Health Supervision for Children With Neurofibromatosis

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ABSTRACT

Neurofibromatosis 1 is a multisystem disorder that primarily involves the skin and nervous system. Its population prevalence is 1 in 3500. The condition usually is recognized in early childhood, when cutaneous manifestations are apparent. Although neurofibromatosis 1 is associated with marked clinical variability, most affected children do well from the standpoint of their growth and development. Some features of neurofibromatosis 1 are present at birth, and others are age-related abnormalities of tissue proliferation, which necessitate periodic monitoring to address ongoing health and developmental needs and to minimize the risk of serious medical complications. This clinical report provides a review of the clinical criteria needed to establish a diagnosis, the inheritance pattern of neurofibromatosis 1, its major clinical and developmental manifestations, and guidelines for monitoring and providing intervention to maximize the growth, development, and health of an affected child.

INTRODUCTION

This clinical report was designed to assist the pediatrician in caring for the child in whom the diagnosis of neurofibromatosis has been made. The pediatrician’s first contact with the child is usually during infancy. However, neurofibromatosis occasionally is diagnosed in the fetus during pregnancy, and the parents are referred for advice. Therefore, guidance is also offered for the pediatrician in advising expectant parents whose fetus is affected by neurofibromatosis.

At least 2 distinct types of neurofibromatosis are recognized: neurofibromatosis 1 (NF1 [previously known as von Recklinghausen disease or generalized neurofibromatosis]) and neurofibromatosis 2 (NF2 [previously known as either central or bilateral acoustic neurofibromatosis]). Only issues concerning the diagnosis and management of NF1 are addressed in this clinical report.

NF1 is a multisystem disorder in which some features may be present at birth and others are age-related manifestations. It affects approximately 1 in 3500 individuals. A National Institutes of Health (NIH) Consensus Development Conference regarding NF1 demarcated the following 7 features, of which 2 or more are required to establish the diagnosis of NF1:

1. six or more cafe-au-lait spots (CLSs) equal to or greater than 5 mm in longest diameter in prepubertal patients and 15 mm in longest diameter in postpubertal patients;
2. two or more neurofibromas of any type or 1 plexiform neurofibroma;
3. freckling in the axillary or inguinal regions;
4. optic glioma (optic pathway glioma);
5. two or more Lisch nodules (iris hamartomas);
6. a distinctive osseous lesion, such as sphenoid wing dysplasia or cortical thinning of the cortex of long bones, with or without pseudoarthrosis; and
7. a first-degree relative (parent, sibling, or child) with NF1 according to the aforementioned criteria.

In addition, although areas of increased T2 signal intensity are commonly identified on MRI of the brain, they do not represent an obligatory feature of NF1 and do not have any clinical significance. Therefore, the NIH Consensus Development Conference did not recommend routine neuroimaging of the brain as a means of establishing a diagnosis of NF1.
Diagnosis in nonfamilial pediatric cases, which represent 50% of those affected with NF1, may be difficult, because certain clinical features are age dependent. For the same reason, the severity of NF1 in later life may be underestimated for an affected child.

CLSs usually represent the initial clinical manifestation of NF1 and may be present at birth or first appear in infancy (Fig 1). Although approximately 80% of those with NF1 will have more than 5 CLSs by 1 year of age, occasionally these characteristic lesions are not present. CLSs tend to increase in number and size throughout early childhood.

Plexiform neurofibromas, which are found in at least 25% of individuals with NF1, usually are congenital and, if located on the face, trunk, or extremities, can result in disfigurement (Fig 2). Early in life, the lesions may only be recognized as soft tissue enlargement or a patch of cutaneous hyperpigmentation with or without hypertrichosis. Tibial dysplasia, when present, occurs at birth and is manifested by anterolateral bowing of the lower leg (Fig 3). Its presence requires early orthopedic intervention because of the risk of fracture and development of pseudoarthrosis that results from healing, which occurs in approximately 2% to 3% of children with NF1. Skinfold freckling (Fig 4) that develops in early childhood, typically between the ages of 3 and 5 years, usually is the second feature noted in children with NF1 and is present in three fourths of affected individuals. Dermal neurofibromata usually first appear in the prepubertal period but may develop at a much earlier age and are present in virtually all affected individuals by adulthood (Fig 5). They become evident as skin nodules or tags located in cutaneous or subcutaneous tissues, as depressions in the skin with overlying purplish discoloration, or as firm nodules or cords in the deeper subcutaneous tissue. Increase in size and number of dermal neurofibromas coincide with puberty and pregnancy, but intermittent growth can persist throughout the life of an individual with NF1. Plexiform neurofibromas may present as subcutaneous masses that involve deep tissues. These lesions can be found in all
organ systems, giving rise to specific symptoms depending on size, location, and degree of encroachment on surrounding tissues. Marked growth of these lesions can occur anytime in childhood, followed by long periods of quiescence. Optic pathway gliomas are present in up to 15% of children with NF1 and represent the most common central nervous system tumor related to this disorder (Fig 6). They develop in children younger than 6 years. Although their natural history is often indolent, in approximately one third of patients with NF1, optic pathway tumors become symptomatic, and in approximately 5% of cases, the lesion results in visual loss, severe proptosis, and/or hydrocephalus. Precocious puberty also can be an occasional complication when the
optic pathway tumor involves the optic chiasm.\textsuperscript{20,21} In
the small proportion of symptomatic tumors in which clinically
significant growth or progressive visual loss develops, treatment is necessary.\textsuperscript{22} Treatment with car-
oblastine and vincristine sulfate has been effective in
amed-orbital plexiform neurofibroma.\textsuperscript{12}

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Malignant peripheral nerve sheath tumors represent the
most common neoplasm, occurring in approximately
5\% to 10\% of individuals with NF1.\textsuperscript{12,24} They usually
develop in adulthood and are heralded by the presence of
pain or rapid growth of a plexiform or deep nodular
neurofibroma; however, similar manifestations can oc-
cur with a benign lesion. Other malignancies occur less
frequently in patients with NF1, including pheochromocy-
toma, rhabdomyosarcoma, leukemia, and brain tu-
mors other than optic gliomas.\textsuperscript{12,25,26} Other associations
exist with NF1, such as vascular changes. Macrocephaly
affects most individuals with NF1.\textsuperscript{27} Short stature occurs
in one third of individuals with NF1 and does not seem
to be related to disease severity. Height-growth velocity
is normal for both genders during childhood, but the
pubertal growth spurt is slightly reduced.\textsuperscript{27} Growth
charts made specifically for children with NF1 are avail-
able.\textsuperscript{27,28} Neurofibromas develop in the gastrointestinal
tract in a small proportion of patients with NF1 and
usually present after early childhood. They may cause
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tract in a small proportion of patients with NF1 and
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bleeding and anemia or signs of functional or mechan-
ical obstruction. Rare forms of intraabdominal secretory
or nonsecretory neoplasms also represent low-frequency
associations. Evaluation for gastrointestinal complica-
tions should be pursued in the presence of unexplained
anemia or weight loss, abdominal bloating, sudden or
persistent abdominal pain, chronic diarrhea, signs of
malabsorption, gastrointestinal bleeding, or recurrent
emesis.29,30 Seizures occur in 6\% to 7\% of cases.12 Al-
though electroencephalographic abnormalities are com-
monly reported, electroencephalography is not routinely
recommended. If seizures are present, an intracranial
tumor must be excluded, although usually no etiology is
found. Nonossifying fibromas of the long bones and
especially the distal femur and proximal tibia, on occa-
sion, occur in adolescence or adulthood and can result in
fracture. Therefore, a screening radiograph of both knees
may be considered in early adolescence to provide ap-
propriate intervention for individuals in whom lesions
are detected.31 Scoliosis is present in 10\% to 30\% of NF1
cases. Both idiopathic and dystrophic forms occur12 and
can lead to diminished pulmonary function. Variability
in progression, however, makes it difficult to determine
the prognosis once scoliosis is detected, and close mon-
itoring is necessary after it has been discovered. An
increased risk for osteoporosis in adulthood also exists.32
Hypertension affects approximately 4\% of individuals
with NF1. Although essential hypertension is the most
common cause of hypertension, in NF1 it can also result
from renovascular disease, tumors that secrete vasoac-
tive compounds, and coarctation of the aorta.12 There-
fore, monitoring blood pressure on a yearly basis is in-
dicated, and if hypertension is found, additional
evaluation and treatment or referral to an appropriate
specialist for management is indicated.

NF1 is associated with an increased incidence of men-
tal retardation (4\%–8\%)\textsuperscript{13}; however, in most instances,
intellectual abilities are in the average to low-average
range. In contrast, specific learning disabilities are ob-
served in as many as 40\% to 60\% of affected chil-
don,12,34 and impaired performance on at least 1 test of
academic achievement is present in 65\% of children
with NF1.31 Deficits in visual-spatial-perceptual skills can
result in reading and spelling difficulties. Poor fine-mo-
tor coordination can lead to problems with handwriting.
Attention-deficit/hyperactivity disorder also occurs

\begin{figure}[h]
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\includegraphics[width=0.5\textwidth]{multiple_lisch_nodules}
\caption{Multiple Lisch nodules.}
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more frequently in children with NF1. Children with
NF1 have a higher likelihood of being hypotonic and of
having subtle neurologic abnormalities that affect bal-
ance and gait.3,15,36 Speech problems also may occur, and
an association with velopharyngeal insufficiency exists.37
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 diagnostic criteria and variable use of imag-
ing techniques. Generally, complications are overesti-
imated, because most studies involve patients in hospitals
or referral clinics.38 Approximately one third of patients
with NF1 develop serious complications, and approxi-
mately one half are mildly affected. However, because of
the extreme degree of variability even within a family
and the progressive nature of NF1, it is not possible to
determine the prognosis after establishing a diagnosis,
especially at a young age.

GENETICS
NF1 is inherited in an autosomal dominant fashion. In
approximately one half of patients, the condition is
caused by a new mutation in that conception. In such
instances, neither parent has any clinical features of
NF1, and risk for recurrence of NF1 is likely not to
exceed 1%. Rare instances of recurrence from pheno-
typically unaffected parents are attributed to germ-line
or somatic mosaicism. However, individuals with NF1
caused by a new mutation are at a 50% risk of trans-
mitting the gene to each of their offspring. The NF1 gene
has a high penetrance rate; therefore, an individual who
carries the mutation can be expected to have clinical
manifestations of the disorder. Some individuals are mo-
saic for an NF1 mutation and may have localized signs,
referred to as “segmental neurofibromatosis.” These in-
dividuals may be at risk of transmitting the mutant gene
to their offspring if the germ line includes cells with the
mutation, which results in an increased risk of NF1 in
their offspring.

The NF1 gene is located on the long arm of chromo-
some 17 at band q11.2.39-41 Neurofibromin, the protein
product of the normal gene, acts as a tumor suppressor
by downregulating another cell protein, Ras, that en-
hances cell growth and proliferation.12,42,43 A wide vari-
ety of mutations have been identified within the NF1
gene, which give rise to diminished function of neuro-
fibromin in affected persons. Detection of mutations in
the NF1 gene by DNA analysis has proven to be complex
because of the gene’s large size, presence of pseudo-
genes, and great variety of possible abnormalities. Mo-
olecular technology that is capable of detecting 95% of
mutations in NF1 is now available,44 but it is typically not
indicated because a diagnosis of NF1 in 95% of cases can
be established on the basis of clinical findings alone by
11 years of age.28 However, when there is uncertainty
regarding a definitive diagnosis, for instance, in the pres-
ence of some of the clinical manifestations of NF1, such
as only CLSs, but not enough to establish a clinical
diagnosis, consideration should be given to seeking ge-
netic consultation and determining whether genetic
testing is indicated at that time to expedite a diagnosis.

Molecular testing also may represent an option in those
instances when a couple in which one person has NF1 is
seeking prenatal diagnosis. Although establishing a di-
agnosis is achievable when a mutation has been detected
in an affected partner, determining its possible clinical
effects after establishing a diagnosis in utero is not.

CLINICAL MANAGEMENT
The multiorgan occurrence of neurofibromas and their
complications often requires care from a variety of med-
ical subspecialists and surgical specialists. The medical
home has the opportunity and responsibility to coordi-
nate such care. In addition, patients with more than
minimal manifestations of NF1 may benefit from referral
to a multidisciplinary neurofibromatosis clinic for pri-
mary or specialty care or to a physician with expertise in
the care of individuals with NF1. Such clinics and/or
physicians are valuable consultation resources for med-
ical homes that care for affected patients.

Longitudinal care for NF1 is aimed at the early detec-
tion and symptomatic treatment of complications as they
occur. Some of the medical problems, such as hyperten-
sion resulting from renal artery stenosis, can be managed
successfully if detected early. Enlarging plexiform neu-
rofibromas may be managed surgically, although re-
growth may occur. In addition, surgical removal of a
plexiform neurofibroma, especially when it compro-
mises an essential organ system, may not be possible
because of an inaccessible site or infiltration into sur-
rounding tissue. In most instances, management of most
malignancies including leukemia is the same as for chil-
dren without NF1. On the other hand, outcome of treat-
ment of malignant peripheral nerve sheath tumors is
poor. Therefore, early suspicion that there may be ma-
lignant degeneration of a plexiform neurofibroma is crit-
ical from a prognostic standpoint.

In providing medical supervision to a child with NF1,
general clinical evaluation through the medical home
should be provided regularly, but the frequency should
increase to address disease complications. Therefore, rec-
ommendations for ongoing assessment and periodic re-
view throughout life (Table 1), including the following:

1. Evaluate the child for new neurofibromas and pro-
gression of lesions. Examine the skin carefully for
signs of plexiform neurofibromas that may impinge
on or infiltrate underlying structures.
2. Check the child’s blood pressure yearly to determine
if there is evidence of hypertension, which occurs
more frequently with NF1 and could be secondary to
renal artery stenosis, aortic stenosis, and pheochro-
mocytoma, the latter being more common in adults.
A variety of vascular hypertrophic lesions may be
found.
3. Evaluate neurodevelopmental progress of an affected
child.
4. Obtain a formal ophthalmologic evaluation yearly.
5. Evaluate the child for skeletal changes. Look for sco-
liosis, vertebral angulation, and limb abnormalities.
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X indicates to be performed; S, subjective, by history; O, objective, by a standard testing method.

<sup>a</sup> Advise semiannual visits, as indicated.
<sup>b</sup> See "Discussion."
<sup>c</sup> Or at the time of diagnosis.
<sup>d</sup> Once in this time period.
<sup>e</sup> As needed for significant abnormalities and/or new signs.
<sup>f</sup> Refer to subspecialist.

**TABLE 1  Health Supervision Guidelines for Children With Neurofibromatosis**
particularity tibial dysplasia. Sometimes localized hypertrophy of a leg, arm, or other part of the body results from plexiform neurofibromata. Nonossifying fibromas of the long bones infrequently occur in adolescence or adulthood and have been associated with fracture; although a screening radiograph of the knees in adolescence has been suggested as a routine study, evidence is not sufficient to support routine screening at this time.

6. If any unexplained complications occur or if cutaneous lesions appear to be growing rapidly, refer the patient to the appropriate subspecialist for further evaluation.

7. Refer to the review of NF1 at www.genetests.org to obtain rapid access to updated clinical information on the condition.

8. Recommend available resources for patients with NF1 (eg, neurofibromatosis clinics, support groups, and families of children with NF1). Books, pamphlets, and Web-site addresses can be obtained from the Children’s Tumor Foundation (www.ctf.org). The Children’s Tumor Foundation can also provide additional information and clinic locations.

THE PREGNATAL VISIT
At times, the pediatrician may be asked to counsel a family when one of the parents-to-be is affected and the fetus is at risk or has been diagnosed prenatally to have NF1 by DNA testing. In this situation, the family most likely already has been counseled about the disorder and its inheritance pattern. However, the pediatrician may be called on to review the information and assist the family in the decision-making process. When appropriate, pediatricians who have experience in the care of individuals with NF1 may wish to have a discussion with the family, or those with less experience may seek consultation from a geneticist to provide more in-depth information to:

1. review the results of the prenatal diagnostic study;
2. explain the mechanism for occurrence of the disorder in the fetus and the risk of recurrence;
3. review the clinical manifestations, variability, progressive nature, and prognosis of the disorder;
4. review the various forms of treatment and intervention that are currently available, including their efficacy, complications, and adverse effects;
5. discuss the options available to the family for management and rearing of the child (in cases of early prenatal diagnosis, this may include discussion of available options after in utero diagnosis, including continuation of the pregnancy or its termination, and discussion of appropriate management strategies and options for child rearing after delivery);
6. when appropriate, consider referral to a clinical geneticist for a more in-depth discussion of clinical findings, recurrence risk, future reproductive options, and evaluation of risks of disease for other family members; and
7. inform the family that, in many parts of the country, there are specialty neurofibromatosis clinics that are available for guidance, therapy, and consultation.

HEALTH SUPERVISION FROM BIRTH TO 1 MONTH: NEWBORN INFANTS

Examination
1. Confirm the diagnosis by the presence of cutaneous manifestations. CLSs may be present, and in 10% to 15% of neonates, a plexiform neurofibroma will be recognized. However, the clinician must be aware that a normal examination at this age does not exclude the diagnosis of NF1.

2. All first-degree relatives should be advised to have a physical examination, including a slit-lamp examination to look for Lisch nodules, which are found in >90% of adults with this disorder but are uncommon in children younger than 5 years.

3. Some specialists recommend an initial MRI study to determine if an optic glioma is present when the diagnosis of NF1 is made.1,18 In addition to being able to identify an optic pathway glioma, if present at this age, areas of increased signal intensity on T2-weighted images, also known as unidentified bright objects (UBOs), which are present in approximately 60% of affected children, also can be detected. These lesions are well circumscribed and nonenhancing, and they are located in the brainstem, cerebellum, basal ganglia, and thalamus. An association between UBOs and learning disabilities or cognitive deficits may exist. The lesions are not space occupying and tend to disappear in adulthood. Although potentially helpful in establishing an early diagnosis when clinical findings are equivocal, because of the lack of specificity and the inability to consistently identify UBOs, the benign nature of most optic gliomas, and the need to sedate the child, neuroimaging of the brain may not be warranted. Therefore, the NIH Consensus Development Conference13 did not recommend computed tomography or MRI studies for asymptomatic patients with NF1 and generally recommended special studies only when they were clinically indicated. Neuroimaging of the brain, on the other hand, would seem to be indicated for a small percentage of the NF1 population for whom a deletion of the entire NF1 gene and flanking DNA is found.40,45 Affected individuals have a distinct phenotype, including facial dysmorphism, a large number of neurofibromas, severe cognitive impairment, and, frequently, evidence of structural brain anomalies.

Anticipatory Guidance
1. Review the natural history and genetics of NF1.
2. Advise the parents to report any unusual or new symptoms.
3. Stress the need for regularly scheduled visits, including careful cutaneous, skeletal, and neurologic examinations and evaluation of blood pressure.
4. Emphasize the need for a yearly ophthalmologic evaluation.

HEALTH SUPERVISION FROM 1 MONTH TO 1 YEAR: INFANCY

Examination
1. Compare the infant’s growth and development with figures on growth charts. As a group, children with NF1 are shorter than average but have a larger head size. Rarely, aqueductal stenosis can cause obstructive hydrocephalus, but in most children with NF1, the basis for macrocephaly is likely to be increased brain volume.
2. Examine the patient for the presence of CLSs. Inform the family that new ones may appear, and preexisting CLSs often increase in size. Reassure the family that CLSs have no functional significance.
3. Check for proptosis, a rapidly increasing head size, and focal neurologic signs.
4. Perform a careful physical examination and look for skeletal abnormalities, especially in the spine and legs. This is particularly important before the child begins to bear weight because of the risk of cortical thinning of the long bones, which increases the likelihood of fracture.
5. Refer the infant for formal ophthalmologic evaluation and to other appropriate specialists and subspecialists, as indicated.
6. Check the infant’s neurodevelopmental progress at each visit.

Anticipatory Guidance
1. Review the family’s psychological support and intrafamilial relationships.
2. Advise the parents to use sunscreen after the child reaches 6 months of age. Sun exposure deepens pigment in CLSs. Although this is usually of cosmetic significance only, melanoma and basal cell carcinoma have been reported in adults with NF1; however, the risk for developing these malignancies is not known to be increased for patients with NF1.
3. If appropriate, review future pregnancy planning with the affected infant’s parents.

HEALTH SUPERVISION FROM 1 TO 5 YEARS: EARLY CHILDHOOD

Examination
1. Examine the child for neurofibromata and the presence of skinfold freckling, which can appear in any intertriginous area. Assure parents that CLSs and freckling only have cosmetic significance.
2. Consider taking photographs to document lesion size for future reference.
3. Evaluate the child’s vision and recommend that the child undergo an ophthalmologic examination annually throughout childhood.
4. If there are visual changes, persistent headaches, seizures, marked increase in head size, or a plexiform neurofibroma of the head, obtain a brain MRI.
5. Assess the child’s speech and motor skills for deficits that require further assessment. Hypernasal speech attributable to velopharyngeal insufficiency can be present, and there may be delayed expressive language development.

Anticipatory Guidance
1. Review the child’s preschool program.
2. Obtain appropriate developmental evaluations of the child for assessment of learning, speech/language, and motor abilities if developmental concerns are raised. The child may benefit from preschool services, speech/language and/or motor therapy, and special education programming to address delays. With NF1, the risk of hearing impairments is not increased appreciably.
3. Discuss indications for surgery, as appropriate. If there is a change in the size of superficial neurofibromata or evidence of a space-occupying internal lesion, refer the child to a neurofibromatosis clinic or other appropriate subspecialists.
4. Pruritus can occur in young children and may be found to be associated with cutaneous neurofibromata. However, antipruritic medications are not helpful in relieving symptoms.

HEALTH SUPERVISION FROM 5 TO 13 YEARS: LATE CHILDHOOD

Examination
1. Examine the child for skin tumors causing disfigurement and obtain a consultation with a specialist if surgery is desired to improve appearance or function. Severe cosmetic disfigurement is seen more often in adults than in children.
2. Evaluate the child for signs of puberty. Premature onset of sexual maturation or delayed puberty may occur. If sexual precocity is present, evaluate the child for the presence of an optic glioma or hypothalamic lesion.
3. Check for signs of learning disabilities and attention-deficit/hyperactivity disorder.
4. Review the child’s social adjustment.
5. Monitor the child’s ophthalmologic status yearly under 8 years of age, followed by complete eye examination every 2 years.

Anticipatory Guidance

1. Review the child’s development and appropriateness of school placement.
2. Refer the child to a clinical psychologist or child psychiatrist for further evaluation and therapy should problems with self-esteem related to his or her physical findings or developmental problems exist.
3. Review the effects of puberty on the disease.
4. Discuss the possibility of the growth of neurofibromata during adolescence and pregnancy.
5. Counsel the parents about how and when to discuss the diagnosis with their child.

HEALTH SUPERVISION FROM 13 TO 21 YEARS OR OLDER: ADOLESCENCE TO EARLY ADULTHOOD

Examination

1. Examine the adolescent for signs of abnormal pubertal development.
2. Perform a thorough skin examination to evaluate for and determine the status of plexiform neurofibromata and a complete neurologic examination to check for findings that might suggest the presence of deep plexiform neurofibromata.
3. Obtain a surgical consultation with a specialist if signs of pressure on deep structures are found.
4. Continue monitoring blood pressure yearly.
5. Continue ophthalmological examination every 2 years until 18 years of age.23

Anticipatory Guidance

1. Discuss the genetics of NF1 or refer the adolescent for genetic counseling.
2. Discuss sexuality.
3. Discuss birth control, including the risks and benefits of birth control pills, and reproductive options.
4. Discuss the effect of pregnancy on NF1, if appropriate. Women with NF1 may have complications during pregnancy because of enlargement of the neurofibromata46,47 and, not uncommonly, eruption of more dermal neurofibromas.
5. Review prenatal diagnosis by using available molecular DNA studies and discuss its applicability to the patient with NF1 or refer the patient to a geneticist for further discussion of diagnostic options.
6. Facilitate transition to adult medical care.

REFERENCES


RESOURCES

For further information please contact the Children’s Tumor Foundation, 95 Pine St, 16th Floor, New York, NY 10005; telephone: 800-323-7938 or 212-344-6633; Web sites: www.ctf.org or www.genetests.com.