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Cancer and Central Nervous System Tumor Surveillance in Pediatric Neurofibromatosis 1

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Abstract

Although the neurofibromatoses consist of at least three autosomal dominantly inherited disorders, neurofibromatosis 1 (NF1), neurofibromatosis 2 (NF2), and schwannomatosis, NF1 represents a multisystem pleiotropic condition very different from the other two. NF1 is a genetic syndrome first manifesting in childhood; affecting multiple organs, childhood development, and neurocognitive status; and presenting the clinician with often complex management decisions that require a multidisciplinary approach. Molecular genetic testing (see article for detailed discussion) is recommended to confirm NF1, particularly in children fulfilling only pigmentary features of the diagnostic criteria. Although cancer risk is not the major issue facing an individual with NF1 during childhood, the condition causes significantly increased malignancy risks compared with the general population. Specifically, NF1 is associated with highly elevated risks of juvenile myelomonocytic leukemia, rhabdomyosarcoma, and malignant peripheral nerve sheath tumor as well as substantial risks of noninvasive pilocytic astrocytoma, particularly optic pathway glioma (OPG), which represent a major management issue. Until 8 years of age, clinical assessment for OPG is advised every 6 to 12 months, but routine MRI assessment is not currently advised in asymptomatic individuals with NF1 and no signs of clinical visual pathway disturbance. Routine surveillance for other malignancies is not recommended, but clinicians and parents should be aware of the small risks (<1%) of certain specific individual malignancies (e.g., rhabdomyosarcoma). Tumors do contribute to both morbidity and mortality, especially later in life. A single whole-body MRI should be considered at transition to adulthood to assist in determining approaches to long-term follow-up. *Clin Cancer Res; 23(12); e46–e53. ©2017 AACR.*

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Introduction

The neurofibromatoses, including neurofibromatosis 1 (NF1), neurofibromatosis 2 (NF2), and schwannomatosis, have for most of their known existence been lumped together as a single entity. This was largely due to the significant influence of the renowned neurosurgeon Harvey Cushing, who described that bilateral eighth nerve tumors were part of von Recklinghausen disease in the early 20th century (1). The clinical and genetic distinction between NF1 and NF2 was not fully recognized until the past three decades, and in prior reports, NF1 and NF2 were frequently referred to interchangeably (2). Gradually, beginning in the latter 20 years of the 20th century, the differences in clinical presentation and genetic etiology resulted in the definition of two distinct conditions, NF1, formerly von Recklinghausen neurofibromatosis, and NF2, previously bilateral acoustic/central neurofibromatosis. The conditions were eventually recognized as distinct and separate molecular entities, with the localization of their respective genes to chromosomes 17q and 22q (3, 4), and subsequently and formally, clinically delineated at an NIH (Bethesda, Maryland) consensus meeting in 1987 (5). The gene and disease-associated mutations for *NF1* were identified in 1990 (6) and for *NF2* in 1993 (7–9). Evidence consistently suggests that classical NF1 and NF2 fulfilling NIH criteria are both heterogeneous conditions. There are additional conditions with phenotypic overlap with classic NF1 and/or NF2. Families with multiple café au lait (CAL) macules and macrocephaly without neurofibromas or other typical NF1 features may have either a three base-pair deletion (c.2970_2972 delAAT) in *NF1* (10) or a *SPRED1* mutation (11), and a third type of neurofibromatosis called schwannomatosis is now accepted (12–14), with clinical and tumor features that overlap with NF2.

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.

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NF1

Clinical manifestations

Diagnostic criteria. The NIH diagnostic criteria for NF1 are shown in Table 1 (5). When these criteria are used, misdiagnosis or confusion is unlikely unless a diagnosis is made based on only pigmentary criteria. Patients with segmental neurofibromatosis (neurofibromatosis features limited to one area of the body) can fulfill these criteria, and clinicians should note any segmental involvement, as this may mean the child has a partial or "mosaic" form of NF1. Clinicians need to be aware that a subset of individuals and families with multiple CAL macules, without other NF1 primary features, may have mutations in the *SPRED1* gene, a condition called Legius syndrome (11). Furthermore, patients with constitutional mismatch repair deficiency syndrome (CMMRD) can fulfill the criteria for NF1 but have a very different cancer spectrum and much higher cancer penetrance [see the *CCR* Pediatric Oncology Series article by Tabori and colleagues (15)]. A high index of suspicion for CMMRD is recommended in children with NF1 features who are from consanguineous families, have the cancers typical of CMMRD (i.e., high-grade glioma, colorectal polyps and carcinoma, and hematopoietic malignancies, especially acute lymphoid leukemia and lymphoma), and/or have family history of cancer suggestive of Lynch syndrome, and/or lack the characteristic developmental issues typically seen in NF1.

NF1 clinical features

NF1 clinical features include some of the diagnostic criteria categories (Table 1). In childhood, CAL macules are small, as reflected in the diagnostic criteria, but they become larger and often merge as individuals age. They typically have a linear rather than ragged-edge border and are often described as similar to the "coast of California" in contrast to the "coast of Maine" appearance observed in individuals with McCune–Albright syndrome or CMMRD. The CAL macules in NF1 often fade in later life and may be less easy to recognize without a Wood's light/lamp. CAL macules are flat with no associated hair and have no propensity for malignant transformation. Freckling usually occurs in non–sun-exposed skin, with the axilla more frequently affected than the groin. Freckling usually appears later than the CAL macules. Neurofibromas on and under the skin are the characteristic feature of NF1. These often start as pinkish-purple, raised, soft lesions that can then transform into more "wart"-like growths. Plexiform tumors, which likely represent an early embryonic origin tumor, are often visible from birth with diffuse involvement of the skin and underlying structures. Approximately 2% to 3% of patients with NF1 have unsightly plexiform tumors affecting the head and neck (16, 17). The overlying skin is often hyperpigmented and loses elasticity, leading to a gravity effect of "sagging" of the tumor. Subcutaneous nodular tumors occur as growths on peripheral nerves, which are separate from the overlying skin. These tumors may appear as fusiform swellings on more major nerve routes and can be painful to the touch. The deeper fusiform subcutaneous and plexiform tumors may undergo malignant change to malignant peripheral nerve sheath tumor (MPNST). Although this is uncommon in childhood, malignant transformation can occur beginning in adolescence and very rarely earlier (Table 2). The appearance of iris Lisch nodules (benign hamartomas) typically occurs early in childhood and usually precedes the appearance of cutaneous neurofibromas. Lisch nodules of melanocytic origin appear as light brownish-orange out-swellings from the latticework of the iris, in contrast to iris nevi, which are flat and usually dark brown or black. Ophthalmic examination by slit lamp is, therefore, a useful diagnostic aid in equivocal cases. Another common feature in childhood are spots on the skin called xanthogranulomas that are self-limiting. They usually appear between 2 and 6 years of age, disappearing within a year, and have been linked to an apparent increased risk of leukemia, (18) although this association is not totally compelling.

Table 1. Diagnostic criteria for NF1 (two or more must be present)

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

Genetics and epidemiology

A number of studies have addressed the genetics, prevalence, and incidence of NF1 (19). The autosomal dominant inheritance pattern of NF1 has been confirmed for many years (2). At least 50% of cases present as *de novo* mutations of the gene and appear as isolated cases. NF1 has a birth incidence of one in 1,900 to 2,800 (20, 21) and a diagnostic prevalence of one in 4,150 to 4,950 (20, 21). The prevalence is lower than birth incidence due to undiagnosed cases in populations and an earlier mean age at death. The highest frequency was reported in an Israeli study of military recruits, with a prevalence of around one per 1,000 (22); however, this was based largely on the presence of CAL macules and could represent a founder effect for a three base-pair deletion in *NF1* or a *SPRED1* mutation (10, 11, 20). Nearly all children who inherit an *NF1* mutation from their parent can be diagnosed on the basis of pigmentary features in very early childhood; however, clinical diagnosis in *de novo* cases may take longer. Indeed, recent molecular evidence shows that although the sensitivity for *NF1* mutation detection based on RNA analysis is around 96% (23–26), children meeting NIH criteria based solely on pigmentary features (e.g., $\geq$6 CAL macules) only appear to have approximately a 67% chance of having NF1 versus 8% to 10% having Legius syndrome (26). For the remainder of individuals meeting some criteria, particularly those with more ragged-edge CAL patches and a history of malignant cancers, consideration should be given to CMMRD, as the diagnoses may be confused given the overlapping NIH criteria and similar tumor spectrum [e.g., neurofibroma and optic pathway glioma (OPG); ref. 27]. Other conditions such as LEOPARD syndrome (Noonan syndrome with multiple lentigines) and other RASopathies may also present with pigmentary features mimicking NF1.

Clinical course and childhood tumor risk

NF1 is widely variable in its clinical course. This variation is frequently great even within families with an identical *NF1* mutation (28). As such, predicting disease severity is difficult. Children with early manifestations of a more severe disease course, such as multiple tumors, may have undergone loss in early development of the wild-type *NF1* allele, have a

Table 2. NF1: tumor features, with typical ages at presentation and childhood risk

Disease feature	Frequency (pediatric risk) in %			Age of presentation
Series	**Huson (15)**	**McGaughran (16)**	**Update for key tumors[a]**	
Patients in series	135	523	1,500	
Peripheral neurofibromas	>99	60 (20–60)		≥7 years
Plexiform neurofibromas				
All plexiforms	30	15 (15)		0–18 years
Large lesions of head and neck	1.2	6 (6)		0–3 years
CNS tumors				
Optic glioma (symptomatic)	1.5	5 (5–6)	6%	Childhood
Other CNS tumors	1.5	2.0 (1)	2%	Lifelong
Spinal neurofibromas	1.5	2.0 (0.2)	0.2%	Lifelong
Malignancy				
Malignant peripheral nerve sheath tumors	1.5	5 (0.2)	0.2%[b]	Lifelong
Embryonal rhabdomyosarcoma	1.5	0.2 (0.2)	0.3%	0–5
Gastrointestinal tumors[c] (neurofibromas and GISTs)	2.2	2.0 (0)	0%	Lifelong
Pheochromocytoma	0.7	0.4 (0.2)	0%	≥10 years
Duodenal carcinoid	1.5	2 (0.1)	0%	≥10 years
Glomus tumors in nail beds	0	0.2 (0.1)	0%	Adults (usually)

Abbreviation: GIST, gastrointestinal stromal tumor.
[a]Update based on 1,500 NF1 patients in the Manchester register.
[b]0.5% by age 20 years.
[c]Frequency of GIST in adulthood has been found to be as high as 6%, but this may reflect MRI surveillance detecting asymptomatic tumors.

constitutional whole germline deletion of the *NF1* gene, or inherited a pattern of modifier genes that alter the phenotype (28). Diagnosis of one clinical feature does not usually imply a high risk of another complication, although there are exceptions. For example, OPG is associated with a higher risk of symptomatic gliomas occurring elsewhere in the brain (often later in childhood; ref. 29), and the presence of multiple subcutaneous peripheral nerve neurofibromas increases the risk of MPNST (30–32).

Large studies in which children with NF1 have been screened with MRI scans indicate that approximately 15% have at least a unilateral OPG (33). It is unclear how many children who have an OPG detected by surveillance imaging will ever develop symptoms, as studies that have not specifically screened using imaging find much lower rates of between 0.7% and 6% (16, 17, 29). Symptomatic OPGs usually present between birth and 6 years of age, peaking at around 3 to 4 years and having a more benign course than sporadic OPG (33, 34). However, adult onset of symptoms does occur. Brain stem gliomas are less frequent and affect approximately 1% to 2% of patients but are more frequent in those with optic glioma (Table 2; ref. 29). Approximately 2% of individuals with NF1 present with symptoms from spinal tumors that require surgery, but on MRI imaging, more than 60% appear to have spinal nerve root involvement in adulthood (27). It is not clear why so few spinal tumors present symptomatically, which is in contrast to NF2. Other nonneoplastic, NF1-associated central nervous system (CNS) lesions include macrocephaly (45% with head circumference >97th percentile), aqueduct stenosis (<1%), and neurofibromatosis-associated white matter tract enhancement or vacuolation changes on T2-weighted MRI (33%–78%; refs. 35–37).

Malignancies in NF1. *MPNST* MPNST is a rare tumor occurring in only one per million annually in the general population, and between 20% and 50% of patients with MPNSTs have NF1 (38), with NF1 patients having an 8% to 12% lifetime risk (38, 39). MPNSTs are rare in childhood, and a rapidly growing deep-seated tumor with pain or neurologic deficit needs to be investigated. MRI often shows a heterogenous tumor, and ^{18}F-FDG PET imaging is useful in differentiating a benign plexiform tumor from malignant change, with a number of studies showing increased FDG uptake associated with MPNST (39–41). Indeed, FDG PET/CT–guided biopsy has been advocated as a means of increasing the likelihood of obtaining accurate biopsy specimens in patients with large plexiform neurofibromas (42). "Atypical neurofibromas" are a transition phase from a pure benign nodular plexiform neurofibroma to MPNST. Not all atypical neurofibromas will eventually develop into MPNST, but there is an increased risk, and these tumors should be considered premalignant lesions. A total-body MRI is able to identify nodular neurofibromas with an increased growth rate suspected of atypical neurofibroma. Individuals with NF1 with an atypical neurofibroma tend to have more than one atypical neurofibroma, and as a group, these individuals have a high risk of developing MPNSTs.

Gliomas High-grade gliomas occur at increased frequency in NF1 and are often associated with the presence of an optic glioma (29). Overall, they occur in <1% of patients (22, 27), and due to their rarity, a child with NF1 and high-grade glioma should be investigated for CMMRD if an *NF1* mutation has not been previously identified.

Juvenile myelomonocytic leukemia Juvenile myelomonocytic leukemia is a definitive NF1 complication. It is generally thought to be incurable except by autologous bone marrow transplantation but occurs in only about one in 300 NF1 patients (43), with none occurring in one large population–based series of 1,404 patients with NF1 (44).

Embryonal rhabdomyosarcoma (eRMS) Although the prevalence of embryonal rhabdomyosarcoma in NF1 populations had been estimated as high as 1.4% to 6%, larger series confirm a risk of less than 1% (17, 45, 46) but still higher than in the general population. The urogenital system is the most common anatomic site involved, although other localizations have been reported (orbit is the second most frequent localization). eRMS in NF1 patients are characterized by particularly early onset (0–5 years)

and male sex predominance. All the cases reported are histologically embryonal type. The prognosis and overall survival are equivalent to non-NF1 eRMS. Because of their location, eRMS in NF1 are typically symptomatic at presentation, and together with the good prognosis and low incidence in NF1 populations, there are insufficient data to recommend any routine screening for eRMS.

Endocrine tumors and other tumors Duodenal endocrine (carcinoid) tumors and pheochromocytoma occur in NF1 with a frequency of around 1% (Table 2), but they are rare in childhood. "Glomus" tumors can occur as painful swellings in the nail beds and are being increasingly recognized (47). Gastrointestinal stromal tumors were previously called gastrointestinal neurofibromas and occur symptomatically in around 2% of patients with NF1 but again, rarely in childhood.

Previous guidelines. Guidelines for management of NF1 have been published by several different professional organizations and concentrate on the diagnosis and management of OPG (48–51).

Genetic Summary

The *NF1* gene on chromosome 17q is the only known gene to cause typical NF1. The gene contains 62 coding exons spread over 282 kb. There are multiple *NF1* pseudogenes in the genome that can complicate mutation analysis. It produces multiple mRNA and protein isoforms by alternative splicing and also by RNA editing. The *NF1* gene encodes neurofibromin, a large 2,839 amino acid cytoplasmic protein that is predominantly expressed in neurons, Schwann cells, oligodendrocytes, lung, colon, muscle, and leukocytes (19). The multidomain protein regulates several intracellular processes, including the RAS/ERK/MAP kinase cascade and cytoskeletal assembly. Most described mutations result in truncated proteins and are spread throughout the gene. Loss of function of both alleles of the *NF1* tumor suppressor gene leads to loss of the NF1 protein (neurofibromin) in the causative precursor cell. This causes loss of tumor suppressor function leading to a high risk of tumor development due to decreased RAS signaling inhibition and, hence, to increased proliferation, particularly in cells of neural crest origin.

NF1 is autosomal dominantly inherited with virtually complete but variable penetrance. The first genotype–phenotype relationship reported was based on whole gene deletions (48). These large deletions occur in 2% to 7% of individuals with NF1 and are associated with larger body size, intellectual disability, and greater tumor burden as well as a 2- to 3-fold greater risk of MPNST (23–26, 52). Other clear correlations were reported later with certain nontruncating mutations being associated with a milder form of NF1 (26, 53–55). In particular, an in-frame deletion (c.2970_2972 delAAT; ref. 53) appears to cause a CAL macules–only type of NF1 without tumor risk, similar to *SPRED1* causing Legius syndrome (11). Other missense mutations (particularly at residue p.Arg1809) cause a Noonan-like association with pulmonary stenosis (54, 55), whereas certain missense mutations cause a severe spinal form of NF1 characterized by absence of pigmentary features, leading to diagnostic challenges in childhood due to relative absence of CAL macules (56).

Genetic testing recommendations

The clinical criteria for diagnosing NF1 have historically been based on meeting two or more of the criteria listed in Table 1. Previously, *NF1* molecular testing was not routinely recommended unless needed for reproductive decision making in patients with a clinical diagnosis of NF1, as molecular diagnosis would not alter management for individuals with an established clinical diagnosis. This classic paradigm is shifting, however, based on new knowledge that a variety of syndromes have overlapping features with NF1 but a very different clinical course and on the emerging therapeutic benefits observed with targeted therapies aimed at the RAS/MAPK pathway in children with NF1 (57). A child who meets one or more clinical criterion (as outlined in Table 1) should now have *NF1* molecular genetic testing (sequencing and deletion/duplication analysis) offered to confirm if NF1 is the correct diagnosis, as a misdiagnosis could lead to inappropriate surveillance. A mutation will be detected on RNA analysis in 67% of individuals who meet pigmentary-only criteria and approximately 95% to 96% who meet clinical diagnostic criteria (23–26). If a mutation is not detected, however, several other conditions, some with cancer risk associated and others without, may be contributing to the phenotype. Some examples include pigmentary abnormalities due to mutations in *SPRED1*, CMMRD due to biallelic

Table 3. Summary of recommendations for childhood management

1. Genetic testing	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
2. Genetic testing	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)
3. General	Annual history and physical exam (including skin and neurologic exam and also blood pressure, height, weight, and pubertal development)
Tumor surveillance	
4. OPG	Children with NF1 should have 6–12 monthly ophthalmic assessments from birth to 8 years. One baseline assessment of color vision and visual fields should be undertaken when the child is developmentally able.
5. MPNST	Assess with history and clinical examination annually for typical signs of MPNST: any nondermal neurofibroma with rapid growth, loss of neurologic function, or increasing pain or change in consistency
6. JMML	Assess for risk of JMML in NF1 in children with juvenile xanthogranulomas
7. Internal burden	A baseline whole-body MRI should be considered between ages 16 and 20 years to assess internal tumor burden to determine adult follow-up regimen
8. Routine MRI	MRI surveillance is not currently recommended unless symptomatic or with an already diagnosed tumor. Specific biochemical or imaging surveillance for tumors with absolute risks in childhood below 1% is not recommended such as for pheochromocytoma, neuroendocrine tumors, MPNST, or non-optic glioma.

Abbreviation: JMML, juvenile myelomonocytic leukemia.

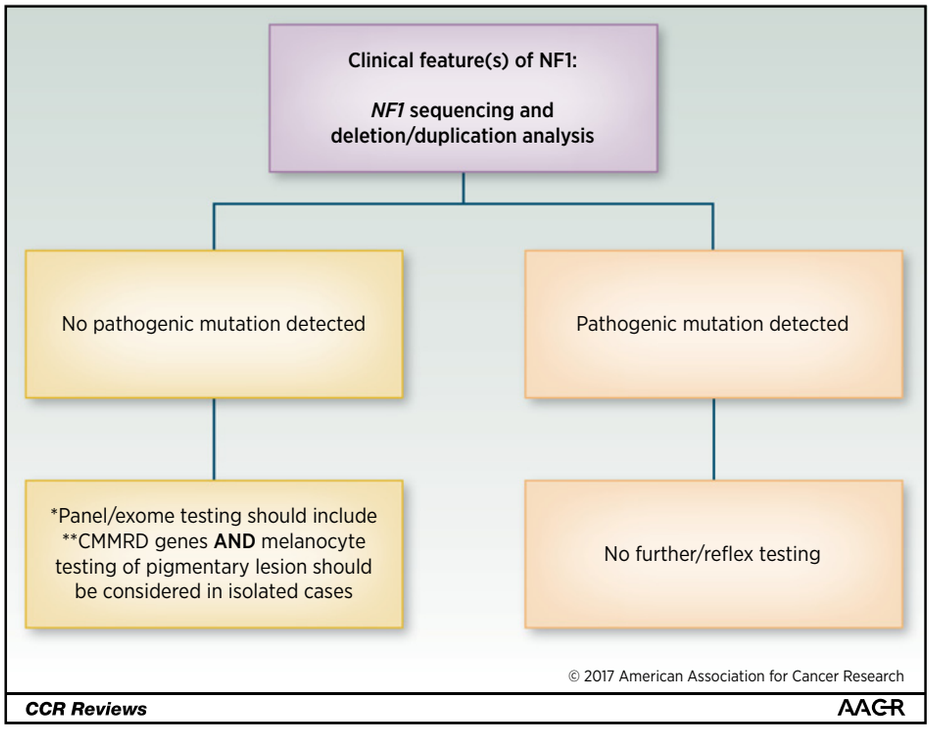

Figure 1.
Summary of expert recommendations for genetic testing and clinical management of NF1. *, Next-generation sequencing panel/focused exome should include at least *GNAS, MLH1, MSH2, MSH6, NF2, PMS2,PTPN11, SOS1, and SPRED1* (if not already tested) and either reflex to, or include, deletion/duplication analysis of each gene. *SPRED1* can be tested as a combined first-line test with *NF1* in those children with pigmentary-only criteria. Alternatively, those isolated cases with pigmentary-only phenotype could be tested for a panel/exome first in centers with sufficient expertise to interpret and communicate variants of uncertain significance, particularly if the CAL macules are not typical for NF1 (ragged edges). If no mutation is detected on panel/exome, however, RNA testing for *NF1* may still be required, as DNA-based approaches are less sensitive. **, CMMRD genes: *MLH1, MSH2, MSH6, PMS2.* Note that (i) if CMMRD is strongly suspected, *PMS2* is not covered well in most panels, and (ii) CMMRD genes may be excluded from panels when family history clearly suggests dominant inheritance of features to reduce the chance of an incidental finding of Lynch syndrome in childhood.

MLH1, *MSH2*, *MSH6*, or *PMS2* mutations (58), RASopathy syndromes (such as LEOPARD/Noonan) due to mutations in *PTPN11*, or McCune–Albright syndrome due to mutations in *GNAS* (Table 3; refs. 11, 27, 59).

Given the predominance of NF1 and Legius syndrome as the underlying diagnoses, most centers begin genetic testing with the *NF1* and *SPRED1* genes (Fig. 1). If negative, then consideration of a larger panel or whole-exome analysis is undertaken. For countries in which panel analysis is available, the primary concerns discussed by the workshop committee were 2-fold. First, initiating first-tier testing with a panel that includes *NF1* and *SPRED1* is preferred prior to moving onto a larger panel that might result in incidental finding of single heterozygous mismatch repair mutations associated with adult-onset Lynch syndrome in childhood unrelated to the child's phenotype. Second, predictive genetic testing for adult onset conditions generally should be deferred unless an intervention initiated in childhood may reduce morbidity or mortality (59, 60). If an *NF1* or *SPRED1* mutation is not detected, however, the risk of identifying Lynch syndrome is outweighed by the potential benefit of early CMMRD detection in this subpopulation.

In general, for any hereditary gene panel, the likelihood of identifying variants of uncertain significance (VUS) increases as more genes are evaluated, with many panel studies in adults resulting in on average more than one VUS per panel test reported (61). By only pursuing panels in children without a molecular diagnosis of NF1, fewer patients will have the uncertainty of VUS than if all patients pursued panel testing including *NF1* as a first tier.

Therefore, we recommend the algorithm presented in Fig. 1. Ideally, *NF1* genetic testing should be performed on lymphocytes using a combined DNA/RNA–based approach. If no mutation is detected in isolated cases, testing for *NF1* mutations from melanocyte cultures from at least two pigmentary lesions may be considered to evaluate for mosaicism, especially in the absence of family history of clinical features of NF1. Prior to panel/exome testing, children could be referred to subspecialty clinics if not already in one and then proceed to additional testing.

Cancer/Tumor Screening/Surveillance Protocols

OPG does not affect overall survival of children with NF1 (unlike in children with sporadic OPG; ref. 34), and little is known about the natural history of OPG. Nonetheless, there is a clear need to make an early diagnosis of OPG before significant loss of vision occurs. As the greatest risk of developing OPG is during childhood (especially in children <7 years of

age), ophthalmologic exams should start when the NF1 diagnosis is established and continue throughout childhood. These can detect both visual loss and changes over time that will require therapy.

Although the gold standard for the diagnosis of an OPG is MRI, early detection of an asymptomatic OPG has not been proven to reduce the incidence of visual loss, nor does an initial normal MRI exclude the development of a subsequent OPG. As treatment for an OPG is not required in the absence of progressive visual disturbance or proptosis, most previous protocols do not recommend routine screening by MRI, as this would need to be carried out frequently, often requiring sedation, and as many as two thirds of the OPGs would never become symptomatic (48–50).

Newer (bio)imaging techniques, such as magnetic resonance diffusion tensor imaging or diffusion tensor tractography, are under further study to detect microstructural abnormalities in the visual pathway that can predict visual function but do not yet have an established role in routine surveillance, particularly given the need for sedation in younger patients.

In addition, other emerging novel technologies, such as optical coherence tomography (OCT; refs. 62, 63), are even more promising and may enable early detection of optic nerve damage, especially in early childhood when ophthalmologic examination is difficult. OCT measures the width of the retina and can measure nerve loss even before that is measurable by vision assessment. The OCT technology is evolving, and newer handheld spectral domain OCT devices that partially account for differences in axial length of the eye in children have led to increased enthusiasm for use of OCT in monitoring neurofibromatosis-related optic nerve pathology, although the need for sedation in younger patients limits its universal application. Although OCT data are encouraging, it is not yet ready to be added as a robust tool for visual surveillance in young children with NF1. Similarly, there is not enough evidence to recommend the use of visual evoked potentials as a screening tool in OPG.

Clinicians should be aware that the risk of other CNS tumors, although low (1%–2%), is still much higher than in the general population. In childhood, they are usually low-grade gliomas, are often located in the posterior fossa (brainstem and cerebellum), and have a low growth rate. Most of them do not produce progressive symptoms, but families should be informed about the clinical warning signs. A comprehensive annual history and neurologic examination may be useful in detecting these lesions. This risk of other malignant tumors in childhood, including MPNST, is generally <1% and, therefore, below the threshold to suggest clinical benefit by surveillance (Table 2). However, parents should be alerted to the potential for malignant transformation of existing plexiform neurofibromas during adolescence. Nonetheless, if new emerging therapies, such as MEK inhibitors, show benefits (they already do for benign plexiforms) additional to tumor treatment, then earlier detection may well be warranted.

Surveillance

1. Annual history and physical exam [including skin and neurologic exam, and also blood pressure (renal artery stenosis/pheochromocytoma risk), height, weight, and pubertal development].
2. Ophthalmic assessment [detailed ophthalmologic protocol (ideally in specialist center); refs. 51, 64].
3. Assess with history and clinical examination annually for typical signs of MPNST: any nondermal neurofibroma with rapid growth, loss of neurologic function, or increasing pain or change in consistency. Have increased suspicion in those with features in Table 4.

Table 4. Features that should heighten awareness about likelihood of MPNST

Feature	How to assess
Large internal nodular neurofibroma burden	Whole-body MRI
Hard and painful subcutaneous neurofibroma(s)	Clinical history and examination
Previously irradiated body region	Clinical history
Germline NF1 microdeletion including SUZ12	Mutation testing
Atypical neurofibroma (neurofibroma with regions of hypercellularity and nuclear atypia)	Previous history and biopsy
Acute symptom/sign	
Pain especially that wakes person at night	MRI and FDG PET
Focal neurologic sign/loss of function	MRI and FDG PET
Rapid growth of a neurofibroma or part of a plexiform	MRI and FDG PET

Young children do not complain of visual impairment until it is advanced and sometimes only when they have bilateral visual loss. Parents need to be alert to possible signs of visual problems such as failure to pick up small toys and bumping into objects. Furthermore, visual assessment is often problematic in those with cognitive deficits.

Quantitative testing methods (teller acuity cards) exist for children as young as 6 months of age and are reliable measures of visual acuity (VA; ref. 65). In older children (usually at developmental age of 3 years), testing methods measure the ability to recognize ("recognition acuity") a figure (e.g., Lea symbols) or letters (e.g., HOTV or Snellen). Color vision can be obtained at 5 years and comprehensive peripheral visual fields at 8 years (whereas more basic confrontation visual fields can be obtained much earlier).

Besides vision loss and proptosis, OPG can also present as endocrine disturbances (precocious or delayed puberty, increased growth velocity) or hydrocephalus, and physicians should be aware of the possibility of an underlying OPG if any of these occur.

Surveillance for OPG should, therefore, include:

- Six to 12 monthly ophthalmic assessments from birth to 8 years (63, 65), including objective and quantitative VA [teller acuity cards and when the child is mature enough for a more reliable VA testing (e.g., HOTV)], confrontation visual fields, pupillary reflexes, and fundus exam. Every 1 to 2 years thereafter until 20 years of age.
- One baseline assessment of color vision and visual fields should be undertaken when the child is mature enough to cope with the test.
- In specialized settings where available, OCT in every ophthalmologic assessment may be considered as an objective measure of axonal integrity/axonal loss and thickness of retinal nerve fiber layer.
- During screening, if a vision loss is detected, and once other causes are excluded (refractive error, opacities, etc.), a repeated test in 2 weeks should be obtained. If vision loss persists, an MRI would be indicated.

Once diagnosed with OPG [refer to multidisciplinary team (MDT)]:

- Follow-up under neuro-oncology MDT
- May require chemotherapy treatment, but radiotherapy not recommended (29)
- Three to 6 monthly MRIs

Recommendations for transition to adulthood

Young adults with NF1 should be counseled on the future risk of MPNST and the cardinal signs. Women ages 30 to 50 should be advised of the increased breast cancer risks of 4- to 5-fold (39, 66) and to access extra breast screening according to guidelines for moderate (20%) lifetime risk or high risk if additional family history of breast cancer. Because of the risk of MPNST being associated with high internal tumor burden, whole-body MRI should be considered between ages 16 and 20 years to assess this (30–32, 52, 67). NF1-affected individuals with high internal tumor burden and/or whole gene deletions (52) should be referred to a specialist NF1 network clinic for long-term follow-up and surveillance. All adults with NF1 should have at least annual blood pressure checks and access to specialist clinics if they develop cardinal features of MPNST, gastrointestinal stromal tumors, or other NF1-related major complications.

Conclusions

This report makes a number of recommendations for the diagnosis and surveillance of children and young adults with NF1, which are summarized in Table 3.

Disclosure of Potential Conflicts of Interest

S.E. Plon is a consultant/advisory board member for Baylor Genetics. No potential conflicts of interest were disclosed by the other authors.

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