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PROFESSIONAL ISSUES

Neurofibromatosis Type 1 in Genetic Counseling Practice: Recommendations of the National Society of Genetic Counselors

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Abstract The objective of this document is to provide recommendations for the genetic counseling of patients and families undergoing evaluation for neurofibromatosis type 1 (NF1) or who have received a diagnosis of NF1. These recommendations are the opinions of a multi-center working group of genetic counselors with expertise in the care of individuals with NF1. These recommendations are based on the committee's clinical experiences, a review of pertinent English language medical articles, and reports of expert committees. These recommendations are not intended to dictate an exclusive course of management, nor does the use of such recommendations guarantee a particular outcome. These recommendations do not displace a health care provider's professional judgment based on the clinical circumstances of an individual patient.

Keywords Neurofibromatosis type 1 · NF1 · Genetic counseling · Practice guidelines · National Society of Genetic Counselors · von Recklinghausen disease

Our geneticist convinced us that in reality nothing had changed with our daughter when we walked through the door. We just had more information. She convinced us that although life was uncertain, we need to make sure that our child was given the opportunity to reach her full potential, no matter what that might be. Medically, if we were out having fun prior to the diagnosis, then that shouldn't change. We should continue to enjoy life and not let the information affect the child. In that sense, information can be harmful and NF will have already caused harm. I will say that we were still devastated, but her words helped us get through the process more quickly than if someone had just sat there and told us the facts and answered our questions. She set us out with goals in our life and a framework with which to use that information in our child's best interest.

-Parent of a child with NF1, commenting on his experience with the genetic counseling process.

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Purpose

The purpose of these guidelines is to serve as a comprehensive resource for health care professionals providing genetic counseling to patients and families undergoing evaluation for neurofibromatosis type 1 (NF1) or who have received a diagnosis of NF1. In this document, we review the diagnosis, natural history, and genetics of NF1. We suggest relevant items to be included in the genetic counseling session. Specific medical management recommendations will not be discussed in this document.

Disclaimer

These recommendations were approved in March 2007 by the National Society of Genetic Counselors (NSGC)—the leading voice, advocate and authority for the genetic counseling profession. This document is not intended to replace the judgment of an individual genetic counselor with respect to particular patients or special clinical situations and cannot be considered inclusive of all practices or exclusive of other practices reasonably directed at obtaining the same results. In addition, the practice of genetic counseling is subject to regulation by federal, state and local governments. In a subject jurisdiction, any such regulations will take precedence over this statement. NSGC expressly disclaims any warranties or guarantees, express or implied, and shall not be liable for damages of any kind, in connection with the information set forth in this document or for reliance on its contents.

Genetic counseling is a dynamic profession, which undergoes rapid change with the discovery of new genetic information and the development of new genetic tests and treatment options. Thus, NSGC will periodically review and, where appropriate, revise this statement as necessary for consistency with current practice information.

Objectives

The goals of these recommendations are to:

1. Review the history, epidemiology, and genetics of NF1.
2. Summarize the current understanding of the natural history of NF1.
3. Provide a framework for the genetic counseling sessions of individuals and families with NF1.
4. Present a list of resources for patients and families with NF1.

Materials and Methods

The NF1 Working Group was composed of genetic counselors with experience in various NF1 Clinics throughout the United States. MEDLINE, PubMed and Internet databases were searched (using the key words neurofibromatosis type 1, NF1, neurofibromin) to locate relevant English language medical papers published between 1966 and 2007. The literature was reviewed and evaluated according to the following categories outlined by the US Preventive Services Task Force (1995):

I. Evidence obtained from at least one properly designed randomized controlled trial.
II-1. Evidence obtained from well-designed controlled trials without randomization.
II-2. Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group.
II-3. Evidence obtained from multiple time series, with or without the intervention.
III. The opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

The rating of supporting literature for this recommendation is Class III. Particular attention was paid to genetic counseling issues. Following the completion of the initial draft of the guidelines, the NF1 Working Group elicited opinions and feedback from noted medical experts in the field, as well as representatives of NF1 support and advocacy organizations (See "Patient Resources"). These recommendations were approved by the NSGC Board of Directors in March, 2007.

Overview of Neurofibromatosis Type 1

Historical Background

Over the centuries, NF1 has been known by many names, including peripheral neurofibromatosis, von Recklinghausen disease, and, erroneously, the "Elephant Man Disease." The history of NF1 is briefly summarized in Table I.

Historically, there has been confusion regarding the relationship between neurofibromatosis types 1 and 2. It was initially thought that these two conditions represented different manifestations of the same underlying entity. In 1930, Garner and Frazier first suggested that individuals with only central nervous system tumors should be differentiated from those with other manifestations of the condition. Genetic linkage to two distinct loci confirmed that these two conditions were not only clinically but also etiologically distinct (Rouleau *et al.* 1987).

Another historical confusion is the belief that the "Elephant Man" had neurofibromatosis. Joseph Merrick had a debilitating disfigurement originally presumed to be NF. His life was originally documented by Treves in 1923.

Table I Significant Milestones in the History of NF1

1768	First published English-language description of neurofibromatosis
1882	Von Recklinghausen published paper on clinical entity, suggesting that tumors originated in the nervous system
1970s–1980s	NF1 and NF2 are recognized as distinct clinical entities
1978	National NF Foundation (NNFF) is founded (currently known as the Children's Tumor Foundation)
1979	NNFF establishes first comprehensive NF clinic
1986	Tibbles and Cohen suggest that the Elephant Man had Proteus syndrome instead of NF1
1987	*NF1* locus mapped to chromosome 17 Diagnostic criteria for NF1 developed at NIH Consensus Conference
1990	*NF1* gene cloned
2000	Molecular testing for *NF1* identifies mutation in more than 95% of individuals meeting diagnostic criteria

(Huson 1998; Korf and Rubenstein 2005; Messiaen *et al.* 2000; Riccardi 1999a)

Later, a play and a movie introduced this story to the public. Current knowledge suggests that Joseph Merrick had Proteus syndrome rather than NF (Tibbles and Cohen 1986). However, the repercussions of the initial presumption persist, and many families continue to be misinformed that NF1 is the "Elephant Man Disease."

Epidemiology

NF1 is one of the most common genetic conditions with an estimated prevalence of 1 in 3,500 people (Huson *et al.* 1989; Poyhonen *et al.* 2000; Rasmussen and Friedman 2000). A distinct feature of the NF1 gene is the very high spontaneous mutation rate (1×10^{-4} per gamete per generation), which is about 100-fold higher than the typical mutation rate for a single locus. This high mutation rate cannot be accounted for strictly by the size of the gene (Upadhyaya and Cooper 1998). NF1 affects all races, ethnicities, and genders.

Diagnosis

Although the diagnosis of NF1 has historically been established by clinical evaluation, continued advances in the study of NF1 may lead to modification of diagnostic strategies. In recent years, advances in molecular testing offer another diagnostic approach.

Clinical Evaluation

Traditionally, NF1 has been a clinical diagnosis, based on a set of diagnostic criteria established in 1987 (NIH Consensus Development Conference 1988). These criteria are listed in Table II and are also available online: (http://consensus.nih.gov/1987/1987Neurofibramatosis064html.htm) (NIH Consens Statement Online 1987).

The appearance of many of the diagnostic manifestations of NF1 is age-dependent. This may make the diagnosis in a young child without a family history of the condition challenging. As a result, children may need to be followed for several years before the clinical diagnosis of NF1 can be confirmed. Approximately 90% of individuals with NF1 will have two or more diagnostic criteria by 6 years of age, 97% by age 8 and all do so by 20 years of age (DeBella *et al.* 2000; Korf 1992). The most common NF1 referral indication is multiple café-au-lait spots; however, not all children with cafe-au-lait spots will be diagnosed with NF1.

Molecular Testing

Genetic testing is clinically available and identifies approximately 95% of mutations in individuals that fulfill the clinical diagnostic criteria (Messiaen *et al.* 2000). Testing may be beneficial to individuals meeting only one of the diagnostic criteria or when the diagnosis is unclear. A positive DNA test result cannot predict the presence, age of onset, or severity of NF1 symptoms (See "Molecular Basis of Disease"). Likewise, a negative result, in the absence of a known familial mutation, cannot exclude the diagnosis.

Natural History

Phenotypic Variability

NF1 exhibits an extreme degree of inter- and intra-familial variability. Modifier genes may play a role in this variability (Szudek *et al.* 2002). One study estimated that two-thirds of individuals with NF1 are relatively mildly affected, not

Table II Criteria for the Clinical Diagnosis of NF1 (At least two are required)

Criterion	Notes
Six or more café-au-lait macules	>5 mm before puberty >15 mm after puberty
Freckling	Axillary, inguinal
Neurofibromas	Two or more neurofibromas or one plexiform neurofibroma
Skeletal dysplasia	Sphenoid or tibial lesion
Lisch nodules	Two or more iris hamartomas
Optic glioma	Detected by imaging (usually MRI)
First degree relative with NF1	Sibling or parent with NF1

(NIH Consensus Development Conference 1988)

requiring major surgery or having life-threatening problems (Carey *et al.* 1979). However, at the time this study was completed, many of the serious complications that are now known to be associated with NF1 had not yet been recognized. Therefore, this may represent an underestimate of the rate of serious complications of NF1.

Clinical Features

Table III lists the frequency and age of onset of common symptoms of NF1.

Café-au-lait Spots

Café-au-lait spots (CALS) are pigmentary lesions proportionately darker than one's skin color with uniform pigmentation and smooth borders. The presence of multiple CALS is one of the most well-recognized features of NF1. Ninety-nine percent of individuals with NF1 meet the CALS diagnostic criteria by 1 year of age (DeBella *et al.* 2000). In the newborn, typical CALS are oval-shaped lesions between 1 and 4 cm in diameter (Alper and Holmes 1983). As the child ages, the number and size of CALS may increase. In adults, CALS tend to fade and may be more difficult to identify.

Freckling

Another characteristic but innocuous finding of NF1 is freckling, which is present in over 90% of patients by 7 years of age (DeBella *et al.* 2000). The freckles are similar in color to café-au-lait spots but are much smaller and often occur in clusters (Friedman and Riccardi 1999). They are most commonly found in the axillary and inguinal regions, but they can also occur in other areas of skin-to-skin contact, such as the underside of the breast in female patients, between skin folds in obese patients, and on the back of the neck.

Lisch Nodules

Lisch nodules are a common feature of NF1. Lisch nodules are pigmented hamartomas of the iris that do not affect vision. They are typically not present at birth, but they develop during childhood. More than 95% of individuals with NF1 have Lisch nodules by the age of 20 (Flueler *et al.* 1986; Huson *et al.* 1987; Lubs *et al.* 1991). Slit lamp examination by an ophthalmologist is necessary to determine the presence or absence of Lisch nodules as well as the distinction between these and iris nevi, which are not associated with NF1 (Friedman and Riccardi 1999).

Optic Pathway Gliomas

Optic pathway gliomas (OPG), or pilocytic astrocytomas of the optic nerve, are the most common central nervous system tumors seen in NF1 and typically present in early childhood (less than 6 years of age) (Listernick *et al.* 1999; Singhal *et al.* 2002). It has been estimated that up to 70% of all OPGs are related to NF1 (Listernick *et al.* 1999). OPGs may be either unilateral or bilateral and may involve the optic nerve, the chiasm, or both. Approximately 15% of NF1 patients will develop an OPG, half of whom have no clinical symptoms (Korf 2000; Listernick *et al.* 1994;

Table III Age of Onset and Frequency of Common NF1 Symptoms

Symptoms	Typical age at presentation	Frequency
Café-au-lait spots	Early presentation (occasionally visible at birth; usually present by 2 years of age)	99%
Freckling (axillary, inguinal)	Between 3 and 5 years	>90%
Lisch nodules	Late childhood/adolescence	95%
Cutaneous neurofibromas	Variable; may see increase in size and number during adolescence and pregnancy	0–9 years 14% 10–19 years 44% 20–29 years 85% >30 years 95%
Diffuse plexiform neurofibromas	Congenital; manifest early in life	25%
Tibial dysplasia and/or sphenoid dysplasia	Typically visible clinically by 1 year	1–4% tibial 3–7% sphenoid
Learning disabilities	May not be identified until school age	20–50%; MR uncommon (4.8–11%)
ADHD	Childhood	20–40%
Optic nerve glioma	Childhood; may be asymptomatic	15%
Malignant peripheral nerve sheath tumor (MPNST)	Average age at diagnosis is 28 years	4–13%

(DeBella *et al.* 2000; Evans *et al.* 2002; Korf *et al.* 2005; Levy *et al.* 2005; Listernick *et al.* 1999)

Singhal *et al.* 2002). Most NF1-related OPGs do not progress or metastasize. If progression does occur, presenting symptoms often include proptosis, precocious puberty or increased growth velocity. Other symptoms include loss of visual acuity, abnormal color vision, optic atrophy, and afferent pupillary defect. Some optic nerve tumors may spontaneously regress (Korf 2000).

Skeletal Findings

Scoliosis is the most common skeletal finding in NF1 with an estimated frequency ranging from 10 to approximately 25% (Akbarnia *et al.* 1992; Crawford and Schorry 1999; Friedman and Birch 1997; Riccardi 1999b; Vitale *et al.* 2002). The scoliosis can be either dystrophic or non-dystrophic (Alwan *et al.* 2005). The dystrophic type of scoliosis is associated with bony abnormalities evident on radiographic films and tends to be more severe with rapid progression. This form of scoliosis typically presents between 6 and 10 years of age, and, if not present by 10 years, is unlikely to develop (Riccardi 1999b). The non-dystrophic form of scoliosis has no apparent bony abnormalities and has findings similar to idiopathic scoliosis in individuals without NF1; it presents during adolescence and tends to be less severe. Kyphoscoliosis may also develop (Alwan *et al.* 2005). Occasionally, these spinal abnormalities may be caused by an underlying neurofibroma.

Sphenoid dysplasia is present in 3–7% of NF1 patients and typically presents as a unilateral defect (Riccardi 1999b; Alwan *et al.* 2005). Over 50% of cases of sphenoid dysplasia are associated with NF1. The lesions are usually asymptomatic and are diagnosed by skull radiographs or CT scans (Alwan *et al.* 2005). In rare instances, progression of a lesion may lead to medical complications such as enophthalmos and herniation of the brain into the orbit (Riccardi 1999b).

Lesions of the long bones are another feature of NF1 with a prevalence of 1–4% (Crawford and Schorry 1999; Friedman and Birch 1997; Vitale *et al.* 2002). The tibia is most frequently involved, although other long bones may also be affected (Ali and Hooper 1982; Alldred 1963; Floyd and Percy-Lancaster 1987; Gregg *et al.* 1982; Keret *et al.* 2000; Riccardi 1999b). Congenital pseudarthrosis, or "false joint" abnormality, occurs in 1–2% of NF1 patients (Friedman and Birch 1997; Riccardi 1999b). These lesions are often detected during infancy or early childhood and present as bowing or fracturing of the affected bone (Alwan *et al.* 2005). Other potential abnormalities of the long bones include changes associated with a plexiform neurofibroma or localized lytic defects (Riccardi 1999b).

NF1 patients also have an increased risk for osteoporosis and osteopenia. (Kuorilehto *et al.* 2005). Other skeletal anomalies found in NF1 patients may include pectus deformities, genu varum, and genu valgum (Riccardi 1999b).

Neurofibromas

Neurofibromas (NFs) are benign tumors that can occur anywhere in the body. They most commonly develop along peripheral nerves or less frequently in the deep nerves. Neurofibromas are typically multicellular in origin, composed of Schwann cells, axons, fibroblasts, mast cells, endothelial cells and perineurial cells (Peltonen *et al.* 1988). Pruritis, or itching, is a somewhat common feature of NF1 and when localized, often precedes the development of cutaneous neurofibromas.

NFs can be classified into different types (Friedman and Riccardi 1999; Korf and Rubenstein 2005):

1. Discrete Neurofibromas

Discrete NFs are benign tumors that arise from a single site on a peripheral nerve. They are rarely present at birth, often appearing just before the time of puberty (Dugoff and Sujansky 1996; Korf and Rubenstein 2005). The number of dermal neurofibromas tends to increase with age and varies widely between individuals. They may increase in size and number during pregnancy. Discrete NFs are encapsulated; they may grow in size and press on other tissues, but will not invade them.

Discrete Cutaneous Neurofibromas. Discrete cutaneous NFs usually protrude above the skin and are soft and fleshy. They may be flesh-colored, pink or purple. They may be sessile or pedunculated. They often initially appear on the chest, abdomen and back. Typically, these NFs are not painful, but may cause pruritis and often have a significant cosmetic burden.

Discrete Subcutaneous Neurofibromas. Discrete subcutaneous NFs develop along nerves contained in deeper body tissue under the epidermis. They are usually firm and rubbery to palpation and can be distinguished from cutaneous neurofibromas because the skin can be moved over the nodule. These tumors may present clinically as beadlike nodules along the length of the nerve and they range in size from pea-sized to several centimeters. They may be painful or tender. Tumors in deeper nerves can compress a nerve root, causing radicular pain, weakness or loss of sensation.

2. Plexiform Neurofibromas

Plexiform NFs (PNFs) grow along the length of a peripheral nerve sheath. They are non-encapsulated and therefore may grow into healthy tissue and interfere with normal development of tissue or bone. These tumors tend to be supported by a network of blood vessels and therefore are usually difficult to surgically remove. Most PNFs are benign, but there is a risk

for transformation to malignant peripheral nerve sheath tumors (MPNST) (See 'Tumors and Malignancy').

Diffuse Plexiform Neurofibromas. Diffuse PNFs are usually congenital, but may not be recognized until they increase in size or are found incidentally. They may spread out from the area of origin and develop numerous extensions that infiltrate extensively into adjacent normal tissues, making complete surgical removal difficult. They may also engulf nerves. The tumors can occur superficially, in deep tissues, or a combination thereof. With superficial involvement, skin may be thickened, redundant, and/or hyperpigmented. There may also be thick, coarse hair or localized hypertrophy over the affected area. Diffuse PNFs are described as having a "bag of worms" feel on palpation and most often develop in the head, neck and abdomen. They typically grow most rapidly during childhood, although they sometimes increase during adolescence and pregnancy.

Nodular Plexiform Neurofibromas. Nodular PNFs are less common than diffuse PNFs and are discrete lesions that arise in peripheral nerve trunks. The most frequent site of involvement is along the spinal nerves. They cannot usually be detected by palpation. They vary in size and are sometimes painful. These types of NFs frequently cause neurological symptoms.

Seizures

Although not common, there are some studies that suggest an increased frequency of seizures (range 3.5–7.3%) in NF1 (Friedman and Riccardi 1999; North 1993). The seizures that are suggested to be associated with NF1 do not differ from those seen in the general population. When not associated with an intracranial lesion or stenosis, these seizures are generally well-controlled with routine anti-epileptic drugs (Gutmann 1999).

Headaches

Individuals with NF1 have an increased frequency of headaches. These range from a mild "tension" headache to a true migraine (Riccardi 1981). Although common, a new onset of headaches or ones that are atypical for the patient and/or accompanied by neurologic deficits, may warrant investigations for other causes including brain tumors, pheochromocytomas or cerebrovascular etiologies (Friedman and Riccardi 1999; Riccardi 1981).

UBOs

Cranial MRI scans in NF1 patients often show focal areas of high signal intensity on T2 or FLAIR weighted images. They are typically referred to as Unidentified Bright Objects (UBOs) or "NF spots." They exert no mass effect and are not observed on CT scan. They often resolve with time and are rarely seen in NF1 patients over the age of 20 (Aoki *et al.* 1989). Some researchers have suggested a connection between the presence of UBOs and lower IQ, language skills, visuospatial functioning and academic achievement (Denckla *et al.* 1996), although this has not been found in other studies (Friedman and Riccardi 1999).

Growth

Individuals with NF1 tend to be below average in height and true short stature (<10th percentile) occurs in more than 40% of adults with NF1 (Carmi *et al.* 1999). One study found growth hormone deficiency in 3 of 122 children, although this does not appear to be the cause of short stature in most patients with NF1 (Cnossen *et al.* 1997).

Macrocephaly, either relative or absolute, is present in 29–45% of individuals with NF1 and usually develops during childhood (Clementi *et al.* 1999; Friedman and Riccardi 1999; Riccardi 1999b; Szudek *et al.* 2000). Rarely, underlying hydrocephalus is identified (Friedman and Riccardi 1999).

Onset of Puberty

Most individuals with NF1 undergo normal pubertal development (Friedman and Riccardi 1999). However, in approximately 1–4% of patients, puberty may be premature or delayed (Friedman and Birch 1997). Precocious puberty typically results from an optic chiasm glioma or other tumor proximal to the region of the hypothalamus (Friedman and Riccardi 1999; Habiby *et al.* 1995).

Pregnancy and NF

Although NF1 appears to have no intrinsic effect on fertility, negative pregnancy outcome has been reported (Friedman and Riccardi 1999). Early reports suggest a significant increase in complications including intrauterine growth retardation, preterm labor, and stillbirth (Belton *et al.* 1984; Edwards *et al.* 1983; Weissman *et al.* 1993). However, these findings are controversial, and more recent studies suggest that most pregnancy outcomes for healthy women with NF1 are normal, although there appears to be an increased need for cesarean-sections (Dugoff and Sujansky 1996). Pregnancy is frequently associated with an exacerbation of existing maternal symptoms as well as the new presentation or rapid increase in tumors and hypertension (Ansari and Nagamani 1976; Dugoff and Sujansky 1996; Swapp and Main 1973). A subsequent decrease in the size of the exacerbated neurofibromas in the postpartum period is sometimes seen (Dugoff and Sujansky 1996).

Cardiovascular Findings

Hypertension is a common finding in individuals with NF1. The incidence of hypertension increases with age and can lead to heart attack, stroke, kidney failure, and other medical problems. In most cases, the hypertension is essential. However, less common causes of hypertension include renal artery abnormalities, pheochromocytomas, and, in rarer instances, aortic coarctations or brain tumors (Friedman 1999a).

Congenital heart defects have been reported in patients with NF1 with an estimated frequency between 0.4 and 6.4% (Carey *et al.* 1979; Crowe *et al.* 1956; Lin *et al.* 2000; Schorry *et al.* 1989). The most common cardiac abnormality is valvar pulmonic stenosis (Friedman and Birch 1997; Lin *et al.* 2000). This abnormality has been described in individuals with the Watson and the NF1-Noonan phenotypes as well as individuals with a large gene deletion (See "Variants of NF1"); however, the incidence of pulmonic stenosis is also increased in patients with NF1 without these variant phenotypes. Coarctation of the aorta and other heart defects have also been reported (Friedman and Birch 1997; Lin *et al.* 2000). Several reports have identified NF1 patients with hypertrophic cardiomyopathy. Current evidence is insufficient to determine whether these reflect manifestations of NF1 or are simply coincidental.

Vasculopathies are a well-recognized cardiovascular complication of NF1 (Friedman 1999a). They may be peripheral or cerebrovascular. The specific types of lesions include stenoses, dilations, aneurysms, and fistulas (Friedman *et al.* 2002). Arterial involvement is most common, although venous involvement has also been reported (Lehrnbecher *et al.* 1994). These lesions frequently occur in the renal arteries, but may also occur in the cerebral or visceral arteries (Criado *et al.* 2002; Serleth *et al.* 1998; Westenend *et al.* 1994). The exact frequency of vasculopathy in patients with NF1 is unknown and many patients with vasculopathy remain asymptomatic throughout their lives (Friedman *et al.* 2002). Symptomatic vascular lesions are most commonly detected in childhood or early adulthood and may be identified during a pregnancy (Friedman *et al.* 2002; Pilmore *et al.* 1997). A study by Rosser *et al.* (2005) identified a cerebrovascular abnormality in 2.5% of patients with NF1. These abnormalities may present with neurological symptoms secondary to cerebral ischemia (Friedman *et al.* 2002).

Pruritis

Pruritis, or chronic itching, is a relatively common feature of NF1. It may be generalized or restricted to a certain area of the body. When localized, the itching may precede the development of cutaneous neurofibromas. The itching is thought to be related to the large amount of mast cells in neurofibromas and is often relieved by anti-histamines (Korf and Rubenstein 2005; Riccardi 1981).

Tumors and Malignancy

The malignancy rates in individuals with NF1 are higher than the general population risk, though precise risk estimates vary. Literature reports suggest that the risk for malignancy in individuals with NF1 is 5–15% higher than the general population risk (Walker *et al.* 2006). On average, the onset of malignancy in NF1 patients appears to be earlier than the general population (Kim *et al.* 2002; Walker *et al.* 2006). A prospective study by Walker *et al.* suggests that the increased malignancy rate comes primarily from a higher incidence of central nervous system and connective tissue malignancies (Walker *et al.* 2006).

Malignant Peripheral Nerve Sheath Tumors

Approximately 4–13% of patients with NF1 will develop a malignant peripheral nerve sheath tumor (MPNST), also called malignant schwannoma or neurofibrosarcoma (Evans *et al.* 2002; Korf 2000; Levy *et al.* 2005). The most common locations of these tumors in NF1 patients are the abdominal paraspinal region, the extremities, and the head and neck regions (Levy *et al.* 2005). Approximately 20–50% of patients with MPNSTs also have NF1 (Evans *et al.* 2002; Korf 2000; Levy *et al.* 2005). Compared to individuals without NF1, individuals with NF1 tend to be diagnosed with an MPNST at a younger age and have a poorer prognosis. Most of the time, MPNSTs in NF1 are associated with an underlying plexiform neurofibroma (Evans *et al.* 2002; Levy *et al.* 2005; Korf 2000). While plexiform neurofibromas may be very large tumors, the malignant component of the tumor may be very small and can easily be missed by a single biopsy. Symptoms commonly reported by patients with an MPNST include pain, enlarging tumor mass, and neurologic symptoms (Korf 2000).

Pheochromocytomas

Pheochromocytomas are catecholamine-secreting tumors that occur most often in the adrenal gland They occur in approximately 0.1–5.7% of NF1 patients. In the majority of cases, the NF1-related pheochromocytoma will be a single, unilateral tumor (84%). Roughly 10% of patients will have a bilateral pheochromocytoma and a small percentage (6%) will have an extra-adrenal pheochromocytoma (Walther *et al.* 1999). Pheochromocytomas often lead to increased production of adrenaline which may cause hypertension and a variety of other associated symptoms such as headaches, cardiac palpitations, diaphoresis and tremors. They may become metastatic. (Walther *et al.* 1999).

Gastrointestinal Tumors

There is a wide spectrum and diverse nature of tumors that occur along the gastrointestinal (GI) tract in NF1 patients. Neurofibromas are the most common tumor of the gastrointestinal tract in patients with NF1, however most of these are benign and asymptomatic. When symptomatic, abdominal pain, constipation and bleeding are the most common presenting symptoms. The incidence of gastrointestinal carcinoids is higher in NF1 patients than in the general population; however, the malignancy rate is comparable between the two groups (Levy *et al.* 2005). Gastrointestinal stromal tumors (GIST) are associated with NF1. Contrary to non-NF1 patients, NF1-related GIST occur primarily in the small intestine and typically present as either multiple tumors or are associated with other GI neoplasms (Levy *et al.* 2004).

Leukemia and Lymphoma

There have been several reports suggesting an increased risk for acute lymphoblastic leukemia, non-Hodgkin lymphoma and juvenile myelomonocytic leukemia (JMML) in NF1 (Stiller *et al.* 1994; Zvulunov *et al.* 1995). As many as 14% of individuals with JMML have NF1 (Niemeyer *et al.* 1997). However, the risk of an individual with NF1 developing JMML is low. (Gutmann and Gurney 1999). An association between leukemia and the cutaneous finding of juvenile xanthogranulomas (JXG) has been suggested, but this association has not been well-established (Cambiaghi *et al.* 2004; Morier *et al.* 1990).

Gliomas

Optic gliomas are seldom malignant and are discussed earlier in this document. Other than optic gliomas, individuals with NF1 are at risk for other types of gliomas, including cerebellar astrocytomas, ependymomas, third ventricle astrocytomas, cerebral astrocytomas, brain stem gliomas, and spinal cord tumors. The risk of malignant transformation in these tumors in NF1 patients was found to be higher than in those without NF1 (Ilgren *et al.* 1985).

Embryonal Tumors

Rhabdomyosarcomas are seen with disproportionately high frequency in individuals with NF1. An association of NF1 with neuroblastoma and Wilms tumor has been suggested but has not been confirmed (Korf 2000; Levy *et al.* 2005).

Breast Cancer

Questions have been raised regarding a potentially increased risk for breast cancer in individuals with NF1 due to the possible role of neurofibromin in some breast cancers (Guran and Safali 2005). This concern has been further supported by a prospective study suggesting an increased risk for early onset-breast cancer among women with NF1 (Walker *et al.* 2006). Additional data and larger studies are necessary to determine whether the breast cancer risk in individuals with NF1 is truly increased.

Miscellaneous Tumors

A variety of other tumors occur in NF1 including leiomyosarcomas, ganglioneuromas and adenocarcinomas (Levy *et al.* 2005).

Cognitive Phenotype

The vast majority of individuals with NF1 have intelligence within the normal range. However, there is a documented leftward shift in the IQ curve, as well as an increased incidence of both mental retardation (MR) and learning disabilities as compared to the general population (Barton and North 2004; Eliason 1986; Ferner *et al.* 1996; Mazzocco *et al.* 1995).

The incidence of MR in the NF1 population is estimated to be between 4.8 and 11% (Dilts *et al.* 1996; Ferner *et al.* 1996; Hyman *et al.* 2005; North *et al.* 1995; Wadsby *et al.* 1989). Large *NF1* gene deletions are a frequent finding in patients with MR, and patients with such deletions tend to exhibit a more severe phenotype overall (Ainsworth *et al.* 1997) (See "Variants of NF1"). Accordingly, MR is not typically expected in individuals without the deletion. The occurrence of MR in a patient with NF1 without a full gene deletion may warrant further evaluations to rule out other more common causes of MR, such as chromosomal duplications/deletions, and fragile X syndrome.

Learning disabilities are a much more common occurrence in NF1. Historically, most studies have estimated the incidence of learning disabilities to be between 40 and 60%, although the criteria for defining a "learning disability" have varied (Hyman *et al.* 2005; Kayl and Moore 1995; North 1999; Ozonoff 1999; Samuelsson and Axelsson 1981; Stine and Adams 1989; Wadsby *et al.* 1989). The *Diagnostic and Statistical Manual of Mental Disorders IV* (DSM IV) defines a specific learning disability as "the achievement on standardized tests that is more than two standard deviations below that expected for the individual's level of intelligence" (American Psychiatric Association 2000). Using this definition, a study by Hyman *et al.* (2005) examined a cohort of 81 children with NF1, in which 81% of individuals showed some sort of cognitive impairment, but only 25% of individuals met the DSM IV diagnostic criteria for learning disabilities when controlling for IQ. Thus, some individuals with NF1 do not qualify for a formal diagnosis of a learning disability but will still

require intervention for other neuropsychological deficits. These deficits can include but are not limited to visuospatial skills, executive function, expressive and receptive language, social skills and motor coordination (Barton and North 2004; Chapman *et al.* 1996; Dilts *et al.* 1996; Ferner *et al.* 1996; Hyman *et al.* 2005; Johnson *et al.* 1999; Mazzocco *et al.* 1995; North *et al.* 1994, 1995, 2002; Varnhagen *et al.* 1988; Zoller *et al.* 1997).

Several studies have suggested a frequency of attention deficit disorder (ADD) with or without hyperactivity in approximately 30–40% of the NF1 population (Bawden *et al.* 1996; Cutting *et al.* 2000; DeWinter *et al.* 1999; Hyman *et al.* 2005; Kayl and Moore 1995).

In summary, the cognitive phenotype of NF1 is complex, variable, and unpredictable, and can include a wide range of learning disabilities, other neuropsychological deficits, and less often, mental retardation. Formal neuropsychological evaluation can help elucidate the specific challenges of an individual with NF1 to allow for appropriate intervention. Intervention is based on the presenting cognitive features, and these are managed in the same way as they would be in the non-NF1 population.

Life Expectancy

Individuals with NF1 are predicted to have a lifespan of approximately 15 years less than that seen in the general population (Rasmussen *et al.* 2001; Zoller *et al.* 1995). Khosrotehrani *et al.* (2005) reviewed data on 703 NF1 patients. The major cause of death in this population was malignancy. The second major cause was tumor-related neurological complications, and less frequent were vascular complications and accidents, suicide or causes of death that were indeterminate. Other reports demonstrate that cardiovascular disease is a frequent cause of premature death in individuals with NF1, and that myocardial infarction and cerebrovascular accidents occur at a younger than expected age among NF1 patients (Friedman *et al.* 2002; Zoller *et al.* 1995). Complications from surgery also may lead to a decreased life span (Korf and Rubenstein 2005).

Molecular Basis of Disease

The elucidation of the molecular basis of NF1 began in 1990 when the gene, *NF1*, was identified and the protein product, neurofibromin, were characterized (Cawthon *et al.* 1990b; Wallace *et al.* 1990). The *NF1* gene, located at 17q11.2 is approximately 350 kb in size and contains 60 exons. Within the *NF1* gene are three additional genes contained within an intron, which are transcribed in the opposite direction (Cawthon *et al.* 1991, 1990a; Mikol *et al.* 1990). The protein, neurofibromin, contains 2,818 amino acids.

The various functions of neurofibromin are still being investigated. It appears to serve a tumor suppressor function within the Ras signaling pathway (Zhu and Parada 2001). Typically, neurofibromin inactivates Ras by stimulating its conversion from Ras-GTP to Ras-GDP, thus controlling cell proliferation. However, when neurofibromin is abnormal or absent, Ras remains active and promotes cell proliferation and tumor growth. This is thought to be the mechanism responsible for the formation of tumors associated with NF1. It is also thought that abnormalities in this pathway contribute to the occurrence of learning disabilities (Korf and Rubenstein 2005).

To date, hundreds of mutations in the *NF1* gene have been identified, many of which are unique to an individual or family (Messiaen *et al.* 2003). Mutations identified include deletions, insertions, splice site mutations, amino acid substitutions, full gene deletions and chromosomal rearrangements. In the majority of cases, the mutation results in a truncated protein. A majority of molecular studies have not identified a strong genotype–phenotype correlation. (Rasmussen *et al.* 1998; Upadhyaya *et al.* 1998). However, in 2007, Upadhyaya *et al.* identified 21 patients with an atypical presentation and a 3-bp in-frame deletion in exon 17. All patients lacked cutaneous neurofibromas or clinically obvious plexiform neurofibromas. Other exceptions that demonstrate a possible genotype–phenotype correlation include some of the NF1 variants, including Spinal NF, NF-Noonan syndrome and individuals with deletions of the entire *NF1* gene. (See "Variants of NF1").

There appears to be a parent-of-origin effect on the types of *de novo* mutations that arise in the *NF1* gene, with gene deletions being more frequent on the maternally derived chromosome and other types of mutations occurring preferentially on the paternally derived chromosome (Ainsworth *et al.* 1997; Stephens *et al.* 1992; Upadhyaya *et al.* 1998).

It should be noted that although NF1 is common, no convincing evidence of homozygous *NF1* mutations have been reported, suggesting that at least one functional NF1 allele is essential in early fetal development (Friedman 1999b). This is further supported by the fact that homozygosity for *NF1* mutations in mice leads to abnormal heart development and mid-gestation embryonic lethality (Jacks *et al.* 1994).

Differential Diagnosis

Individual signs and symptoms of NF1 can be seen in the absence of other clinical findings. Isolated tumors, including optic gliomas and neurofibromas, are well documented, although Lisch nodules are rarely seen outside of the NF1 spectrum. The presence of one or two CALS is fairly common in the general population; however, having multiple (three or more) CALS is noted in less than 1%

of children without other features of a genetic condition (Tekin *et al.* 2001). The diagnosis of NF1 is subsequently confirmed in a majority of these patients (Fois *et al.* 1993; Korf 1992). Some individuals with red hair, fair skin, and, often, Irish ancestry are referred to clinics to rule out NF1 due to multiple CALS. These CALS are paler and more irregular than typical NF1 CALS. It is unclear whether this is an extremely mild variant of NF1 or a normal pigmentary variation (Schneider and Korf 1996).

Several conditions have features that overlap with NF1. See Table IV.

Variants of NF1

Segmental Neurofibromatosis

Clinical findings of NF1 that are confined to one or more well-circumscribed regions of the body have been described in many individuals. This entity is known as "segmental NF." Typically, these manifestations do not encompass the entire clinical spectrum of NF1 and may include only dermatologic findings and/or neurofibromas. Ophthalmologic findings are seldom observed (Ruggieri *et al.* 2004). Usually, a mild clinical course is anticipated for those patients who present with only pigmentary features. However, studies looking at long-term outcomes of these patients are very limited. Therefore counseling patients about clinical prognosis based on the assumed presence of a mutation in a mosaic state must be undertaken with caution.

It is believed that segmental NF1 is caused by a post-zygotic mutation in the *NF1* gene. Tinschert *et al.* (2000) reported the first molecular evidence of this phenomenon. The timing of the post-zygotic event is believed to determine the extent of involvement. Mutations arising early in embryologic development may result in a more widespread mosaicism that may appear as classic NF1 (Colman *et al.* 1996). A milder phenotype presenting as patchy distribution, smaller segment involvement, or isolated findings, may be the result of mutations arising later in embryologic development.

Providing an accurate risk assessment for the offspring of an individual with segmental NF1 presents a great challenge. There have been reports of individuals with segmental NF1 having children with classic NF1 (Oguzkan *et al.* 2004; Poyhonen *et al.* 2000). Since individuals with segmental NF1 are presumed to have some proportion of cells that harbor an NF1 gene mutation, they should be counseled that the risk to their offspring for classic NF1 could be as high as 50%, though it is likely to be considerably lower. Lymphocyte molecular testing in segmental NF may not be informative as the sample may not include the affected region or cells. However, for individuals who have had informative molecular confirmation in the affected cells, prenatal genetic testing for that mutation could be pursued in future pregnancies.

Spinal Neurofibromatosis

A subset of patients with NF1 has a variant in which their tumors are primarily localized to the spinal nerve roots. These individuals exhibit variable skin manifestations. This variant is referred to as spinal neurofibromatosis (SNF). The hallmark of this condition is multiple bilateral symmetrical enlargement of the nerve root on the spine (Korf *et al.* 2005; Kluwe *et al.* 2003). Cord compression is a frequent complication in SNF (Korf *et al.* 2005). In contrast, spinal cord tumors associated with clinical symptoms are uncommon in classic NF1, affecting less than 7% of patients (Kluwe *et al.* 2003; Von Deimling *et al.* 1995). Lisch nodules may or may not be present. The diagnosis of spinal neurofibromatosis by physical examination alone can be difficult, as individuals can be affected and not meet diagnostic criteria for the classic form of NF1. Most patients with SNF will have a variable number of CALS, but even in adults, the dermal neurofibromas may not be present (Korf *et al.* 2005). Spinal neurofibromatosis is also inherited in an autosomal dominant fashion and appears to be associated with mild mutations, such as missense, nonsense, or splicing mutations in the *NF1* gene (Kluwe *et al.* 2003).

NF-Noonan Syndrome

Noonan syndrome is characterized by short stature, characteristic facial features, a webbed neck and congenital heart disease (most commonly pulmonic stenosis). In 1985, Allanson *et al.* first reported the concurrence of NF1 and Noonan syndrome (NFNS). In subsequent years, controversy has remained as to whether NFNS represents a variable manifestation of either NF1 or Noonan syndrome; a chance occurrence of two common genetic disorders; or a distinctive clinical entity (Carey *et al.* 1995). De Luca *et al.* (2005) identified NF1 mutations in 16/17 patients with the NFNS phenoytype. They found an increased prevalence of in-frame mutations involving exons 24 and 25 of the NF1 gene. No mutations in PTPN11, the gene most commonly associated with Noonan syndrome, were observed, suggesting that most cases of NFNS are due to mutations within the NF1 gene.

Watson Syndrome

Watson syndrome is characterized by pulmonic stenosis, multiple café-au-lait spots, and decreased IQ in addition to other various manifestation of NF1 (Allanson *et al.* 1991; Leao and da Silva 1995; Watson 1967). Linkage analysis, as well as identification of a gene deletion in one patient, support the hypothesis that this is an allelic variant of NF1 (Allanson *et al.* 1991; Upadhyaya *et al.* 1992).

Table IV Differential Diagnoses for NF1

Condition and gene (if known)	Overlapping features	Distinguishing features
Neurofibromatosis type 2 (*NF2*)	CALS Dermal and spinal cord tumors Autosomal dominant	Pathology of tumors is more often schwannoma, meningioma Vestibular schwannomas (acoustic neuromas) leading to deafness in mid-adulthood Juvenile posterior subcapsular cataract CALS do not meet NF1 diagnostic criteria
LEOPARD Syndrome (*L*entigines, *E*lectocardiographic abnormalities, *O*cular Abnormalities, *P*ulmonic Stenosis, *A*bnormal Genitalia, *R*etardation of Growth and *D*eafness) *(PTPN11)*	CALS and hyperpigmented lesions Pulmonic stenosis Autosomal dominant	Deafness Multiple lentigines
McCune–Albright Syndrome (*GNAS1*)	CALS Premature puberty	Polyostotic fibrous dysplasia Endocrine abnormalities such as sexual precocity, hyperthyroidism, hyperparathyroidism CALS are atypical—fewer in number, larger in size and have irregular margins Sporadic (only compatible with life when in the mosaic state)
Bannayan–Riley–Ruvalcaba Syndrome *(PTEN)*	CALS Multiple tumors Macrocephaly Learning problems Autosomal dominant	Subcutaneous tumors are usually lipomas or hemangiomas Polyposis of colon Pigmentary changes of penis in males
Multiple Lipomas	Subcutaneous tumors Autosomal dominant	Tumors are lipomas No other features of NF1
Proteus Syndrome *(PTEN)*	CALS Hemihypertrophy, Subcutaneous tumors Overgrowth of limbs Learning disabilities	Epidermal nevi Tumors are lipomas, lymphangiomas, and hemangiomas Bony abnormalities including: prominences of skull, macrodactyly and hyperostosis Soft tissue hypertrophy may appear as gyriform especially over plantar surfaces of feet Sporadic
Tuberous Sclerosis *(TSC1; TSC2)*	CALS Seizures Learning problems Behavior problems/ADHD Autosomal dominant	Additional dermatologic findings including: ash leaf spots, shagreen patches Pits in dental enamel Cardiac rhabdomyoma Angiomyolipomas of kidneys Glioma/angioma lesions in cortex and white matter (“tubers”)
Familial Multiple CALS	CALS Autosomal dominant	No other features of NF1
Schwannomatosis (*INI1*)	Multiple tumors	Schwannomas of cranial, spinal or peripheral nerves No other features of NF1 Mostly sporadic, though some reports of autosomal dominant inheritance
Multiple Endocrine Neoplasia, Type IIB *(RET)*	CALS Tumors including pheochromocytoma Autosomal dominant	Tumors usually involve the endocrine system Marfanoid habitus

Table IV (continued)

Condition and gene (if known)	Overlapping features	Distinguishing features
Klippel–Trenauney–Weber *(VG5Q)*	Overgrowth	Port wine stains Hemangiomas Usually unilateral involvement Sporadic
Homozygous mismatch repair gene mutations *(PMS2, MLH1)*	CALS Tumors Hematologic malignancies	Family history consistent with Hereditary Nonpolyposis Colorectal Cancer Early onset HNPCC-related cancers Autosomal recessive, consanguinity common

(Bandipalliam 2005; Jones 2005; Raevaara *et al.* 2004; Trimbath *et al.* 2001)

NF1 Gene Microdeletion

Approximately 4–5% of NF1 patients have deletions of the entire *NF1* gene. (Kluwe *et al.* 2004). The phenotype in these patients tends to be more severe, with an earlier onset of neurofibomas and the presence of mental deficiency, variable dysmorphic features and other congenital anomalies. (Kayes *et al.* 1994; Wu *et al.* 1995; Rasmussen *et al.* 1998). In addition, some of these individuals appear to have connective tissue abnormalities such as mitral valve prolapse and joint laxity. (Mensink *et al.* 2006). A study by De Raedt *et al.* suggested that the risk of MPNSTs is higher in this group of patients than in individuals with other types of mutations (De Raedt *et al.* 2003).

Ongoing Research

Research in NF1 is concentrated on the underlying causes of the various symptoms of the condition as well as potential therapies and treatments. Current studies are listed on the Children's Tumor Foundation webpage (http://www.ctf.org), the Neurofibromatosis, Inc. webpage (http://www.nfinc.org), and at http://www.clinicaltrials.gov. Active areas of investigation include genotype–phenotype correlations; the role of modifier genes; etiology of extensive phenotypic variability; neurodevelopmental issues; and treatments for neurofibromas and other tumors.

Genetic Counseling

Contracting

As with other genetic counseling indications, ascertaining the family's understanding of the reason for the visit as well as their primary questions and concerns, and mutually developing a plan to address these concerns, are key components of establishing rapport in the NF counseling process (Weil 2000).

Medical and Developmental History

See Figure 1 at the end of the text for a sample clinic intake form.

Family History

To identify additional family members who may be affected with NF, obtain at least a three generation, targeted pedigree from the consultand or proband using standardized pedigree symbols (Bennett *et al.* 1995). When possible, verify positive or questionable family history with medical records. Suggestions for a targeted family history are listed in Table V.

Psychosocial Assessment and Counseling

Similar to genetic counseling for other conditions, obtaining a thorough psychosocial history and assessment is critical to the NF counseling process. General suggestions for a targeted psychosocial history are listed in Table VI.

In addition to topics that are covered during a typical genetic counseling session, individuals with NF1 may have some unique psychosocial concerns may need to be addressed.

a. Realize that many individuals have received information about NF1 from other sources (internet, physicians, etc.), and that this information may be inaccurate, outdated, or only representative of the most severe cases of NF1.
b. Recognize that the list of potential complications associated with NF1 is extensive. Appreciate that the information may be overwhelming for some individuals. The genetic counselor should use his or her clinical judgment in gauging the appropriate amount of information discussed during a session and may wish to continue discussions at subsequent appointments.
c. Assess perception of the risk for malignancy. The term "tumors" can be especially frightening and it should be stressed that most NF tumors are benign. Malig-

nancy risks should be discussed in the context of the general population's cancer risk, which is approximately 41% (http://seer.cancer.gov/csr/1975_2003/results_merged/topic_lifetime_risk.pdf).

d. Address concerns and fears regarding the variable and unpredictable natural history of NF1. Explain that the majority of individuals lead productive lives, meaning that they are able to attend school, be employed and live independently. Providing the family with a list of concerning symptoms (See "Education") can be helpful in giving the family a sense of control when they are experiencing anxiety about the unpredictable nature of NF1.
e. Assess perception of the impact of NF1 on the individual's daily life, with a focus on cosmetic and medical concerns. Wolkenstein *et al.* (2001) found that quality of life in adults with NF1 was negatively correlated with the visibility of the manifestations of NF1.
f. Discuss family's concerns regarding labeling and self-fulfilling prophecies. Many parents are concerned that the diagnosis of a genetic condition will lower a child's self-expectations or the expectations of others for the child.
g. Assess the family's knowledge and perception of the Elephant Man. Despite the current belief that "The Elephant Man" did not have NF1, older literature and resources often refer to NF1 as the disease of "The Elephant Man." Families of patients with NF1 may still be affected by the association of NF1 with the difficult life of Joseph Merrick (Ablon 1995).
h. Elicit the individual's experiences at school, work and other social situations. In addition to the learning disabilities, many NF1 patients have difficulty with social skills. This may also be impacted by the co-occurrence of ADHD.
i. Be aware of issues regarding counseling an individual with a learning disability. In familial cases of NF1, a parent may also have a learning disability. This may affect an individual's understanding and perception of the disorder, their ability to recognize or cope with the potential medical issues, and their comprehension of the genetic implications for future offspring. In these families, it is particularly important to determine the level of understanding and adjust the counseling session to reflect the family's comprehension level. It is also important to keep in mind that individuals with learning disabilities may prefer alternate methods of receiving information and may benefit from reinforcement at follow-up visits (Finucane 1998).
j. As indicated, assist the family in navigating the complexities of special education and/or other interventional services. Many individuals with NF1 require additional services in school, and obtaining these services may prove challenging and frustrating.

Table V Suggestions for Targeted Family History

Birthmarks or other targeted skin findings
Benign growth or tumors
Malignant tumor or cancer
Significant hearing problem such as hearing loss or ringing of the ears
Significant vision problem such as tumor, poor vision or blindness
Bone or joint problems (fractures, dislocations, curved spine)
Developmental delay, learning disability, ADHD or MR
Seizures, epilepsy or other nervous system problems
Macrocephaly

These targeted questions may also aid in differential diagnosis.

Risk Assessment

In order to complete an accurate risk assessment, it is crucial to determine whether the disease and/or mutation was inherited or *de novo*. This can often be accomplished through physical and ophthalmologic examination of the proband's parents. Alternatively, if a DNA mutation has been identified in the patient, molecular genetic testing can be performed.

If the Mutation is De Novo

Risk for siblings of proband is low (thought to be less than 1%), but remains increased due to the possibility of germline mosaicism (see "Special Considerations").

If the Mutation is Familial

Apply principles of autosomal dominant inheritance to pedigree. All offspring of an affected parent have a 50% risk

Table VI Suggestions for Targeted Psychosocial History/Assessment

Level of education
Possible barriers to communication, including cultural/language diversity or the presence of learning disabilities
Current level of knowledge regarding diagnosis of NF1
Family's understanding and perception of medical information
Previous experiences with NF1, if any
Family's perception of the etiology of NF1
Emotional reaction to the diagnosis of NF1
Family structure and functioning
Family and community support systems
Coping skills
Meaning of a genetic diagnosis for the family, including implications for family planning and parenting

to inherit the mutation. As indicated, identify nearest genetics/NF clinic for affected relatives not living in the area.

Education

Clinical Features and Natural History

Review the main features of the condition, its natural history, and the typical timeline for the development of features. See "Natural History."

Inheritance Pattern and Recurrence Risk

NF1 is an autosomal dominant condition. Approximately 50% of NF1 cases are inherited from a parent. The remaining 50% of cases of NF1 are due to a *de novo* mutation in the proband. This is felt to be due, in part, to the large size of the NF1 gene, which makes it more susceptible to mutation. Penetrance is essentially 100%, but expressivity is variable, even amongst family members.

If neither parent of the proband has NF1, the chance of recurrence is low. However, because of the possibility of germline mosaicism, the recurrence risk is likely somewhat higher than the general population risk (see "Special Considerations").

Please see "Variants of NF1" for recurrence risks for segmental NF.

Prenatal Testing and Reproductive Options

Prenatal molecular genetic testing is available for families in which the mutation has been identified in the proband. Alternatively, if there are multiple affected family members, and linkage has been established within the family, linkage analysis is an option. In these situations, prenatal diagnosis is possible via chorionic villus sampling (CVS) or amniocentesis. In the vast majority of cases, ultrasound is not useful in the prenatal diagnosis of NF1. There are some reports of prenatal identification of NF1-related abnormalities (Drouin *et al.* 1997; Hoyme *et al.* 1987; McEwing *et al.* 2006). These abnormalities included cardiac and craniofacial anomalies as well as tumors. However, the abnormalities included in these reports were atypical for NF1, and in only one instance was the diagnosis of NF1 considered before birth (McEwing *et al.* 2006).

Given the variability and unpredictable nature of the condition, genetic counseling is critical for a couple considering prenatal testing for NF1. Genetic counseling informs a couple about the signs, course, and genetics of NF1. It also facilitates the discussion of personal, moral, and ethical issues they need to explore in order to make an autonomous decision that meets their needs.

Alternate Risk Reduction Options

In families where a parent is affected and the risk to offspring is 50%, various options can reduce the risk in a future pregnancy. The use of assisted reproductive technology with a donor gamete from an unaffected individual in place of the gamete from the affected parent can greatly reduce the risk to future children. Alternatively, preimplantation genetic diagnosis (PGD) may be available for couples in which the causative NF1 mutation has been identified or if linkage phase has been established.

Signs and Symptoms that Warrant Immediate Referral and Evaluation

Parents and patients often find it helpful to be informed of what types of symptoms warrant an immediate referral and evaluation.

See Table VII for signs and symptoms warranting emergent evaluation.

Follow-up

Management

Management recommendations for patients with NF1 vary between centers and must be tailored to the individual. It is not the intention of this manuscript to address specific management recommendations. It should be noted, however, that management of these patients typically requires a multidisciplinary team. Disciplines that may be involved in the care of a patient with NF1 are listed in Table VIII.

Documentation

Providers are encouraged to thoroughly document all patient interactions. This may be done via a patient summary letter and/or a physician note. In many centers, these two forms of documentation are combined. Please see Table IX for a list of suggested items to be included.

Special Considerations

Germline Mosaicism

Germline mosaicism is a recognized phenomenon occurring in a number of dominant genetic disorders and has been observed in NF1 (Lazaro *et al.* 1995; Zlotogora 1998). Therefore, caution must be used when discussing recurrence risks with the parents of a child with an apparently *de*

Table VII Signs/Symptoms Warranting Immediate Referral

Pain of unknown etiology
Weakness, numbness, tingling in the extremities
Change in balance or coordination
Change in vision
Change in intensity or frequency of headaches
Neurofibromas that change rapidly in size and/or color, or cause pain
Abnormal neurologic exam
Sudden onset of hypertension
Regression of cognitive skills or loss of developmental milestones
Significant deviation from individual's established pattern of growth

novo case of NF1, even if parental lymphocyte analysis is negative following mutation identification in the proband. Nevertheless, it is estimated that the risk for recurrence due to germline mosaicism is less than 1%.

Consent for DNA Testing

Informed consent for molecular analysis should be obtained from the patient or legal guardian prior to the acquisition of a sample for DNA testing. A consent form from the clinical testing laboratory should be reviewed with the family. Typically, this form describes the limitations and benefits of testing, how results will be reported, and any other potential uses of the specimen.

Table VIII Potential Referrals

Neurology
Neurosurgery
Surgery
Oncology
Endocrinology
Dermatology
Orthopedics
Ophthalmology
Otolaryngology
Gastroenterology
Urology/Nephrology
Cardiology
Obstetrics/Gynecology
Physical therapy
Occupational therapy
Speech therapy
Birth-to-three/Early intervention program
Social work
Psychiatry
Psychology
Support groups

Table IX Suggested Items to Include in Documentation of NF Visit

Patient summary letter to include:	Physician note to include:
Diagnostic criteria	Medical and family history
Natural history	Physical examination
Genetics Inheritance	Impression
Recurrence risks	Recommendations/follow-up plan
Reproductive options	Resource information
Impression	Contact information for further questions
Recommendations/follow-up plan	
Resource information	
Contact information for further questions	

Table X Patient Resources

Children's Tumor Foundation (formerly NNFF): http://www.ctf.org; 800-323-7938
Neurofibromatosis, Inc: http://www.nfinc.org; 800-942-6825
Understanding NF1: http://www.understandingNF1.org
British Columbia Neurofibromatosis Program: http://www.bcnf.bc.ca; 800-385-BCNF (2263)
National Society of Genetic Counselors: http://www.nsgc.org
American College of Medical Genetics: http://www.acmg.net
American Society of Human Genetics: http://genetics.faseb.org/genetics/ashg/ashgmenu.htm
Gene Tests: http://www.genetests.org

Patient Resources

It is important to aid the family in identifying additional sources of support, such as advocacy and support groups, and other families. A list of patient resources is listed in Table X.

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Figure 1 Sample Intake Form for an NF1 Clinic Visit

Neurofibromatosis Visit Form:

Name: _____ DOB: _____ DOV: _____
Age: _____ Age at Diagnosis (if applicable): _____
Medical Record #: _____
Referring Physician: _____
Primary Care Physician: _____
Reason for Referral: _____
Chief complaint:

Medical History:

Work-up to date (neuroimaging, radiographs, EEG, audiogram, DNA testing, etc.):
Developmental History:
Pregnancy history:
Labor and delivery history:
Developmental milestones:
Surgeries:
Therapies:

Current review of systems:

General Health:
- Illnesses
- Itching
- Medications

Café-au-lait spots/Hyperpigmented lesions:
Neurofibromas/Dermal tumors:
- Location
- Increased growth
- Pain
- Itching
- Other

Neurologic:
- Headaches
- Pain
- Tingling/Numbness
- Seizures
- Dizziness
- Balance problems

Joint/Muscle:
- Strength
- Symmetry
- Coordination
- Handwriting

Cognitive function:
- Education/grade level
- School grades
- Therapies
- Employment
- Behavior
- Attetion/Distractibility issues

Eating/Elimination:
- Problems chewing/gagging
- Bowel/bladder control
- Constipation
- Diarrhea

Vision:
- Blurriness/Double vision
- Sudden changes
- Most recent Ophthalmologic results
- Lisch nodules present or absent

Orthopedic:
- Scoliosis
- Pseudarthrosis

Physical Exam:

- Height, weight, head circumference
- BP
- Dermatologic exam
- Skeletal exam (long bones, scoliosis)
- Neurologic exam

Social History:

Knowledge of condition:
- Natural history
- Genetics

Psychosocial assessment:

Assessment/Impression:

Recommendations/Plan:

Referrals: (see TableVIII)

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