CLINICAL REPORT Guidance for the Clinician in Rendering Pediatric Care

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Health Supervision for Children With Neurofibromatosis Type 1

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Neurofibromatosis type 1 (NF1) is a multisystem disorder that primarily involves the skin and peripheral nervous system. Its population prevalence is approximately 1 in 3000. The condition is usually recognized in early childhood, when pigmentary manifestations emerge. Although NF1 is associated with marked clinical variability, most children affected follow patterns of growth and development within the normal range. Some features of NF1 can be present at birth, but most manifestations emerge with age, necessitating periodic monitoring to address ongoing health and developmental needs and minimize the risk of serious medical complications. In this report, we provide a review of the clinical criteria needed to establish a diagnosis, the inheritance pattern of NF1, its major clinical and developmental manifestations, and guidelines for monitoring and providing intervention to maximize the health and quality of life of a child affected.

INTRODUCTION

Neurofibromatosis type 1 (NF1) is 1 of the most common inherited genetic conditions, affecting approximately 1 in 3000 individuals.[1] NF1 is a multisystem disorder in which some features may be present at birth but most are age-related manifestations. Since the publication of the article "Health Supervision for Children With Neurofibromatosis," the health supervision and treatment rationale has evolved, necessitating this update.[2] In this report, we only address issues concerning the diagnosis and management of NF1, which should not be confused with neurofibromatosis type 2, a separate and distinct disorder that typically presents in childhood and adolescence with cutaneous and vestibular schwannomas and has an incidence of 1 in 33 000 and a prevalence of less than 1 in 50 000.[1] Most pediatricians and pediatric medical subspecialists follow multiple children with NF1 in their practices, and NF1 has a wide spectrum of health implications. This document seeks to educate and provide guidance for the clinician on the current understanding of the

abstract

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The guidance in this report does not indicate an exclusive course of treatment or serve as a standard of medical care. Variations, taking into account individual circumstances, may be appropriate.

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TABLE 1 NIH Consensus Development Conference Criteria

Clinical Criteria	Clinical Pearls
1. Six or more CALMs equal to or greater than 5 mm in longest diameter in prepubertal patients and 15 mm in longest diameter in postpubertal patients	• 2–3 or fewer CALMs are normal in the population • Typically, CALMs are present since infancy in people with NF1 • Typically have smooth edges
2. Two or more neurofibromas of any type or 1 plexiform neurofibroma	• Dermal and subcutaneous neurofibromas not typically detectable until later in childhood • Plexiform neurofibroma typically changes the color and/or texture of overlying skin
3. Freckling in the axillary or inguinal regions (Crowe sign)	• Not typically detectable until age 5 or later • Freckling in areas not exposed to the sun is unexpected in people without NF1
4. Optic glioma (OPG)	• Not detectable without direct ophthalmoscopy • May be present in infancy • Early detection critical for preserving vision
5. Two or more iris hamartomas (Lisch nodules) (Fig 1)	• Occurrence is age related (rarely present in infants and toddlers; present in about half of children by school age; present in most teenagers) • Not detectable (without slit-lamp examination) • Does not affect vision
6. A distinctive osseous lesion, such as sphenoid wing dysplasia or long-bone dysplasia (with associated cortical thickening and medullary canal narrowing), with or without pseudoarthrosis	• Tibial dysplasia is the most common type of bone dysplasia • Infants and toddlers with anterior-lateral tibial bowing on examination should have tibial radiographs and referral to orthopedics
7. A first-degree relative (parent, sibling, or child) with NF1 according to the aforementioned criteria	• Parent who is affected should have some symptoms even if mildly affected (100% penetrance) • NF1 does not skip a generation

Two or more criteria are required to establish the diagnosis of NF1. Adapted from Neurofibromatosis. Conference statement. National Institutes of Health Consensus Development Conference. *Arch Neurol.* 1988;45(5):575–578; National Institutes of Health Consensus Development Conference Statement: neurofibromatosis. Bethesda, Md., USA, July 13-15, 1987. *Neurofibromatosis.* 1988;1(3):172–178; and DeBella K, Szudek J, Friedman JM. Use of the national institutes of health criteria for diagnosis of neurofibromatosis 1 in children. *Pediatrics.* 2000;105(3, pt 1):608–614.

pathophysiology of NF1, health supervision for children with NF1, and the role of the medical home in caring for children with NF1.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

In a National Institutes of Health (NIH) consensus development conference regarding NF1, 7 criteria were demarcated, of which 2 or more are required to establish the diagnosis of NF1 (see Table 1).[3–6] The diagnosis of NF1 in nonfamilial pediatric cases may be difficult because certain clinical manifestations are age dependent. The variability of clinical expressivity in NF1 also makes it difficult to predict future manifestations of NF1 in a child who is affected.

The diagnosis of NF1 in a child is usually first suspected on the basis of café-au-lait macules (CALMs) (Fig 2). The differential diagnosis (Table 2) includes other conditions that present with CALMs or other pigmentary manifestations. In general, CALMs in NF1 have uniform and regular borders ("coast of California"). Atypical CALMs that are irregularly shaped ("coast of Maine") or have heavy pigment compared with adjacent skin may be seen in NF1, but if typical CALMs are not also present, other conditions should be considered. Other signs and symptoms delineate these conditions, and referral to a specialist experienced in diagnosing NF1 and related conditions (usually a medical geneticist, dermatologist, or neurologist) may be helpful to establish a diagnosis. Finally, there are individuals who have fair complexion with up to 6 lightly pigmented, irregularly marginated CALMs who may have a pigmentary dysplasia unrelated to an underlying medical condition.[7]

There are families in which individuals have typical multiple CALMs inherited as an autosomal dominant trait with no other manifestations of NF1. Some of these

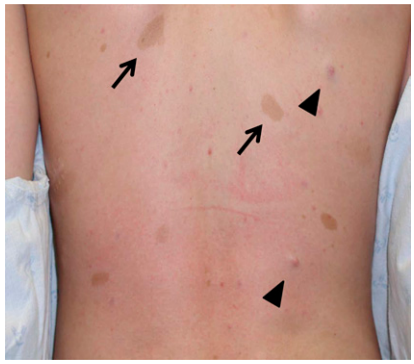

FIGURE 1
Multiple CALMs over the back and cutaneous neurofibromas below the right scapula and right side of the lower back.

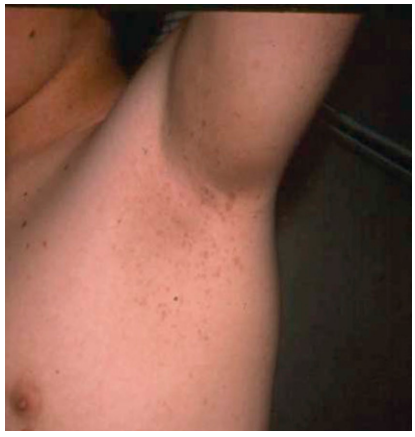

FIGURE 2
Axillary freckling.

TABLE 2 Differential Diagnosis of Patients With CALMs

Diagnosis	Clinical Features
Legius syndrome	• Typical NF1-like CALMs; mild freckling • No neurofibromas or OPGs • Similar cognitive impairment
McCune-Albright syndrome	• Jagged (coast of Maine) CALMs • Polyostotic fibrous dysplasia with fracture • Precocious puberty or other tumors • No neurofibromas
Noonan syndrome	• Typical CALMs but fewer • Lentigines rather than Crowe sign freckling • Pulmonic valve stenosis with neck webbing • Short stature, cryptorchidism, pectus excavatum, curly hair, distinctive facial gestalt
Silver-Russell syndrome	• Typical CALMs but fewer; no freckling • Intrauterine growth retardation with postnatal growth retardation, normocephaly • Fifth digit clinodactyly, hypospadias, body asymmetry
Chromosomal or DNA instability syndromes: FS, BS, MMRCS	• Atypical CALMs; no freckles • Postnatal growth retardation with microcephaly • UV sensitivity (BS), brain and blood cancers (MMRCS), congenital malformations (FS)
PTEN hamartoma tumor syndrome	• Typical CALMs but fewer; no freckles • CALMs of the glans and/or penile shaft in males • Macrocephaly (≥3 SD from mean) • Hypotonia, family history of thyroid and breast cancer
Chromosomal mosaicism and ring chromosomes	• Atypical CALMs; pigmentary dysplasia • Intellectual disability • Growth retardation with microcephaly • Body asymmetry
Sotos syndrome, Nevoid basal cell carcinoma syndrome, neurofibromatosis type 2, epidermal nevus syndrome, Carney syndrome	• Atypical CALMs; no freckling • Physical manifestations distinct from NF1

BS, Bloom syndrome; FS, Fanconi syndrome; MMRCS, mismatch repair cancer syndrome; PTEN, Phosphatase and tensin homolog.

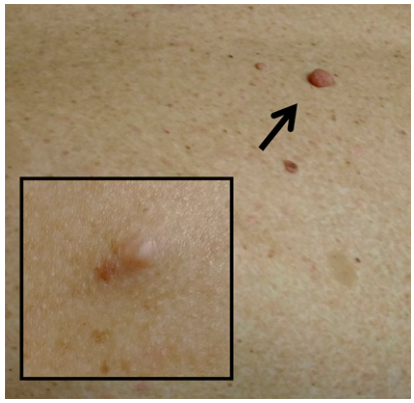

FIGURE 3
Close-up of a 9 mm sessile cutaneous neurofibroma (cNF; inset) and 12mm globular cNF from the same individual. The globular cNF protrudes further from the surrounding skin surface, but both are benign lesions.

families are genetically linked to the *NF1* locus and carry an *NF1* pathogenic variant. There are also other, less common, conditions associated with CALMs. The condition that could appear most similar to NF1 is Legius syndrome, which is caused by pathogenic variants in *SPRED1*, which encodes a protein that also functions within the Ras signaling pathway. People with Legius syndrome have multiple CALMs, intertriginous freckling (Fig 3), learning disabilities, and relative macrocephaly that is indistinguishable from findings in mild cases of NF1.[8] Other manifestations of NF1, such as neurofibromas or other tumors, ophthalmologic findings, and skeletal manifestations, are not present in families with Legius syndrome.[9] The absence of neurofibromas in adults with multiple CALMs in an extended pedigree is helpful to establish a diagnosis of Legius syndrome versus NF1, and molecular testing for *SPRED1* versus *NF1* should be considered in these cases.[9]

GENETICS

NF1 is inherited in an autosomal dominant fashion, although approximately half of individuals affected have sporadic cases caused by a new (or de novo) *NF1* gene mutation, hereafter called a pathogenic sequence variant (PSV). There is complete penetrance (ie, everyone with a pathogenic change in the *NF1* gene will show some features of NF1), although expression is extremely variable, even within members of the same family. An individual with NF1 (whether familial or de novo) has a 50% chance of having a child with NF1 with each pregnancy. In contrast, unaffected parents of a child with a new PSV have a low risk of recurrence in siblings of the child who is affected. The *NF1* gene encodes a protein called neurofibromin, which functions to regulate the Ras signaling pathway that controls cell proliferation. Cells in tumors associated with NF1, such as Schwann cells in neurofibromas, have a PSV of both *NF1* alleles: the germ-line PSV and a somatically acquired PSV of the other allele. *NF1*, therefore, functions as a tumor-suppressor gene.

Role of Genetic Testing in Diagnosis

Molecular diagnosis of NF1 is available on the basis of analysis of DNA for a pathogenic variant in the *NF1* gene. Testing can be performed

on any source of DNA, usually a blood specimen. Thousands of distinct PSVs have been identified in different patients; most lead to loss of function of the gene product, as expected for a tumor-suppressor gene.[10,11]

Thus far, only 4 genotype-phenotype correlations have been established:

1. A deletion of the entire *NF1* gene and more than 10 surrounding genes, comprising 1.4 to 1.5 Mb of DNA, leads to a severe phenotype with intellectual disability, a large burden of neurofibromas, and increased risk of malignant peripheral nerve sheath tumors (MPNSTs) and cardiovascular malformations.[12]
2. A specific 3-base deletion in exon 22 (National Center for Biotechnology Information nomenclature) of the *NF1* gene (c.2970-2972 delAAT) leads to a mild phenotype characterized by CALMs and skinfold freckles with no neurofibromas.[13]
3. Amino acid substitution at codon 1809 (which encodes arginine) is associated with pigmentary features but not neurofibromas, although these patients may also have a Noonan syndrome–like phenotype, including pulmonic stenosis and short stature.[14]
4. Some missense or splicing variants are associated with "spinal NF1," in which there are often few pigmentary findings, few or no dermal neurofibromas, and normal cognitive ability but large numbers of internal tumors involving spinal nerve roots and deep peripheral nerves.[15]

NF1 genetic testing may be performed for purposes of diagnosis or to assist in genetic counseling and family planning. If a child fulfills diagnostic criteria for NF1, molecular genetic confirmation is usually unnecessary. For a young child who presents only with CALMs, *NF1* genetic testing can confirm a suspected diagnosis before a second feature, such as skinfold freckling, appears. Some families may wish to establish a definitive diagnosis as soon as possible and not wait for this second feature, and genetic testing can usually resolve the issue. With a sensitivity rate of 95%, genetic testing is considered highly reliable, although a negative test does not completely rule out the condition.

In rare instances, CALMs may be associated with either of the 2 specific *NF1* PSVs noted above, in which case neurofibromas are unlikely to occur. Also, Legius syndrome, associated with the *SPRED1* gene, can present with multiple CALMs, sometimes with skinfold freckling, but without other features of NF1.[8,9] Some laboratories will initially perform *NF1* testing on a child with multiple CALMs and then test for *SPRED1* if *NF1* testing is negative. It is also possible to test only for *SPRED1* and then to assume that *NF1* is most likely if *SPRED1* testing is negative,[16] although many parents whose child is undergoing genetic testing might prefer to have a definitive diagnosis. Genetic testing for the *NF1* gene can also be helpful in children who present with atypical features such as isolated plexiform neurofibromas, optic glioma, or tibial dysplasia. Blood testing in such instances is usually negative because the genetic changes may have occurred only in the affected tissue. In such cases, testing of tissue obtained from a lesion might be positive and indicative of somatic mosaicism. Children who present with "segmental NF1" (who usually have a limited distribution of CALMs and/or skinfold freckles or, sometimes, of neurofibromas) can also be diagnosed with somatic mosaicism after a biopsy of affected tissue and molecular testing of either melanocytes from CALMs or Schwann cells from neurofibromas.[17] This protocol usually does not guide clinical management, so it is rarely followed, although it can be helpful for adults who are concerned about the possibility of genetic transmission by way of gonadal *NF1* mutation mosaicism and wish to identify the specific PSV for future prenatal testing.

Knowledge of the *NF1* PSV can enable testing of other family members and prenatal diagnostic testing. Because the penetrance of NF1 is essentially 100% by adolescence, a careful physical examination usually suffices to establish the diagnosis in a relative at risk for having inherited the mutant allele. People with NF1 have a 50% risk for each of their offspring to be affected and can be offered prenatal testing or preimplantation genetic diagnosis. Prenatal testing requires previous knowledge of the specific PSV in the affected individual. The unaffected parents of a child who is sporadically affected have a low probability of having another child who is affected, barring the occurrence of germ-line mosaicism or a new de novo PSV in a subsequent pregnancy. The latter scenario has been reported but is expected to occur less often than germ-line mosaicism.[18] Prenatal testing could be performed if the PSV of the child who is sporadically affected is known. Typically, families are counseled that the recurrence risk is 1% or less for parents who are clinically unaffected.

Summary and Recommendations About Genetic Testing

The following can be summarized about genetic testing:

- can confirm a suspected diagnosis before a clinical diagnosis is possible;
- can differentiate NF1 from Legius syndrome;
- may be helpful in children who present with atypical features;
- usually does not predict future complications; and
- may not detect all cases of NF1; a negative genetic test rules out

a diagnosis of NF1 with 95% (but not 100%) sensitivity.

SKIN

Cutaneous pigmentary manifestations are the most common and most well-recognized features of NF1 in children. The morphology and significance of CALMs have already been noted. Axillary and inguinal freckles (Fig 3), commonly referred to as Crowe sign, are small (1–2 mm) pigmented macules that appear in skinfold regions (eg, axillae, inguinal regions, and the neck), typically beginning at about 3 to 5 years of age. In some cases, there may be similar diffuse freckling all over the body. The only importance of skinfold freckling is as 1 of the diagnostic criteria for NF1. Additional skin manifestations include juvenile xanthogranulomas (JXGs) and nevus anemicus.[19] JXGs are small, waxy, yellowish nodules that appear on the skin in a small percentage of young children with NF1. They typically resolve spontaneously. It has been suggested that JXGs might be associated with leukemia in children with NF1,[20] but studies reveal that either they are not a risk factor for leukemia or the risk is too low to warrant surveillance for leukemia.[19,21] Nevus anemicus is a flat skin macule that is paler than surrounding skin; unlike surrounding skin, it will not turn red when rubbed. Nevus anemicus may occur in up to half of individuals with NF1.[22] Pruritus is a common symptom in individuals with NF1, and topical lotions and antihistamines are minimally effective. In older children, gabapentin can be helpful.

NEUROFIBROMAS

Nonmalignant Cutaneous and Subcutaneous Neurofibromas

Various types of neurofibromas are common manifestations of NF1. Cutaneous neurofibromas typically emerge in the teenage years and increase in numbers with increasing

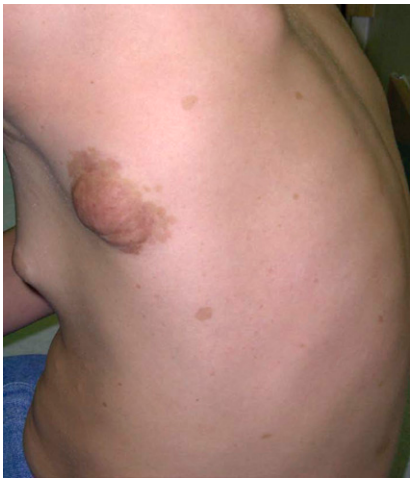

FIGURE 4
Plexiform neurofibroma adjacent to the left axilla.

age (Fig 4). Sometimes they may be seen in younger children, often visible with side lighting as subtle skin bumps. Neurofibromas are present in almost all adults with NF1 (although the numbers vary greatly), and they usually first appear on the trunk and then extend to the extremities, neck, and face. Some people may have relatively low numbers of small cutaneous neurofibromas, and others may be carpeted with hundreds or even thousands. They often have a mild purplish coloration and may either be raised above the skin or pucker subcutaneously. Cutaneous neurofibromas are benign tumors; however, by virtue of sheer numbers and ready visualization, these tumors can significantly affect quality of life. Removal of neurofibromas by a plastic surgeon or dermatologist can be recommended if they rub on clothing or cause discomfort. Laser surgery and electrodessication have been used by some providers, although long-term outcome data are not available.

Summary and Recommendations About Skin and Cutaneous Neurofibromas

The following can be summarized about skin and cutaneous neurofibromas:

- cutaneous manifestations are the usual presenting symptoms of NF1;
- pruritus is common among patients with NF1;
- the number of CALMs does not predict severity of NF1;
- cutaneous neurofibromas (other than cutaneous plexiform neurofibromas) are not at risk for malignant transformation but may have significant impact on quality of life; and
- in a child with NF1, it is not possible to predict future neurofibroma burden.

Plexiform Neurofibromas

Plexiform neurofibromas are a distinct type of neurofibroma that arise from 1 or multiple nerve trunks or branches (Fig 5). Unlike cutaneous neurofibromas, plexiform neurofibromas often come to attention early in childhood and are believed to be congenital lesions. Plexiform neurofibromas are found in approximately 50% of individuals with NF1 by whole-body MRI in adults, but less than 20% of individuals will require any intervention during childhood.[23–25] Plexiform neurofibromas may have overlying skin manifestations (such as thickened orange-peel overlying skin with a purplish brown coloration), may also have an

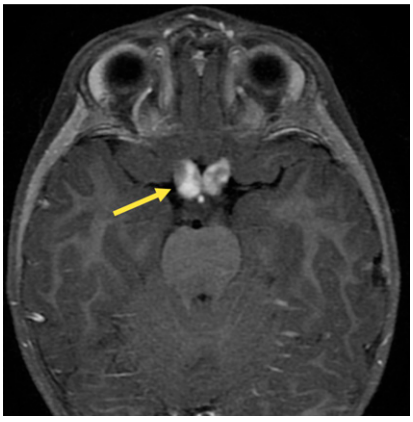

FIGURE 5
OPG affecting the right (greater than left) optic pathway (arrow).

associated hairy patch or region of hyperpigmentation, and may tend to have a heterogeneous texture or nodularity on palpation. Plexiform neurofibromas can occur in any area of the body, including the head and neck, orbit, extremities, thorax, paraspinal nerve roots, abdomen, and pelvis. These tumors may be asymptomatic or can cause pain and morbidity by compression of adjacent structures. Plexiform neurofibromas are usually difficult to remove in their entirety because of interdigitation into normal tissues and peripheral nerves. Persistent pain at the site of a plexiform neurofibroma may indicate transformation to an MPNST (see Malignancies Related to NF1). Nodular neurofibromas are a subtype of plexiform neurofibromas that have a relatively homogenous appearance on MRI and are more likely to have an atypical histology on biopsy; these tumors may be a precursor to MPNSTs.

Summary and Recommendations About Plexiform Neurofibromas

The following can be summarized about plexiform neurofibromas:

- believed to be congenital lesions;
- are present in approximately 50% of people with NF1, but less than 20% will require any intervention during childhood; and
- are benign tumors that may transform into MPNSTs (usually accompanied by symptoms such as pain, rapid growth, or neurologic dysfunction).

GLIOMAS OF THE CENTRAL NERVOUS SYSTEM

Optic Pathway Gliomas

Optic pathway gliomas (OPGs) (Fig 6) are the most common central nervous system (CNS)–associated tumor seen in children with NF1 and can be detected in approximately 15% to 20% of pediatric patients with NF1.[26,27] Symptomatic OPGs are most commonly detected in children younger than 6 years during ophthalmologic surveillance (before any vision complaint). The majority of OPGs are classified as pilocytic astrocytomas (World Health Organization grade 1). The large majority of these lesions remain indolent without effect on vision; however, a small percentage can lead to vision loss and other morbidity such as precocious puberty. There is no way to reliably predict which tumors will result in a decrease in visual acuity or visual function. Lesions located in the optic chiasm and posterior optic tracts appear more likely to require treatment than those in the prechiasmatic optic nerve. Lesions located close to or involving the hypothalamus are more likely to result in precocious puberty.[27] Data also have revealed that female patients with OPGs are more likely to progress and require treatment, but both male and female patients should have the same surveillance.[28–30]

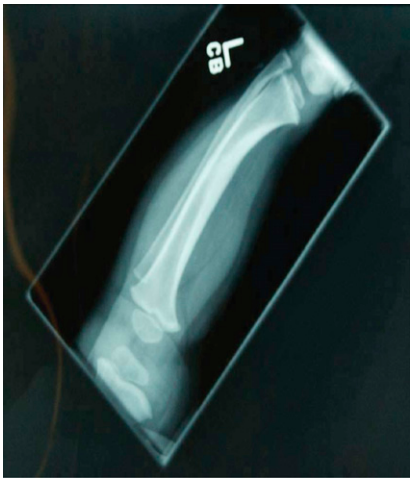

FIGURE 6
Anterior bowing of the left tibia. Note cortical thickening with medullary narrowing proximal to the segment of anterior bowing. The fibula is also bowed.

Children with known or suspected NF1 should undergo screening and surveillance ophthalmologic examinations at least annually from the time of diagnosis of NF1 or suspected NF1 by an ophthalmologist familiar with management of NF1, and this examination should be performed more frequently or repeated if there is concern. OPGs most often develop before 6 years of age, when it may be difficult to obtain a reliable ophthalmologic evaluation and when children are less likely to complain of visual symptoms. For these reasons, there has been some suggestion to screen more frequently, such as every 6 months, before 6 years of age, but this has not yet become standard practice.[31] The use of screening and surveillance neuroimaging in the setting of NF1 also is controversial; the Optic Pathway Task Force has recommended against the use of screening MRI,[26] but others have suggested that outcomes may be improved by early detection in young children.[32,33] Because of the potential for glioma to have contiguous involvement of the hypothalamus, regular monitoring for early pubertal development and monitoring for acceleration in linear growth is recommended for all patients. There is consensus that ophthalmologic examination should be performed at least annually, and decisions about more frequent surveillance or the use of diagnostic imaging in the child who is asymptomatic are best made by the ophthalmologist and clinicians caring for each patient.

OPGs in people with NF1 have a better prognosis than sporadic OPGs in people without NF1. Treatment is considered when there is decrease of visual function such as decrease in visual acuity, constriction of visual fields, change in color vision, or afferent pupillary defect. After treatment, two-thirds of people have stabilization or improvement of vision. Traditional chemotherapy (vincristine and carboplatin) is often used initially, although there are newer targeted, NF1-specific treatments in the pipeline that may be used in cases of progression or recurrence. Radiotherapy and surgery

TABLE 3 Indications for Neuroimaging Studies in Children With NF1

Indications for Consideration of Neuroimaging Studies
• Focal sensory or motor symptoms
• New onset of seizures
• Headaches that are increasing in frequency or severity
• Signs of increased intracranial pressure (headaches, visual disturbance, increased lethargy)
• Transient ischemic attack or stroke-like symptoms
• Decline in visual acuity or visual fields
• Precocious puberty or accelerated growth
• Head and neck plexiform neurofibromas increasing in size or with new development of pain
• Encephalopathy or cognitive deterioration
• Extremity asymmetry (ie, leg-length discrepancy)

are usually contraindicated except in rare situations.

Summary and Recommendations About OPGs

The following can be summarized about OPGs:

- highest morbidity is in children younger than 6 years, but young children are not likely to report symptoms;
- less than half of patients with OPGs develop vision loss or other symptoms;
- changes in linear growth rate may reveal the presence of OPGs affecting the hypothalamic-pituitary axis, but this can be treated by an endocrinologist (if needed) and is not an indication for chemotherapy;
- treatment with modified chemotherapy is often effective in halting further vision loss and/or improving vision, so early treatment is crucial;
- surveillance by a pediatric ophthalmologist familiar with NF1 (at least annually); and
- neuroimaging is an option as a baseline study and is mandatory for signs and symptoms outlined in Table 3.

Characteristic MRI Findings, Low-Grade Gliomas, and Brainstem Expansions

One of the most frequent findings in patients with NF1 is the occurrence of hyperintense lesions on T2-weighted MRI of the brain. These are located predominantly in the basal ganglia, brainstem, and cerebellum. They have been called "unidentified bright objects," "focal areas of signal intensity [FASI]," "NF [neurofibromatosis] spots," or "spongiform changes" because the true nature and significance of these lesions is still undetermined. The most proper designation at this time is "T2 hyperintensities." These lesions become evident between 2 and 10 years of age, and then regress by the second decade.

If an MRI-based T2-weighted hyperintensity reveals contrast enhancement or mass effect, a low-grade glioma should be suspected. Low-grade gliomas in people with NF1 can occur anywhere in the brain.[34] The brainstem is a common region to have both T2-weighted hyperintensities and low-grade gliomas; the latter are often accompanied by expansion of the brainstem with or without enhancement. Similar to OPGs, a biopsy is rarely performed on brainstem gliomas to avoid iatrogenic symptoms. Brainstem gliomas are typically benign and progress clinically in only one-third or fewer of cases.[35] Children with NF1 and a known brainstem-expansive lesion are monitored for development of clinical symptoms referable to the location such as headache, hydrocephalus, or cranial nerve dysfunction. Similar to OPGs, NF1-associated brainstem gliomas are more indolent than those not associated with NF1 and most often do not require clinical intervention or treatment, suggesting that conservative management is optimal.

Malignancies Related to NF1

The most frequent neoplasms associated with NF1 in children are MPNSTs, gliomas, pheochromocytomas, and leukemia. Malignant tumors are the most worrisome complications of NF1. Malignancy, mainly MPNSTs, and cardiovascular complications are the major causes of reduced life expectancy in NF1, but this is reflective mostly of adults. Life expectancy is decreased by 8 to 15 years.[36,37]

MPNSTs usually arise by malignant transformation of an existing plexiform or nodular neurofibroma. For individuals with NF1, there is a lifetime risk of 8% to 13% to develop an MPNST, which typically develops during or after young adulthood.[38] Treatment involves surgical resection, radiotherapy, and chemotherapy; however, 5-year survival remains at less than 20%. The primary care provider should be alert to the possibility of malignant transformation in a patient who has a known plexiform neurofibroma with the development of pain (especially persistent pain or pain that wakes the patient from sleep), rapid growth, or change in consistency (eg, from soft and pliable to firm and hard). Patients and families should also be educated in reporting such symptoms for potential referral to a sarcoma specialist. Patients who are symptomatic should undergo MRI of the affected area and consideration of a positron emission tomography with radiographic computed tomography (PET-CT) scan, which, in some larger studies, has been shown to help in distinguishing benign neurofibromas from MPNSTs.[39,40] These tumors are staged and treated as malignant soft-

tissue sarcomas, preferably at a dedicated sarcoma center. Targeted medical therapies for MPNSTs are under exploration but have not been as effective as wide surgical resection and are only used as adjuvant therapy for surgery.

Other pediatric malignancies occur less frequently in NF1, including low- to high-grade astrocytomas, rhabdomyosarcoma, pheochromocytoma, and juvenile myelomonocytic leukemia.[41] High-grade astrocytomas tend to occur in older people, and low-grade astrocystomas and/or gliomas of the posterior fossa can be symptomatic. Pheochromocytomas can lead to increased catecholamine concentrations and consequent hypertension but are rare in children with NF1. Most experts recommend screening for pheochromocytoma if there is an acute and dramatic increase in heart rate and/or blood pressure. Pheochromocytoma is often diagnosed incidentally in patients with NF1 because of a higher frequency of imaging for other neoplasms.[42] Breast cancer occurs more frequently in young adults with NF1 than in the general population.[43,44]

Summary and Recommendations About Malignancies Related to NF1

The following can be summarized about malignancies related to NF1:

- MPNSTs most often develop within a plexiform neurofibroma;
- diagnostic imaging is an option to assess the extent of a plexiform neurofibroma at the time of diagnosis and is clinically indicated for signs and symptoms outlined this section above and/or in Table 3; a fludeoxyglucose PET-CT scan may be useful in detecting malignant transformation of a plexiform neurofibroma;
- hypertension may be indicative of pheochromocytoma, but most hypertension is detected incidentally;
- there is an increased risk of breast cancer in young adults with NF1; and
- other types of malignancy may occur in NF1.

NEUROLOGIC MANIFESTATIONS

Individuals with NF1 are more susceptible to developing headaches, particularly common migraine headaches.[45] Brain MRI may be indicated depending on the acuity of symptoms but is not necessary if the headaches are easily controlled and if neurologic examination is normal. Brain MRI would be indicated for signs or symptoms suggestive of a new intracranial mass such as symptoms of increased intracranial pressure, a new neurologic deficit with apparent or possible CNS origin, or new onset of seizures (Table 3). Once an acute process is ruled out, headaches in NF1 can be managed as they would be for similar-type headaches in the general population. A referral to a headache specialist may be indicated for headaches that are frequent and/or difficult to control with nonprescription medication. Typical lifestyle modifications for sufferers of common migraines should be offered to the person with NF1 and headaches once more-acute pathology has been ruled out.

Individuals with NF1 are more susceptible to developing seizures compared with the general population. This higher risk of seizures may be attributable, at least in part, to structural or vascular changes in the individual with NF1.[46] Seizures can occur at any age, are usually focal, and warrant concern about a focal CNS lesion; neuroimaging with brain MRI is recommended at presentation with new onset of seizure.

SUMMARY AND RECOMMENDATIONS ABOUT HEADACHES AND SEIZURES

The following can be summarized about headaches and seizures:

- headaches (often migraine) are more common among individuals with NF1;
- imaging is often not needed for a headache that can be controlled with nonprescription medication if neurologic examination is normal, and the approach to treatment is usually the same as for similar-type headaches in a patient without NF1;
- seizures are more common among patients with NF1, and an initial seizure should prompt consideration for neuroimaging; and
- other indications for neuroimaging are summarized in Table 3.

IMAGING CONSIDERATIONS

As described in preceding sections, diagnostic imaging is often used in the care of patients with NF1 for applications such as tumor surveillance (assessment of burden of tumor and progression). It has been standard practice to use clinical assessment to determine if, when, and where to image. MRI is the most common modality for imaging of plexiform neurofibromas and brain lesions such as OPGs and low-grade gliomas. In addition to MRI, PET-CT may be indicated in the assessment of possible malignant transformation of a neurofibroma. The value of imaging to assess the extent of a plexiform neurofibroma in the absence of evidence of progression is debatable because treatment decisions are typically based on clinical, and not radiographic, progression. Therefore, decisions about whether, when, and where to image are judgments best left to providers experienced in caring for children with NF1.

NEURODEVELOPMENTAL

Infants and toddlers with NF1 may have mild motor developmental

delays, such as muscular hypotonia, which typically improves slowly through childhood. The NF1 population has an increased incidence of speech and language issues (particularly oromotor deficits, including speech dyspraxia, which can improve with appropriate speech therapy), velopharyngeal insufficiency, misarticulation, and disfluency.[47,48] Problems with hearing are not typical for patients with NF1, and any suspicion about hearing problems should be approached as they would be for any other pediatric patient.

Approximately 50% of individuals with NF1 have some type of learning problem.[49,50] Intellectual disability occurs in a minority of patients at a rate slightly higher than that in the general population. Intellectual disability should increase suspicion for chromosome 17 microdeletion involving the *NF1* locus, and the microdeletion has other implications such as increased tumor burden and risk of malignancy (including MPNSTs). Typical learning difficulties include problems with executive function and nonverbal learning disabilities such as reduced processing speed. Attention-deficit/hyperactivity disorder also occurs in at least 50% of individuals with NF1, and approaches to treatment are akin to those used in the general population.[49] Having a diagnosis of NF1 does not result in a predictable pattern of learning disability, so each person with NF1 should be carefully monitored and offered psychoeducational and/or neuropsychological and academic testing at the first sign of any academic or social concerns. The goal of such testing is to determine specific areas of strength and weakness and to provide appropriate interventions such as a 504 plan or an individualized education program. A diagnosis of NF1 may help underscore the need for speech, occupational, and/or physical therapy.

Some studies have suggested that NF1 increases susceptibility to autism spectrum disorder, especially in the realm of communication skills.[51–53] Many individuals with NF1, particularly teenagers, demonstrate difficulty with social pragmatics, and this can adversely affect social adjustment, even without a formal diagnosis of autism spectrum disorder. Individuals with NF1 typically have a personality profile with delayed social maturity compared with peers. For this, and perhaps other reasons, they often experience anxiety. Efforts to help in learning coping skills for social anxiety are often indicated.

SUMMARY AND RECOMMENDATIONS ABOUT DEVELOPMENTAL ISSUES

The following can be summarized about developmental issues:

- learning difficulties are common among patients with NF1 and typically are more severe among patients with an *NF1* microdeletion or complete gene deletion;
- speech articulation difficulties are common, and many patients with NF1 require speech therapy;
- executive function and attention are often affected, and neuropsychological testing is desirable to identify the particular challenges faced by each individual;
- a 504 accommodation plan and/or an individualized education program can be considered for school;
- social difficulties are common, but the rate of autism is unknown; consider referral to psychotherapy for social anxiety or coping difficulties;
- the evaluating therapists and educators must communicate back to the primary care provider regarding developmental and educational progress and additional recommendations; and
- support adherence with "2017 Recommendations for Preventive Pediatric Health Care" from the American Academy of Pediatrics.[54]

SKELETAL GROWTH

NF1-related skeletal abnormalities include macrocephaly, short stature, and osteopenia as well as localized bone dysplasias. Macrocephaly and relative macrocephaly (ie, head size disproportionately larger than height) typically require no special follow-up. Congenital hydrocephalus is not more common in NF1, but acquired hydrocephalus attributable to aqueductal stenosis can occur. Postnatal growth delay is seen in approximately one-third of children, and the pubertal growth spurt is slightly reduced. Height growth velocity is typically normal for both sexes during childhood, and growth charts made specifically for children with NF1 are available.[55]

The etiologies of relative macrocephaly and short stature are not understood. Some children have responded to growth-hormone therapy to treat short stature. Although short-term tumor induction has not been observed in those treated with growth hormone, the presence of insulin-like growth factor receptors in Schwann cells is concerning for long-term induction of tumors if treated with growth-hormone therapy. Growth-hormone therapy in NF1 is implemented cautiously and is generally reserved for people who have poor growth velocity and documented test results of low growth-hormone stimulation (ie, <5 ng/mL). Children with NF1 who have accelerated growth velocity or tall stature in childhood with or without precocious puberty should be evaluated for associated gliomas (OPGs) involving the chiasm and/or hypothalamic-pituitary axis. Disproportionate growth of the extremities, including leg-length discrepancy, is generally associated with plexiform neurofibromas causing local bone growth acceleration and soft-tissue hypertrophy.

Childhood osteopenia is frequent in NF1, but there is only a slightly increased risk for fractures.[56] The etiology of osteopenia is unknown,

although it may be related to decreased musculoskeletal strength and poor neuromuscular coordination, leading to decreased bone remodeling. Children with NF1 have a higher prevalence of insufficient concentrations of serum (25-hydroxycholecalciferol) vitamin D, which modulates calcium and phosphorus bone metabolism (important in bone deposition). Periodic assessment of vitamin D concentrations, especially in higher latitudes, cultures without vitamin D fortification of food, and children who have less sun exposure, are helpful in determining the need for and dosing of vitamin D supplementation.

A few distinctive skeletal manifestations are part of the NF1 diagnostic criteria (sphenoid wing dysplasia, dystrophic scoliosis, and long-bone dysplasia[57,58]). Although each of these is relatively uncommon, individually occurring in fewer than 10% of individuals with NF1, each can cause significant morbidity, underscoring the need for careful surveillance. These skeletal anomalies arise as focal manifestations, usually unilateral or involving a short segment of the spine. Sphenoid wing dysplasia is typically congenital, and at least half of cases develop ipsilateral periorbital plexiform neurofibromas. Long-bone dysplasia (especially of the tibia), defined on radiographs as a thickened cortex with a narrowed medullary cavity with or without cysts, usually emerges in late infancy or in toddlers with both anterior and lateral bowing (Fig 7). This dysplasia can progress to fracture with poor bone healing, resulting in pseudarthrosis; therefore, tibial radiography is recommended in children with anterior tibial bowing before they begin to walk. More than two-thirds of infants presenting with congenital pseudarthrosis of the tibia have NF1.

In addition to typical scoliosis that usually arises in early adolescence, children with NF1 also can have dystrophic scoliosis (Fig 8), which is a short-segment, sharply angulated curve associated with underlying vertebral-body and rib abnormalities and sometimes with adjacent plexiform neurofibromas. Specific features of dystrophic scoliosis include vertebral scalloping, penciling of ribs, spindling of transverse processes, and wedging of one or more vertebral bodies. This condition generally presents in early childhood and progresses rapidly over a few years, requiring surgical intervention with spine appliances through the growth years until definitive spinal fusion can be performed. Other distinctive focal skeletal manifestations include nonossifying fibromas of the distal femur or proximal tibia, cranial bone defects, giant-cell tumor of the jaw, and ossifying subperiosteal hematomas.

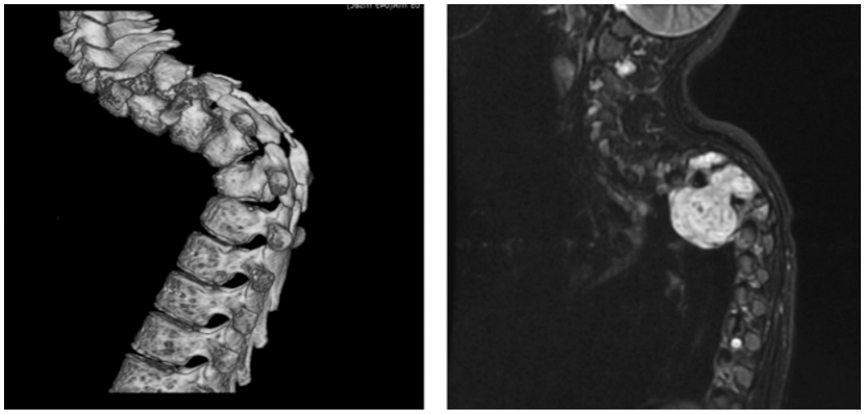

FIGURE 7
Dystrophic scoliosis in a patient with NF1. The image on the left shows a computed tomography reconstruction of the vertebral column revealing acute angle kyphoscoliosis. The image on the right, from the same patient, reveals a relatively large paraspinal plexiform neurofibroma in the area of spinal deformity.

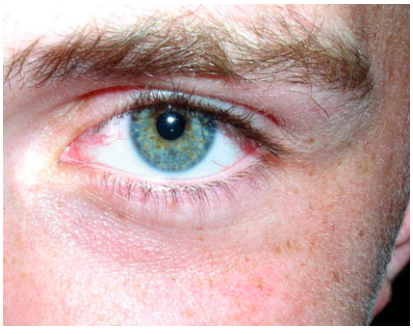

FIGURE 8
Multiple Lisch nodules with peripheral clustering between 3:30 and 8:30.

Chest-wall deformities, such as pectus excavatum or carinatum, occur in approximately one-third of individuals with NF1; this manifestation overlaps with other RASopathy conditions, primarily Noonan syndrome. Localized bone erosions and/or bone dysplasia (sphenoid wing dysplasia) can occur with adjacent growth of plexiform neurofibromas, especially scalp neurofibromas. Dental abnormalities and increased caries may also occur.[59]

Summary and Recommendations of Skeletal Features

General Skeletal Features

The following can be summarized about general skeletal features:

- macrocephaly is typically benign;
- short stature may necessitate an endocrinology referral;
- accelerated growth and/or early puberty indicates referral to endocrinology and brain MRI for a hypothalamic tumor; and
- osteopenia and vitamin D insufficiency is frequent in NF1 in children.

Specific Skeletal Features

The following can be summarized about specific skeletal features:

- sphenoid wing dysplasia is often associated with unilateral periorbital plexiform neurofibromas;
- dystrophic scoliosis and long-bone dysplasia require clinical surveillance and early orthopedic referral; and
- nonossifying fibromas, pectus anomalies, and cranial bone defects do not usually require intervention.

Other Medical Complications

Approximately one-third of patients with NF1 develop serious medical complications; however, with the variability of clinical manifestations and the progressive nature of NF1, it is not possible to determine the prognosis after establishing a diagnosis, especially at a young age. The reported incidence of complications in NF1 varies from study to study, mostly because of biased patient selection by age and specialty referral but also because of inconsistent use of diagnostic criteria and variable use of imaging. The rate of complications is often overestimated because most studies involve patients in hospitals or referral clinics.

VASCULAR

A wide range of congenital cardiac anomalies, vascular stenoses and aneurysms, and cerebrovascular lesions are associated with NF1. NF1 vasculopathy can involve different-sized vessels, ranging from small arterioles to the aorta, and, in many cases, remains asymptomatic.[60] Renal artery stenosis, with and without internal renal arteriopathy, is the most frequent site of symptomatic vasculopathy and can be an important cause of hypertension in children with NF1.[60] The prevalence of hypertension in children and teenagers with NF1 is higher than that in the general population and is often related to vascular lesions (renal artery stenosis, aortic stenosis, and coarctation).[61] The true prevalence may be lower than reported in studies that are based on patients at specialty clinics but still necessitates regular assessment of blood pressure in patients with NF1.

Essential hypertension is also a frequent occurrence in teenage patients with NF1. Workup of hypertension in the pediatric age group should include Doppler ultrasonography of the aorta and renal arteries, renal arteriography, or magnetic resonance angiography.

Congenital heart disease occurs more commonly in patients with NF1 than in the general population, with a frequency of 2% reported in a large international NF1 database. Pulmonic stenosis is by far the most common congenital heart defect seen in NF1.[60,62] Other cardiac malformations include atrial septal defect, ventricular septal defect, aortic coarctation, tetralogy of Fallot, mitral valve prolapse, and hypertrophic cardiomyopathy.[62,63] Congenital cardiac malformations and hypertrophic cardiomyopathy may be more common in patients with large *NF1* deletions.[64] Children with NF1 and a cardiac murmur or those with microdeletion of the *NF1* locus should be evaluated with a cardiology examination and echocardiography. It remains unclear whether screening of all patients with NF1 with echocardiography is indicated; however, those with a large deletion should be evaluated.[64]

Cerebrovascular abnormalities are seen in 2.5% to 6% of children with NF1 screened by MRI or magnetic resonance angiography of the brain.[65] Stenotic lesions, particularly of the internal carotid, middle cerebral, or anterior cerebral arteries, are most common, although aneurysms can also be seen. Lesions may remain stable and asymptomatic but can also develop progressive narrowing over time, leading to an increased risk for stroke and focal neurologic signs. Moyamoya syndrome, a progressive stenosis of internal carotid arteries with concomitant formation of tortuous arterial collaterals, occurs in a subset of patients, particularly those with a history of cranial radiotherapy.[66] Outcomes of NF1 cerebrovascular disease may be improved by treatment with antiplatelet agents such as aspirin and revascularization surgery for those with progressive lesions.[66] Radiotherapy to the brain should be avoided when at all possible for children with NF1 because of the risk of moyamoya syndrome.

SUMMARY AND RECOMMENDATIONS FOR VASCULAR COMPLICATIONS

The following can be summarized about vascular complications:

- Examination of the newborn should include attention to the increased risk of congenital heart malformations such as pulmonic stenosis. Referral to cardiology and/or consideration for an echocardiogram should be based on the clinical examination.
- Blood pressure should be monitored at least annually.
- Persistent hypertension requires assessment of large vessels, including renal arteries.
- Moyamoya syndrome responds well to revascularization surgery, but patients should continue receiving prophylactic-aspirin therapy under the direction of a neurosurgeon even after successful surgery.
- Neuroimaging is an option as a baseline study and is mandatory for signs and symptoms outlined in Table 3.

GASTROINTESTINAL

Constipation and midgastric abdominal pain are common in children with NF1. A recent study revealed that 30% of a small group of children with NF1 met diagnostic criteria for constipation, including an enlarged rectal diameter.[67] Management with diet modification and gentle stool softeners, such as polyethylene glycol, is often helpful. Abdominal migraine has been reported

TABLE 4 Health Supervision Guidelines for Children With NF1

	Infancy, 1 mo to 1 y	Early Childhood, 1–5 y	Late Childhood 5 y to Puberty	Adolescence and Young Adulthood (Postpubertal)
Genetic counseling				
Genetic etiology	X[a]	—	—	X[b]
Genetic testing	As needed[c]	As needed[c]	As needed[c]	As needed[c]
Future reproductive planning	X[a]	—	X[b]	X[d]
Medical evaluation and treatment[e]				
Monitor growth rate	X	Annual	Annual[f]	Annual
Measure head circumference	X	X	X	—
Blood pressure	—	Annual	Annual[fg]	Annual[f]
Attention to cardiac examination	X	—	—	—
Skin examination	X	Annual	Annual	Annual
Bone examination or scoliosis examination	X[b]	Annual	Annual[f]	Annual[f]
Neurologic examination	X	Annual	Annual[f]	Annual[f]
Ophthalmologic examination	Annual	Annual	Annual	As needed
Monitor precocious puberty	—	Annual[f]	Annual[f]	—
Diagnostic imaging examinations[e]	As needed[e]	As needed[e]	As needed[e]	As needed[e]
Developmental and psychosocial evaluation[g]	X	X	X	X
Anticipatory guidance; phenotype review[h]	X[a]	X[b]	X[b]	X[b]
Family support	X	X	X	X
Support groups	X	X	X[b]	X[b]
Long-term planning	X	X	X[b]	X[b]
Sexual and reproductive issues	—	—	X[b]	X

X indicates to be performed; —, not applicable.

[a] Or at the time of diagnosis.

[b] At least once in this time period.

[c] See discussion.

[d] Before transition to adult care.

[e] As needed for significant abnormalities and/or new signs.

[f] Advise for more frequent visits as indicated.

[g] Ensure compliance with "2017 Recommendations for Preventive Pediatric Health Care" from the American Academy of Pediatrics.[54] "Developmental and psychosocial evaluation" in this table should follow the standard recommendations for pediatric preventive care.

[h] Anticipatory guidance; phenotype review: review age-related medical and developmental issues of NF1 with the patient and family, including the following: issues related to motor and language development and potential need for early intervention (eg, speech therapy); learning and behavioral problems (eg, attention-deficit/hyperactivity disorder), school performance, and potential need for neuropsychological testing; and anticipatory guidance about concerning signs and symptoms related to plexiform neurofibromas.

as a cause of episodic abdominal pain in children with NF1 and may be more common than anatomic causes of abdominal pain.[68] Treatment with migraine medications, such as propranolol and cyproheptadine, can be helpful. Plexiform neurofibromas involving the mesentery or retroperitoneum are only rarely a source of abdominal pain, vomiting, and abdominal mass. Intestinal polyps occasionally occur, with pathology consistent with neurofibromas or schwannomas. Gastrointestinal stromal tumors (GISTs) are benign tumors of the small intestine that can cause gastrointestinal bleeding and abdominal pain in patients with NF1.[69] GISTs are rare in childhood and do not respond to tyrosine kinase inhibitors, unlike some GISTs that occur in the general population and can be treated by these medications.

SUMMARY AND RECOMMENDATIONS FOR GASTROINTESTINAL COMPLICATIONS

The following can be summarized about gastrointestinal complications:

- Constipation is common in children with NF1, but treatment does not differ from other children.
- Midgastric abdominal pain is more common in children with NF1, and abdominal migraine should be considered as a possible cause; abdominal tumors are a less common cause of abdominal pain.

MEDICAL HOME AND TRANSITION

The primary care medical home is valuable for children with NF1. In addition to the broad principles of the medical home, surveillance plans for medical, developmental, and behavioral issues are important in NF1, especially during childhood. Determination of appropriate referrals to pediatric medical subspecialists are also important to optimize care.[70,71] Health supervision guidance is outlined in several sections in this document and in Table 4. Referral to and coordination with community-based services, especially educational and behavioral services, are frequently necessary. Collaboration with pediatric medical subspecialists and programs,

particularly genetics, neurology, ophthalmology, orthopedics, oncology, and dermatology, at regional referral centers on an ongoing basis can be helpful for primary care clinicians and families.

NF1 is a lifelong condition, and some of the complications are more likely to occur among adults with the disorder. These include many of the tumor-related complications, ranging from quality-of-life concerns to potentially life-threatening complications. Adults with NF1 also may continue to face social and vocational challenges because of the cognitive profile associated with the disorder. Medical and psychosocial supports should be continued for young adults. The American Academy of Pediatrics offers detailed guidance on how to plan and execute better health care transitions for all patients,[72] including a step-by-step algorithm. Patients with NF1 benefit from avoiding a gap in care during the transition from pediatric to adult providers.[73]

INTO THE FUTURE: PROSPECTS FOR MEDICAL TREATMENT OF NF1

The mechanisms that underlie various complications of NF1 are gradually coming to light, and this is leading to the development of new approaches to therapy. Examples are drugs that target the Ras signaling mechanism that is regulated by the *NF1* gene product or molecules that mediate communication between cells that are important in tumor formation. Preclinical studies and human clinical trials are underway, for the most part, by using drugs that were originally developed for treatment of other disorders that involve aberrant cell signaling such as cancer.[74] Medical therapy for various features of NF1 are likely to become increasingly available; clinical trials can be identified through ClinicalTrials.gov, and sources such as the Children's Tumor Foundation (www.ctf.org) provide up-to-date information on current treatment. This is a time of great hope for individuals with NF1 and their families, with the prospect of new treatments that will significantly improve quality of life and health in the years to come.

Pediatricians can play a critical role in improving outcomes by identifying signs that can lead to a diagnosis and by conducting appropriate surveillance. There are also potential new therapies, primarily for tumor-related aspects of NF1, that are currently in clinical trials and not yet part of standard clinical practice. A few key areas that will benefit from future efforts toward a systematic review to facilitate evidence-based practice guidelines include the following: optimal ophthalmologic, orthopedic, and neuropsychological assessments for timely interventions. Likewise, more data are needed to determine if and when to perform surveillance imaging by whole-body or regional MRI for routine tumor surveillance.[23,24,75]

SUPPORT GROUPS AND RESOURCES

The following are support groups and resources:

Children's Tumor Foundation (includes information about NF1 clinic locations): 120 Wall Street, New York, New York 10005-3904 (phone: 800-323-7938 [toll free] or 212-344-6633; fax: 212-747-0004; e-mail: info@ctf.org; Web site: www.ctf.org);

Neurofibromatosis Network: 213 South Wheaton Avenue, Wheaton, Illinois 60187 (phone: 800-942-6825; fax: 630-510-8508; e-mail: admin@nfnetwork.org; Web site: www.nfnetwork.org); and

ClinicalTrials.gov: a service of the US NIH, ClinicalTrials.gov is a registry and results database of publicly and privately supported clinical studies of human participants conducted around the world (Web site: https://clinicaltrials.gov/).

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ABBREVIATIONS

CALM: café-au-lait macule
CNS: central nervous system
GIST: gastrointestinal stromal tumor
JXG: juvenile xanthogranuloma
MPNST: malignant peripheral nerve sheath tumor
NF1: neurofibromatosis type 1
NIH: National Institutes of Health
OPG: optic pathway glioma
PET-CT: positron emission tomography with radiographic computed tomography
PSV: pathogenic sequence variant

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