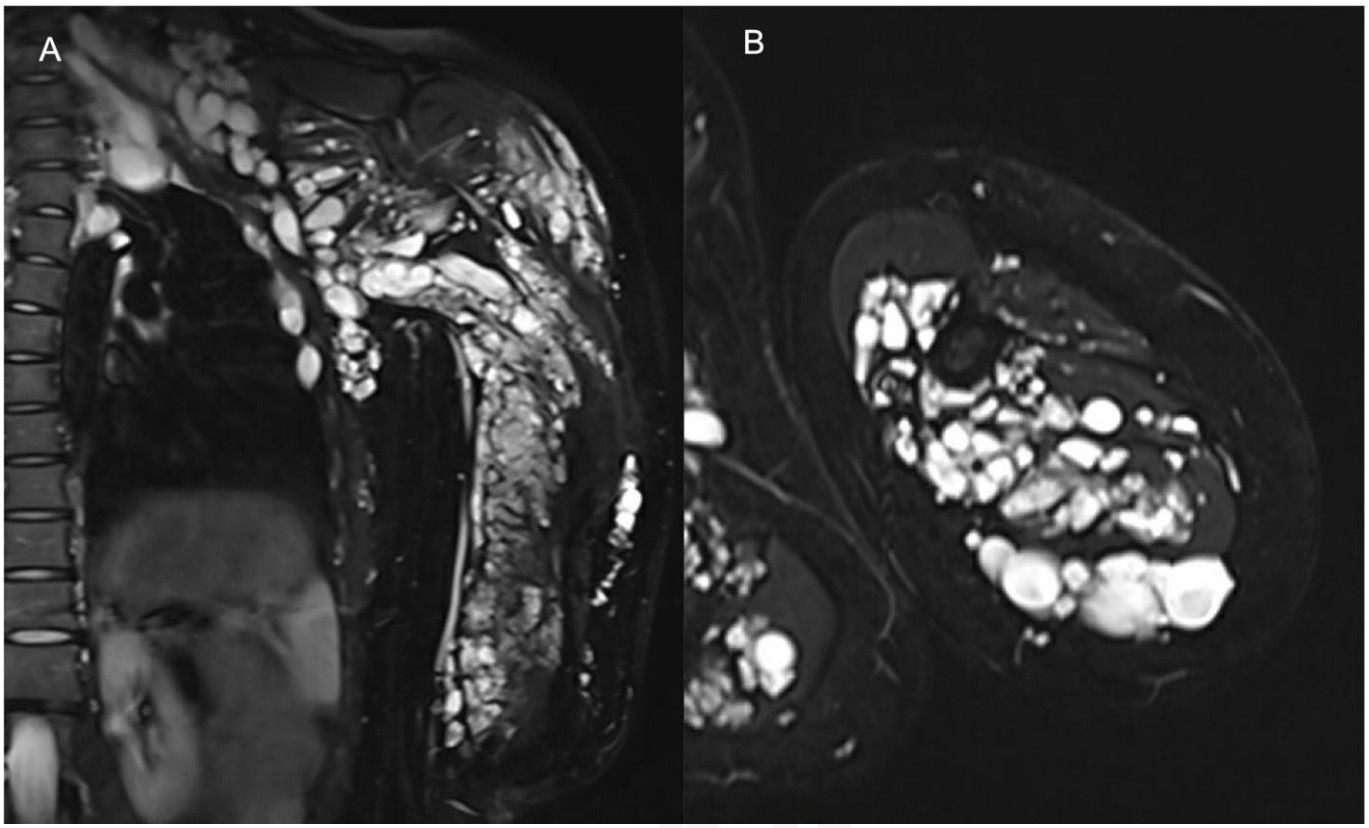
Fig. 2. Large neurofibromatosis type 1-associated high grade glioma of the left thalamus in an adolescent patient with heterogenous T2 hyperintensity (A) and post-gadolinium enhancement (B) on axial magnetic resonance imaging sequences, expanding the thalamus with adjacent extension causing midline shift (C) and dilation of the lateral ventricles.

Fig. 3. Plexiform neurofibroma of the neck, upper chest, and left upper extremity shown on coronal (A) and axial (B) T2-weighted short tau inversion recovery magnetic resonance sequences.

Fig. 4. Bilateral vestibular schwannoma in a pediatric patient with neurofibromatosis type 2 visualized on magnetic resonance imaging (axial T2 turbo inversion recovery magnitude (A) and coronal T1 post-gadolinium (B))







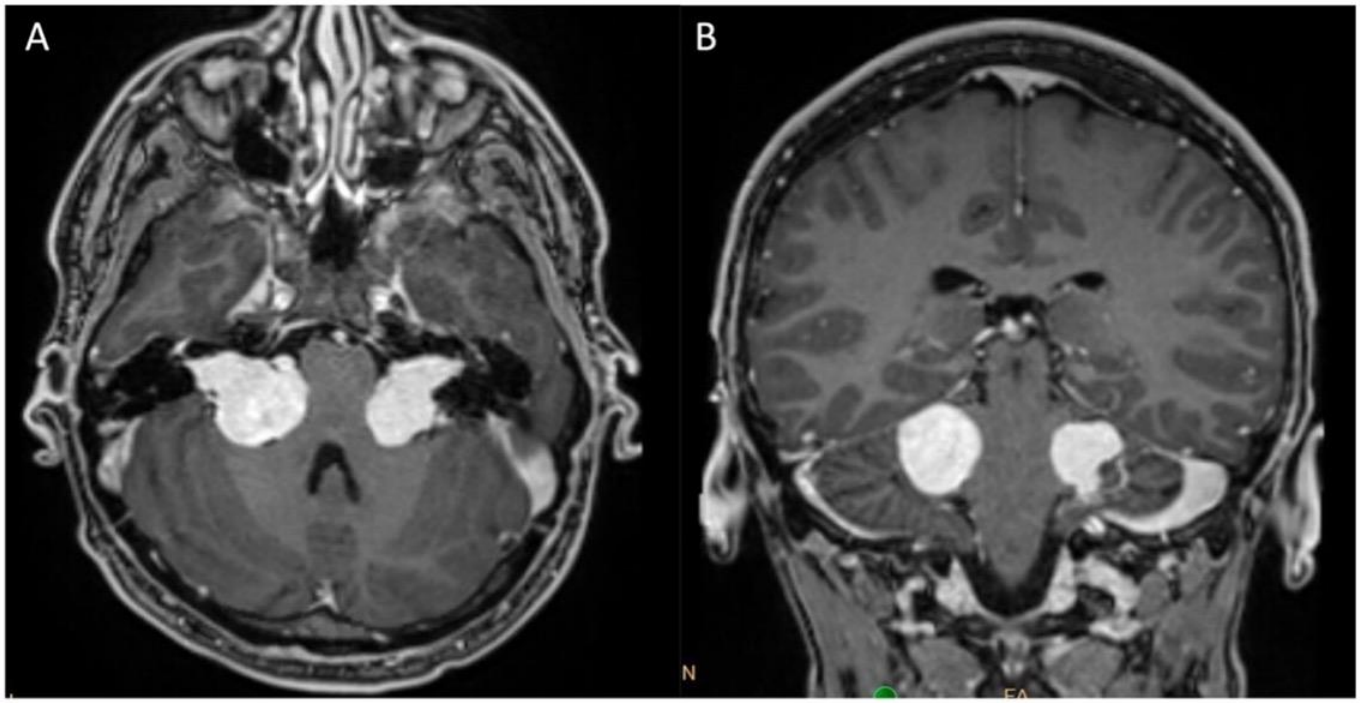


Table 1. Diagnostic Criteria for Neurofibromatosis Type 1

2 or more of the following findings in a child who does not have a parent with NF1 OR 1 or more in the child of a parent who meets diagnostic criteria for NF1:
• 6 or more café-au-lait macules > 5mm in diameter in prepubertal patients and >15mm in post-pubertal patients
• Freckling in axillary or inguinal region
• 2 or more neurofibromas of any type or 1 plexiform neurofibroma
• Optic pathway glioma
• >=2 iris Lisch nodules or >=2 choroidal abnormalities
• Osseous lesion (sphenoid dysplasia, pseudarthrosis of long bone, tibial bowing)
• Heterozygous pathogenic NF1 variant with variant allele fraction of 50% in normal tissue

*Adapted from Legius et al (2021) [3]

Table 2. NF2-related Schwannomatosis Revised Diagnostic Criteria

A diagnosis of NF2-related SWN may be made with one of the following: • Bilateral vestibular schwannomas • At least 2 anatomically distinct NF2-related tumors (schwannoma, meningioma, ependymoma) expressing an identical NF2 pathogenic variant • Either 2 major or 1 major and 2 minor criteria
Major criteria: • Unilateral VS • First-degree relative other than sibling with NF2-related schwannomatosis • 2 or more meningiomas • Pathogenic *NF2* gene variant in blood (or unaffected tissue)
Minor Criteria: • Ependymoma, meningioma, schwannoma (e.g., 2 distinct schwannomas in dermal location would count as 2 minor criteria) • Juvenile subcapsular or cortical cataract, retinal hamartoma, epiretinal membrane in patient < 40 years of age (bilateral findings such as bilateral cataracts count as single minor criterion)

*Adapted from Plotkin et al (2022) [61]