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Cancer and Central Nervous System Tumor Surveillance in Pediatric Neurofibromatosis 2 and Related Disorders

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Abstract

The neurofibromatoses consist of at least three autosomal-dominant inherited disorders: neurofibromatosis type 1 (NF1), neurofibromatosis type 2 (NF2), and schwannomatosis. For over 80 years, these conditions were inextricably tied together under generalized neurofibromatosis. In 1987, the localization of NF1 to chromosome 17q and NF2 (bilateral vestibular schwannoma) to 22q led to a consensus conference at Bethesda, Maryland. The two main neurofibromatoses, NF1 and NF2, were formally separated. More recently, the *SMARCB1* and *LZTR1* genes on 22q have been confirmed as causing a subset of schwannomatosis. The last 26 years have seen a great improvement in understanding of the clinical and molecular features of these conditions as well as insights into management. Childhood presentation of NF2 (often with meningioma) in particular predicts a severe multitumor disease course. Malignancy is rare in NF2, particularly in childhood; however, there are substantial risks from benign and low-grade central nervous system (CNS) tumors necessitating MRI surveillance to optimize management. At least annual brain MRI, including high-resolution images through the auditory meatus, and a clinical examination and auditory assessment are required from diagnosis or from around 10 to 12 years of age if asymptomatic. Spinal imaging at baseline and every 2 to 3 years is advised with more frequent imaging if warranted on the basis of sites of tumor involvement. The malignancy risk in schwannomatosis is not well defined but may include an increased risk of malignant peripheral nerve sheath tumor in *SMARCB1*. Imaging protocols are also proposed for *SMARCB1* and *LZTR1* schwannomatosis and *SMARCE1*-related meningioma predisposition. *Clin Cancer Res; 23(12); e54–e61. ©2017 AACR.*

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Introduction

Neurofibromatosis type 2 (NF2) is an autosomal-dominant monogenic condition caused by mutations in the NF2 gene on chromosome 22q (1, 2). NF2 predisposes to the development of benign nerve sheath tumors that are predominantly schwannomas, meningiomas, and low-grade ependymomas. Recently, a number of related disorders have been characterized with schwannomatosis caused by mutations in *SMARCB1* (3) and *LZTR1* (4) and a predisposition to brain and spinal meningiomas caused by mutations in *SMARCE1* (5). Recommendations for tumor surveillance of gene carriers and members of syndromic families are based upon review of the literature and discussion in the 2016 AACR Childhood Cancer Predisposition Workshop.

NF2

The hallmark of NF2 is the development of bilateral often multifocal eighth cranial nerve schwannomas leading to hearing loss and balance disturbance (Fig. 1A). These predominantly occur on the vestibular branches compressing the cochlear nerve (6, 7). Schwannomas often occur on other cranial nerves except the olfactory and optic nerves, with the greatest deficit perhaps caused by lower cranial nerve involvement (8). Schwannomas also occur on other spinal and peripheral nerve roots, and there are also characteristic "plaque"-like intracutaneous schwannomas that do not appear to occur either in schwannomatosis or sporadically (2, 9, 10). Meningiomas, which are predominantly fibroblastic or atypical, occur throughout the neuroaxis and are associated with increased mortality (11, 12). Intraspinal, low-grade ependymomas also occur and are generally indolent despite their appearances on MRI (9). NF2 typically presents in adulthood with hearing loss and tinnitus (2, 9). However, in childhood, symptoms may first occur due to an apparently isolated

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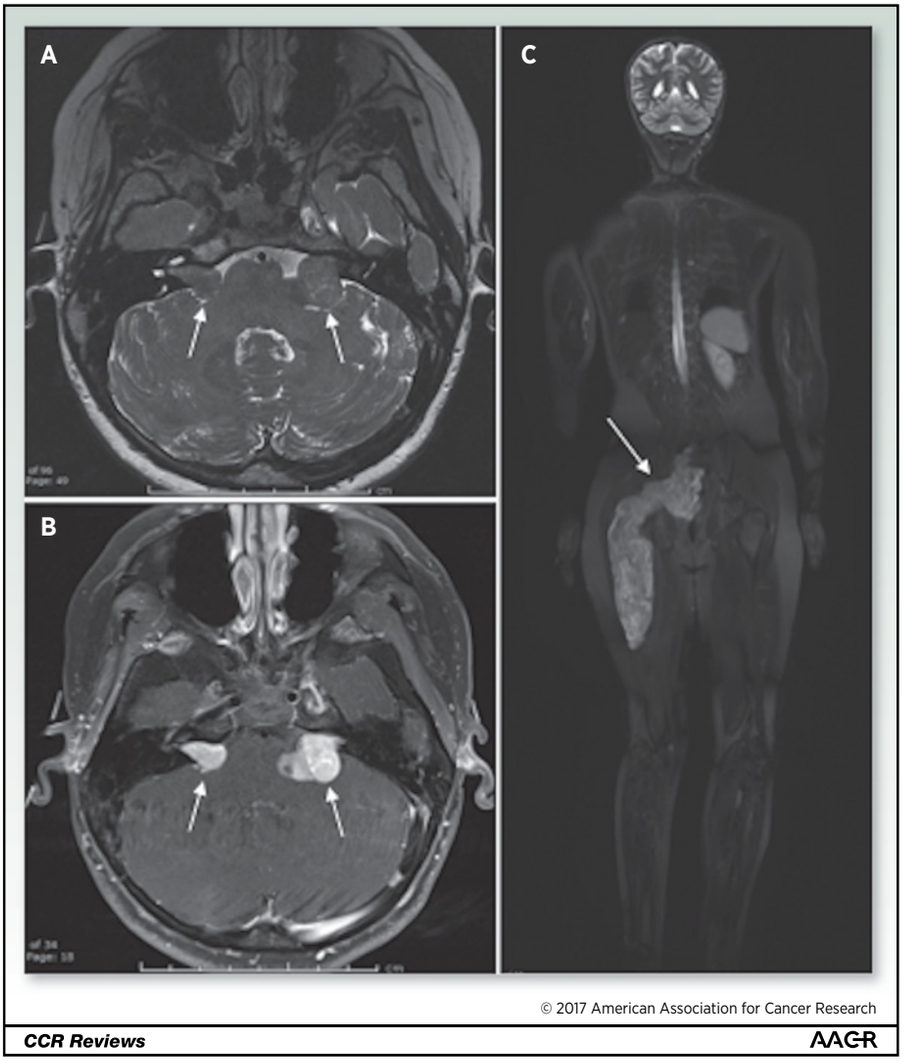

Figure 1.
Characteristic imaging findings in a 12-year-old female patient with NF2. **A** and **B,** Axial FSE-T2 (**A**) and post-gadolinium–enhanced fat-suppressed T1-weighted images (**B**) through the internal auditory canals show bilateral vestibular schwannomas (arrows) with characteristic heterogeneous T2 signal and avid contrast enhancement. **C,** This same patient with NF2 also had extensive peripheral schwannomas, with whole-brain MRI showing extensive schwannomatous involvement of sacral nerve roots and sciatic nerve (arrow).

meningioma or non-cranial schwannoma (13, 14). Children may also present first with a mononeuropathy affecting the seventh and fourth through sixth nerves or a foot drop or wrist drop secondary to sacral nerve root or lower cervical nerve root/brachial plexus involvement, respectively, although definite tumor disease may not be present on MRI scan. These often leave a deficit, even though at least partial recovery is common (13, 14). Presentation with ocular features, such as retinal hamartoma and cataract, are also not infrequent. The Manchester (modified NIH) diagnostic criteria for NF2 are shown in Table 1. The original NIH criteria (1) were expanded to include patients with no family history who have multiple schwannomas and or meningiomas, but who have yet to develop bilateral eighth nerve tumors. These criteria have been shown to be more sensitive (15), but a newer points-based system has also been developed that may improve sensitivity in childhood (16). Indeed, the first sign of more severe multitumor disease in early childhood is often a non-eighth nerve tumor (13, 14). This has been reemphasized by a study of 53 pediatric patients with meningiomas (17), in which five unsuspected cases of NF2 were uncovered in addition to the nine already known, giving a frequency of 14/33 (42%) of the meningioma series. A little over 50% of NF2-affected individuals present without a family history, and about a third of these are mosaic for the NF2 mutation, as it is present only in a subset of cells, with the initial mutation occurring during embryogenesis (18–20). Indeed, around 63% of NF2 diagnosed in patients <20 years is *de novo* (230/337; Manchester; unpublished data). The remainder has inherited NF2 from an affected parent, with a usual 50% recurrence risk for subsequent offspring (9). Around 30% of NF2,

Table 1. Manchester diagnostic criteria for NF2 (these include the NIH criteria with additional criteria; refs. 1, 2)

Bilateral vestibular schwannomas (VS) *or* family history of NF2 *plus*
1) Unilateral VS *or*
2) Any two of: meningioma, glioma,[a] neurofibroma, schwannoma, posterior subcapsular lenticular opacities
Additional criteria: Unilateral VS *plus* any two of: meningioma, glioma, neurofibroma, schwannoma, and posterior subcapsular opacities
Or
Multiple meningioma (two or more) *plus* unilateral VS *or* any two of: glioma, neurofibroma, schwannoma, and cataract

NOTE: "Any two of" refers to individual tumors or cataract, not to tumor types.
[a]Usually spinal cord ependymoma.

Table 2. Childhood tumor risks to age 16 years in NF2

	Chances of symptomatic tumor	Likelihood of finding tumor on MRI	Adult risk
Vestibular schwannoma	25%	~70%–80%	100%
Other cranial schwannoma	<1%	~20%	40%
Meningioma	10%	15%–20%	70%
Ependymoma	0.2%–0.5%	~10%	25%

presents symptomatically in childhood and nearly 50% by 20 years of age (refs. 2, 9, 13, 21; Table 2). There is virtual complete penetrance of NF2, although some mild mutations may mean that individuals in some families may die with hearing loss having never been diagnosed with the condition (22).

Genetics of NF2

NF2 is caused by loss-of-function mutations in the *NF2* tumor suppressor gene on chromosome 22q (23, 24). The gene contains 17 exons spread over 110 kb. It produces two major mRNA and protein isoforms (also called MERLIN) by alternative splicing. Protein isoform 1 is 595 amino acids produced from exons 1 through 15 and exon 17, whereas the inclusion of alternatively spliced exon 16 alters the C terminus of the protein, replacing 16 amino acids with 11 novel residues (isoform 2). Pathogenic variants have not been identified in the alternatively spliced exons. The gene is expressed at high levels during embryonic development, whereas in adults, high expression is found in Schwann cells, meningeal cells, lens, and nerve. Tumors in NF2 are caused by loss of function of the remaining normal copy of the gene, fulfilling Knudson's two-hit hypothesis, although further mutational events are probably required to drive tumorigenesis (25). In the United Kingdom, large population-based estimates of birth incidence for NF2 showed that between one in 25,000 to 33,000 people would be born with a mutation in the *NF2* gene (20, 26, 27). Overall diagnostic disease prevalence is around one in 56,000 (about 10 times more rare than NF1, and as in NF1, prevalence is lower than incidence due to early death and later age at diagnosis) and would be less than one in 150,000 in children due to later age at presentation with symptoms. Risk of transmission is 50% if the parent has inherited NF2 from an affected parent, as the mutation will be in all their cells. However, due to the high rate of mosaicism, there can be less than a 5% chance of transmission if the affected individual has a *de novo* mosaic point mutation not identifiable in lymphocyte DNA on Sanger sequencing, even if they fulfill classical criteria (19).

Genotype–phenotype correlations

Large studies have determined genotype–phenotype correlations with truncating mutations conferring a more severe disease course than missense mutations, splice site mutations, or large deletions (12, 28–34). The position of the mutation also correlates with mutations in the 3′ end of the gene (exons 14/15) being associated with fewer meningiomas (34) and lower mortality (12).

Many mildly affected individuals have mosaic disease, and children presenting asymmetrically should still be suspected of this (20). Although mosaicism is less frequent in childhood, it still occurs even in a classically affected individual. Indeed of 230 *de novo* NF2 cases diagnosed with the condition, 36 (15.5%) had proven mosaicism with a further 24 (10.5%) having no mutation identified on blood analysis (Manchester; unpublished data). Mosaicism may account for the milder disease course in many individuals with unfound mutations. However, mosaic mutations tend to be more likely to be the more severe mutations and less likely to be milder missense variants (35). The risk of transmitting to the next generation will be dependent on the proportion of germinal cells affected. However, if an offspring has inherited the mutation, they will be more severely affected than their parent, as the offspring will carry the mutation in all of their cells.

Apart from mosaicism, the nature of the mutation itself is associated with varying degrees of severity with regard to age of onset and number of tumors.

- Severe (early onset, multiple tumor disease, early death):

Truncating mutations in exons 2 through 13

- Moderately severe: large deletions, splicing mutations exons 1–6
- Moderate: exon 1 truncating; splicing 7 through 15, mosaic for truncating (2–13) in blood
- Mild [late onset, often only vestibular schwannoma (VS)]: missense, mosaic not present in blood

NF2-Related Disorders

Schwannomatosis is characterized by multiple, usually painful peripheral and spinal nerve schwannomas, and most familial cases are caused by mutations in either *SMARCB1* (3) or *LZTR1* (4, 36, 37). SMARCB1-related schwannomatosis has clear genotype–phenotype correlations, with rhabdoid tumor disease with rhabdoid tumor being caused by clear loss-of-function mutations and schwannomatosis by hypomorphic mutations (38). This is exemplified by the staining pattern on IHC in the schwannomas being mosaic for SMARCB1 protein in schwannomatosis and with total loss in rhabdoid tumor. There have been occasional families reported with both tumor types, but these are rare. Meningiomas have also been described in SMARCB1 schwannomatosis, but these are uncommon. Unfortunately, there does appear to be a malignancy risk in SMARCB1 schwannomatosis, with malignant peripheral nerve sheath tumors being reported in a number of individuals (39). LZTR1 schwannomatosis has not yet been clearly linked to the risk of other tumors but has now been clearly shown to cause VS (36, 40) and, thus, results in substantial overlap with the Manchester criteria for NF2 (Table 1). Individuals with a unilateral VS and at least two other noncutaneous schwannomas are at least as likely to carry a constitutional mutation in *LZTR1* as an NF2 mutation (40). Both SMARCB1- and LZTR1-related schwannomatosis can present in childhood with an isolated schwannoma and should be suspected in addition to NF2. Genetic testing revealed that 30 of 155 (19%) isolated schwannoma patients aged <25 years had a germline *NF2* mutation, seven people had a germline *SMARCB1* (5%) mutation, and 10 (6%) had a germline *LZTR1* mutation (41). Likewise, a predisposition to clear cell brain and spinal meningiomas caused by mutations in the *SMARCE1* gene (5) can cause an apparently isolated childhood meningioma, and 17% and 19%, respectively, of apparently isolated meningioma in patients <25 years had a germline *NF2* or *SMARCE1* mutation, respectively (40). Interestingly, *NF2*, *SMARCB1*, and *LTZR1* are all tumor suppressors that likely affect a common cytoplasmic signaling cascade that regulates such fundamental cellular processes as chromatin conformation, cell cycle, and proliferation. Thus, when these genes are mutated, either somatically or constitutionally, key events

are perturbed and lead to the development of schwannomas. Schwannomas caused by germline *SMARCB1* or *LZTR1* mutations almost universally show a "three event, four hit" process involving loss of chromosome 22q (and the wild-type copy of *SMARCB1*/*LZTR1* as well as one copy of *NF2*) and a point mutation in *NF2* in the same chromosome arm as the germline *SMARCB1*/*LZTR1* mutation (3, 4, 36–38).

Cancer/Tumor Screening/Surveillance Protocols

Initial diagnostic evaluation

There are several groups of individuals who should be considered at risk of NF2 and investigated further. These groups include those with a family history of NF2, children presenting with a unilateral VS, other cranial spinal or peripheral nerve schwannoma or meningioma, cutaneous schwannomas, or retinal hamartoma. MRI scanning is vital in their further assessment (42).

Clinical assessment. Although cutaneous features are useful in diagnosis, skin features in NF2 are much more subtle than in NF1. About 70% of NF2 patients have skin tumors, but only 10% have more than 10 skin tumors (2). The tumors appear to be of at least three different types. The most frequent type is a plaque-like lesion, which is intracutaneous, slightly raised, and more pigmented than surrounding skin, often with excess hair (Fig. 2). More deep-seated subcutaneous nodular tumors can often be felt, sometimes on major peripheral nerves. These tumors often occur as a fusiform swelling of the nerve, with thickened nerve palpable on either side. There are also occasional intracutaneous tumors similar to those in NF1. The great majority of these tumors are schwannomas, but occasional definite neurofibromas do occur. Café au lait macules are more common in NF2 than the general population but will only rarely cause confusion with NF1. Ophthalmic examination by a specialized ophthalmologist is important in childhood, and assessment soon after birth may detect juvenile cortical wedge cataracts (and later posterior subcapsular opacities) and amblyopia that can affect vision. MRI with gadolinium enhancement will now detect tumors as small as 1 to 2 mm in diameter on cranial and spinal nerve roots. Many of the small spinal tumors will never lead to symptoms but may aid in diagnosis. Spinal MRI will detect evidence of spinal tumors in 70% to 90% of patients with NF2, although about 50% of children will not have spinal tumors at presentation, particularly if asymptomatic at diagnosis (Tables 1 and 2; refs. 42, 43).

Molecular testing. 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, although practically most clinics start with analysis of a blood sample. However, if negative, directed testing on blood DNA by next-generation sequencing of any point mutations found in tumor will assess low-level mosaic risk. In addition, those with an isolated noncutaneous schwannoma should be panel tested for *NF2*, *SMARCB1*, and *LZTR1*. Isolated meningiomas should also be tested for *SMARCE1* unless the histology is definitively not clear cell. DNA testing with sequencing and deletion analysis [often by performing multiple

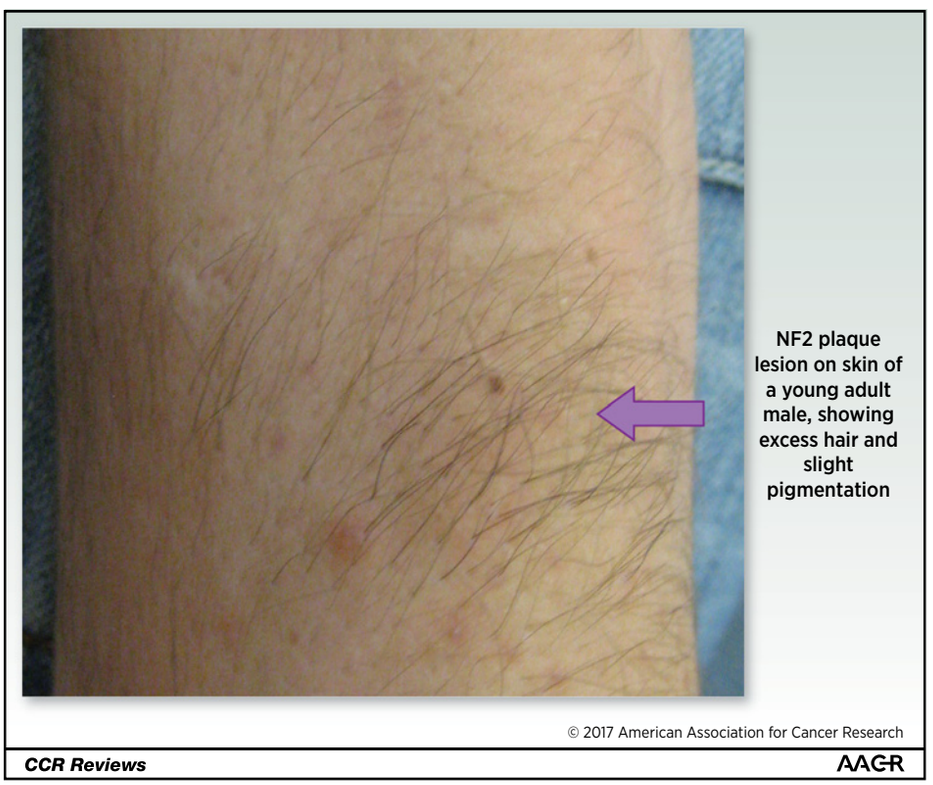

Figure 2.
NF2 plaque lesion on skin of forearm. Slightly raised, slightly pigmented, with excess hair typical of NF2. Clinical features of *NF2* (including diagnostic criteria).

Table 3. Expert recommendations for genetic testing and surveillance for NF2, schwannomatosis, and *SMARCE1*-related meningioma

NF2	
Genetic testing	1. 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. 2. Directed testing on blood DNA by next-generation sequencing of any point mutations found in tumor will assess low-level mosaic risk in sporadic cases.
Surveillance	1. Annual history and physical exam (including audiology with measurement of pure-tone thresholds and Word Recognition Scores). 2. Annual (consider twice yearly in first year since diagnosis or signs of rapid growth) brain MRI starting at 10 years of age. Screening may begin earlier in patients with high-risk genotypes or symptomatic diagnoses. 3. If baseline imaging shows no characteristic sites of involvement, reduce frequency of screening to every 2 years. 4. Protocols should include high-resolution (1–3 mm slice thickness) imaging through the internal auditory meatus, preferably in at least 2 orthogonal planes. 5. Surveillance spinal MRI is recommended at 24- to 36-month intervals beginning at 10 years of age. 6. Whole-body MRI may be obtained.
Schwannomatosis	
Genetic testing	1. Test for mutations in *SMARCB1* and *LZTR1* in children and young adults with one or more non-intradermal schwannoma, including those with VS negative for *NF2*.
Surveillance	1. *SMARCB1*—baseline MRI brain and spine at diagnosis, then every 2–3 years, beginning at age 10. Consider whole-body MRI and increasing surveillance frequency if symptomatic. 2. *LZTR1*—baseline MRI brain and spine at diagnosis, then every 2–3 years, beginning at age 15–19 years. Consider whole-body MRI and increasing surveillance frequency if symptomatic.
SMARCE1	
Surveillance	1. SMARCE1—baseline MRI brain and spine at diagnosis, then every 1–2 years until the age of 18, reducing frequency to once every 5 years if no tumors are identified. If tumor is detected, increase frequency of surveillance to every 2–3 years or more frequently if patients become symptomatic.

ligation–dependent probe amplification (MLPA)] detects 95% of mutations in NF2 in individuals from the second affected generation (10, 12, 20). Consideration should be given for cytogenetic tests in a child with NF2-related tumors who has significant learning difficulties and café au lait macules, as ring chromosome 22 cases [r(22)] have an increased risk of schwannomas and meningiomas due to mosaic loss of NF2 in the unstable ring (44). Even in the absence of a germline mutation, somatic mosaicism should be suspected and follow-up from diagnosis should include thorough physical examination on a 3 to 5 yearly basis until 35 to 40 years of age, accompanied by craniospinal MRI (36, 42, 43).

The timing for presymptomatic genetic tests in childhood has been for some years set at 10 to 12 years (42). The risk of symptomatic VS is very small prior to that age, and the tiny tumors often found earlier than 10 years appear to grow very slowly until puberty. Nonetheless, consideration should be given to testing children of those with a more severe genotype, especially with truncating mutations in exons 2 through 13, at an earlier age.

Surveillance

Surveillance protocol once NF2 is established. The following are recommended on the basis of expert opinion and previous publication (43).

1. Annual history and physical exam (including audiology with measurement of pure-tone thresholds and Word Recognition Scores).
2. Annual (consider twice yearly in first year since diagnosis or signs of rapid growth) brain MRI starting at 10 years of age. If baseline imaging shows no characteristic sites of involvement, reduce frequency of screening to every 2 years. Screening may begin earlier in patients with high-risk genotypes or symptomatic diagnoses. Protocols should include high-resolution (1–3 mm slice thickness) imaging through the internal auditory meatus, preferably in at least 2 orthogonal planes. NF2 lesions have variably increased T2 signal but characteristically show avid contrast enhancement (Fig. 1A and B; ref. 45), and imaging should include post-contrast sequences following infusion of gadolinium-based contrast agents (GBCA). Once a diagnosis has been made and lesions are identified by MRI, the first scan performed after diagnosis should be at 6 months to assess tumors' growth rate. Volumetric images (including T2-weighted and post-contrast imaging) should be acquired when assessing response to drug therapy. Although the lesions characteristic of NF2 can be detected by CT, particularly in the skull base, there is currently no role for routine CT-based surveillance in NF2.
3. Surveillance spinal MRI is recommended at 24- to 36-month intervals beginning at 10 years of age. The interval between scans may be increased if there is no disease detected on baseline imaging. As with brain MRI recommendations, once lesions are detected, the first scan after diagnosis should be at 6 months to evaluate tumor growth rate. For routine spinal MRI surveillance, contrast may be omitted unless patients are symptomatic or carry at-risk mutations such as *SMARCB1* or *LZTR1*. In practice, spinal MRI is often performed together with brain MRI, in which case post-contrast images of the spine are usually obtained.
4. Whole-body examinations may be obtained (Fig. 1C), including the brain and spine, depending on symptoms and known sites of disease. Although ^{18}F-FDG PET/CT can identify lesions with increased metabolic activity, there is insufficient evidence to recommend ^{18}F-PET/CT (or PET/MRI) for routine screening.

Management of NF2. NF2 presents complex management issues, and a child with NF2 should be managed by a multidisciplinary team consisting of a pediatric neurosurgeon, otolaryngologist, audiologist, neurologist, ophthalmologist, neuroradiologist, pediatric neuro-oncologist, and geneticist. An adult neurosurgeon specializing in NF2 is also usually involved. There is clear evidence of a mortality benefit (11, 12) with a significantly increased life expectancy for NF2 patients managed at three specialty centers in the United Kingdom [relative risk (RR), 0.3; 95% confidence interval (CI), 0.12–0.98; ref. 11]. This led to the national commissioning of four centers to cover NF2 in England in 2010 (population 53 million; ref. 46), with further improvements

in survival (12). It is important to balance the use of microsurgery and radiation treatment, which can have a role in patients who have particularly aggressive tumors, who are poor surgical risks, or who refuse surgery. Although, radiation treatment has received a great deal of attention and short-term results show good "tumor control," this has to be balanced against longer term risks such as malignancy, especially in childhood (47, 48), and the fact that tumors grow slowly and sometimes not at all for periods of time. Teams experienced in the positioning of brainstem implants can offer partial auditory rehabilitation to those who are deaf, although results are still behind those achievable for cochlear implants. Although the cochlear nerve may be left initially intact after surgery, its blood supply may be damaged. Nonetheless, a few patients can be rehabilitated successfully with a cochlear implant. Because detection of tumors at an early stage is effective in improving the clinical management of NF2, presymptomatic genetic testing is an integral part of the management of NF2 families. Recently, the use of targeted treatments has been highlighted (49, 50, 51). The VEGF antibody bevacizumab has been shown to shrink schwannomas and has been used in children (49–51). However, use in children should be guarded, as tumors rebound when treatment is stopped and potential side effects on growth and fertility are still a concern.

Management and follow-up of NF2 of adulthood. Management and follow-up should be arranged through a specialized multidisciplinary team that includes, at a minimum, a neurosurgeon, neurootologist, neurologist, neuroradiologist, audiologist, specialist nurse, and geneticist, with annual MRI continuing into adulthood and 3 to 5 yearly spinal MRI unless symptomatic or with a fast-growing tumor (43).

Schwannomatosis

Schwannomatosis is less common than NF2 and is even more rare in childhood. Unless a *SMARCB1* or *LZTR1* mutation is identified, it is a diagnosis that is made after NF2 has been excluded, usually by a combination of cranial imaging to show no evidence of VS, blood *NF2* molecular testing, and, potentially, tumor analysis. Analysis of multiple tumors from the patient show different *NF2* mutations consistent with somatic mutations rather than identical ones, which would indicate *NF2* mosaicism in a patient with negative blood analysis (42). Life expectancy is not usually affected unlike NF2, although pain is a prominent feature. A baseline assessment including full craniospinal MRI should be carried out in late childhood/early adulthood to assess disease, and whole-body MRI can be considered. In Manchester (unpublished data), six of 67 (9%) *SMARCB1* presented with symptomatic spinal schwannomas in patients <20 years and in *LZTR1* two of 71 (2.6%). Management in adulthood is usually coordinated by a neurologist with pain expertise or a neurofibromatosis specialist. Frequent MRI is not required unless symptomatic.

SMARCE1 meningiomatosis

SMARCE1 meningiomatosis often presents in childhood with an isolated meningioma. This appears to be more likely in males who, like in NF2, have an earlier risk of meningioma disease but a lower later risk (34). Until more information is available about the penetrance and tumor spectrum of the condition, we propose the following screening advice for asymptomatic *SMARCE1* mutation carriers: neurologic examination and MRI of the brain and spine yearly from diagnosis until the age of 18 and once every 3 years thereafter, or in between if there are clinical symptoms (53).

Apparent gain-of-function mutations in *SMARCB1* and *SMARCE1* have been associated with Coffin–Siris syndrome and *LZTR1* with Noonan syndrome, but these mutations rarely cause schwannomas/meningiomas (54).

Imaging in related disorders

- *SMARCB1* schwannomatosis [different protocols for rhabdoid disease–related *SMARCB1* mutations are in the *CCR* Pediatric Oncology Series article by Foulkes and colleagues (55)]—baseline MRI brain and spine at diagnosis, then every 2 to 3 years, beginning at age 10. Consider whole-body MRI and increasing surveillance frequency if symptomatic.
- *LZTR1*—baseline MRI brain and spine at diagnosis, then every 2 tp 3 years, beginning at age 15 to 19 years. Consider whole-body MRI and increasing surveillance frequency if symptomatic.
- *SMARCE1*—baseline MRI brain and spine at diagnosis, then every 1 to 2 years until the age of 18, reducing frequency to once every 5 years if no tumors are identified. If tumor is detected, increase frequency of surveillance to every 2 to 3 years or more frequently if patients become symptomatic.

Conclusions

We outline here recommendations for genetic testing to confirm the presence of either NF2, or related *SMARCB1* or *LZTR1* schwannomatosis or *SMARCE1*-related meningioma predisposition. Detailed surveillance protocols dependent on the disorder are provided in Table 3.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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