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***NF1* Mutations: Neurofibromatosis Type 1 (NF1)**

Neurofibromatosis Type 1 (NF1) is a neurocutaneous condition with extremely variable clinical features that increase in frequency with age. Features include multiple cafe-au-lait spots ("birth marks"), axillary and inguinal freckling, Lisch nodules (benign tumors of the iris), optic gliomas, and cutaneous neurofibromas. While most of the tumors seen within NF1 are benign, they can cause complications that require management. Additionally, individuals with NF1 have an increased risk for various malignancies.

NF1 Cancer/ Tumor Risks

Neurofibromas: Nerve tumor that arise from the nerve sheath (cells surrounding the nerves).

- **Cutaneous neurofibromas:** Individuals with NF1 will usually develop multiple benign cutaneous or subcutaneous neurofibromas by adulthood. Though these are benign, but can be disfiguring.
- **Plexiform neurofibromas:** About 50% of people with NF1 will have plexiform neurofibromas, most of which occur internally and are not usually clinically apparent.[1] Most plexiform neurofibromas are slow growing, but rapid growth can be life threatening or cause disfigurement.
- **Malignant peripheral nerve sheath tumors (MPNST):** Deeper subcutaneous and plexiform neurofibromas may undergo malignant change to MPNST in up to 16% of people with NF1.[2,3] These tumors occur at younger ages and have poorer prognosis than in individuals without NF1 who have MPNST.

Glioma/Central Nervous System (CNS) Tumors: Gliomas are tumors that arise from the glial cells that surround nerve cells. The most common tumors apart from benign neurofibromas in people with NF1 are optic nerve gliomas and brain tumors. The frequency of optic glioma is estimated to be between 5-25%.[4] It is also estimated that 4% of individuals with NF1 will develop brainstem tumors.[5] Approximately 20% of individuals with childhood optic glioma will develop subsequent CNS gliomas.

Breast Cancer: Studies have reported as much as a five-fold increased risk for breast cancer in women with NF1 before 50 and a 3.5-fold increased risk of breast cancer overall.[6,7,8]

Pheochromocytoma: These are adrenaline-producing tumors that arise from the adrenal glands. The incidence of pheochromocytoma reported in the literature ranges from 0.1% to 15% of individuals with NF1.[9,10] These tumors rarely present in children with NF1, and are typically benign. When symptomatic, they typically cause hypertension, heart palpitations, headache, dizziness or sweating.

Gastrointestinal Stromal Tumors (GIST): This is a type of tumor that can develop in the GI tract from specialized cells, and can be benign or malignant (cancer). The risk for GIST is increased in individuals with NF1. These tumors typically have a good prognosis.

Leukemia: Children with NF1 have an increased risk for developing myeloid disorders, primarily juvenile myelomonocytic leukemia.[11,12] There also may be an increased risk for non-Hodgkin lymphoma.[21]

Other NF1 Features

Musculoskeletal: There are many bony complications that are associated with NF1. The most common bony complications are osteopenia and osteoporosis, but scoliosis, sphenoid wing dysplasia, vertebral dysplasia,

dysplasia of the long bones (tibia and fibula), and pseudarthrosis also occur.[13] Many of these are congenital or develop in early childhood, usually before the age of 6.

Cardiovascular: Hypertension is common in individuals with NF1, and may be essential, associated with pheochromocytoma (as discussed above), or associated with renal artery stenosis. Pregnant women with NF1 may have additional risk of hypertension and cerebrovascular complications. Additionally, 0.4%-6.4% of individuals with NF1 develop vasculopathy.[3]

Neurocognitive/Psychiatric: Most individuals with NF1 have normal intelligence but approximately 50-75% have been found to have learning disabilities, usually in visual-spatial performance and attention deficits. There is also an increased prevalence of depression and other psychiatric problems, with at least one third of adult individuals with NF1 affected.

NF1 Management Recommendations

Cancer/Tumor and Features	**Management**
Neurofibromas	*Surveillance* • Yearly exam with a physician who is familiar with both the patient and NF1 is advised to monitor neurofibromas and facilitate early detection of MPNST. • Imaging of lesions by MRI can be considered on a per case basis. MPNST should be suspected in any NF1 patient who presents with new pain or rapid growth of a mass.[14] *Treatment* • Current treatment options include surgical excision, laser removal, or electrodesiccation. Physician and patient preference and local expertise typically guide choice of these options.[3] ○ **Plexiform neurofibromas:** Surgical treatment for plexiform neurofibromas often has a poor result since the tumors are intimately involved with nerves and tend to recur.[8] Some success in treating plexiform neurofibromas has been achieved by using carboplatin chemotherapy.[15] ○ **MPNST:** These tumors are typically treated with surgical excision. The effectiveness of chemotherapy for these tumors has not been fully proven.[15,3] *Agents to Avoid* • Radiation therapy should be avoided in individuals with NF1 when possible, as there is an increased risk for developing MPNST within the treatment field.[2,20]
Glioma/CNS Tumors	*Surveillance* • Ophthalmological examination every 6-12 months for children under the age of 8, and every 1-2 years from age 8 to 20 for early detection of optic glioma.[16] ○ Children should be monitored for symptoms of optic glioma, including visual loss, abnormal papillary function, proptosis, optic disc atrophy, and precocious puberty.

	• Some have suggested monitoring children with NF1 for other CNS tumors, but this is not currently recommended due to the indolent course of most of these tumors. ○ CNS tumors should be suspected and investigated in individuals with NF1 who develop headache, signs of increased intracranial pressure, cranial neuropathy, hemiplegia, or ataxia. *Treatment* • Treatment of symptomatic optic gliomas is typically limited to chemotherapy. Surgery is generally reserved for cosmetic palliative treatment for a blind eye.
Breast Cancer	*Surveillance* • Current NCCN guidelines (1.2020) recommend annual mammography with consideration of tomosynthesis starting at age 30, and consideration of breast MRI with contrast from ages 30-50 for women with NF1. *Surgery* • Insufficient evidence is available to recommended risk-reducing mastectomy and management should be based on family history.
Pheochromocytoma	• Regular blood pressure monitoring is recommended for adults with NF1. • Pheochromocytoma should be considered in hypertensive NF1 patients who are over 30 years of age, pregnant, and/or have paroxysmal hypertension, hypertension-associated headache, palpitations, or sweating. If pheochromocytoma is suspected, measurement of plasma free metanephrines should be evaluated.[3]
Gastrointestinal Stromal Tumors (GIST)	• No routine screening is recommended at this time. Individuals with NF1 with anemia or gastrointestinal bleeding should be evaluated for GIST.
Leukemia	• No routine screening is recommended at this time. Children with NF1 presenting with hepatosplenomegaly, lymphadenopathy, pallor, fever, or rash should be evaluated for myeloid disorders.
Musculoskeletal	• All individuals with NF1 are recommended to have an annual clinical evaluation of the back with Adam's forward bend test • Referral to an orthopedic specialist should be placed if there are concerns about scoliosis.[3] • Individuals with NF1 should also discuss the appropriateness of vitamin D supplementation with their physicians.[3]
Cardiovascular	• Regular blood pressure monitoring is advised.[3,17] Selective imaging is recommended for patients in whom there is a clinical suspicion of a vascular lesion.[3] • Treatment for NF1-associated hypertension should be tailored to the specific etiology.
Neurocognitive/Psychiatric	• Children with NF1 should have regular developmental assessments to monitor their progress.[18] Depression screening may be considered for adults with NF1, with appropriate referral as needed.[10]
Pregnancy	• NF1 patients who become pregnant should be referred to a perinatologist to monitor for hypertension and the development of neurofibromas that could complicate delivery.[19]

Support Services for Neurofibromatosis

- A good resource for families with NF1 is a national NF foundation (neurofibromatosis network) that provides networking opportunities, education, advocacy, and support to families coping with this condition (nfnetwork.org).

Implications for Family Members/Reproductive Considerations

- Approximately 50% of individuals with an *NF1* mutation did not inherit the mutation from a parent and have a new mutation (de novo mutation).
- First-degree relatives (i.e., parents, siblings, and children) have up to a 50% risk to have the familial mutation. Second-degree relatives (i.e. nieces/nephews, aunts/uncles, and grandparents) have up to a 25% chance to have the familial mutation.
- For carriers of a known mutation, assisted reproduction (with or without egg or sperm donation), pre-implantation genetic testing, and prenatal diagnosis options exist.
- All family members are encouraged to pursue genetic counseling to clarify their risks. Family members can visit www.FindAGeneticCounselor.com to find genetic services near them.

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