



Cancer Predisposition Clinic

Neurofibromatosis type 1

Also called: NF-1, von Recklinghausen syndrome

What is Neurofibromatosis type 1?

Neurofibromatosis type 1, is a genetic condition that can affect many areas of the body, including the skin, eyes, bones, blood vessels, nerves and central nervous system. People with Neurofibromatosis type 1, also have a higher risk of developing certain kinds of cancerous and non-cancerous tumors, including:

- Nerve tumors known as neurofibromas or plexiform neurofibromas. These often develop from on or under the skin; or from nerves anywhere in the body.
- Central nervous system tumors. These may form on the optic nerve, which connects the eye to the brain or they may form in other parts of the brain.
- Adrenal gland tumors known as pheochromocytomas. The adrenal glands are located on top of each kidney, and they produce important hormones.
- Blood cancer (leukemia).
- Digestive tract tumors known as gastrointestinal stromal tumors.

Neurofibromatosis type 1, is hereditary, which means it can be passed from parents to children in a family. However, the severity of the condition and which body areas are affected can vary from person to person.

How is Neurofibromatosis type 1 diagnosed?

A diagnosis of Neurofibromatosis type 1, can be made with or without genetic testing. Genetic testing can be offered to people who have features that suggest Neurofibromatosis type 1; however, it is possible to establish a clinical diagnosis without genetic testing. A person with two or more of the following features can be given a clinical diagnosis of Neurofibromatosis type 1, even if genetic testing is not done, or if it is performed and the result comes back negative:

- Six or more café-au-lait spots measuring at least :
 - Five millimeters across at the widest point in children
 - Fifteen millimeters across at the widest point in adolescents and adults
- Two or more neurofibromas or one plexiform neurofibroma (a thick, irregular neurofibroma that usually involves multiple nerves)
- Freckles in the armpits or the groin area
- An optic glioma tumor
- Two or more Lisch nodules (small growths in the colored part of the eye known as the iris)
- Specific bone problems, such as abnormality in a skull bone or thinning of the long bones
- A first-degree relative (parent, sibling, child) with a diagnosis of Neurofibromatosis type 1

What is the cancer risk for people with Neurofibromatosis type 1?

Neurofibromas and Malignant Peripheral Nerve Sheath Tumors

Nearly all people with Neurofibromatosis type 1, develop non-cancerous neurofibromas. They usually start to appear in late childhood and adolescence, although they can continue to develop throughout life. Many women with Neurofibromatosis type 1, experience a rapid increase in the number and size of neurofibromas during pregnancy.

The total number of neurofibromas seen in adults with Neurofibromatosis type 1, varies from a few to hundreds or even thousands. Even though most neurofibromas are not cancerous, they can grow to a large size. This may cause pain, nerve damage or disfigurement. Some neurofibromas become cancerous over time. About 10% (1 in 10) of people with Neurofibromatosis type 1, will develop a cancerous neurofibroma, also called a malignant peripheral nerve sheath tumor.

Central Nervous System Tumors

The two most common central nervous system tumors in people with Neurofibromatosis type 1, are optic gliomas and brain tumors. About 20% (1 in 5) of children with Neurofibromatosis type 1, develop optic gliomas, which usually develop in childhood. They often do not cause any symptoms even into adulthood. About 3% (about 1 in 25) of people with Neurofibromatosis type 1, develop brain tumors such as gliomas. Brain tumors are more likely to develop in people who have optic gliomas.

Breast Cancer

Women with Neurofibromatosis type 1, have a slightly higher risk of developing breast cancer under 50 years of age than women without Neurofibromatosis type 1. After age 50 years, the risk is the same for women with and without Neurofibromatosis type 1.

Other Cancers

People with Neurofibromatosis type 1, have a higher risk of developing certain other cancers than people without the disorder. However, the overall risk is still very low. These cancers include:

- Adrenal gland tumors (pheochromocytomas)
- Blood cancer (leukemia)
- Digestive tract tumors (gastrointestinal stromal tumors)

What are other features seen in people with Neurofibromatosis type 1?

Neurofibromatosis type 1, can affect many areas of the body. Not all patients will have all of the following physical findings, even patients in the same family.

Other findings	Chance of having in lifetime
Café au lait spots (smooth, dark, flat birthmarks)	100%
Freckles in groin, underarms, and under the breasts	90%

Benign growths on the iris, the colored part of the eye (Lisch nodules)	60%
Learning disability	50–75%
Autism spectrum disorders	30%
Larger-than-expected head size	25%
Abnormal skeletal growth, including curved spine (scoliosis) and bowing of the legs	15%
High blood pressure (hypertension) and blood vessel disorders	15%
Heart defects	less than 2%

What causes Neurofibromatosis type 1?

Neurofibromatosis type 1, is caused by changes in a gene known as *NF1*. Genes carry information telling cells within the body how to function. The *NF1* gene helps to control how and when cells grow, divide and die.

Most people without Neurofibromatosis type 1, carry two working copies of the *NF1* gene in their cells. One copy of *NF1* is inherited from the mother and one from the father. Cells from people with Neurofibromatosis type 1, carry one working copy of *NF1* and one copy that is changed. This change causes the gene to not work properly. It is called an *NF1* mutation.

About half of children with Neurofibromatosis type 1, inherit the *NF1* gene mutation from a parent who also has the syndrome. The other half of children with Neurofibromatosis type 1, have a new *NF1* mutation that did not come from a parent. These children have no history of the syndrome in their family. In these cases, the change either happened in an egg or sperm cell when the child was formed or in one of the child's cells during pregnancy. These children are the first in their families to have Neurofibromatosis type 1. No matter how they acquired the *NF1* mutation, people with Neurofibromatosis type 1, have a 50% or 1 in 2 chance of passing it on to their children.

As people with Neurofibromatosis type 1 get older, the remaining working copy of *NF1* often becomes changed within some of their cells. When both copies of the gene are changed, tumors (which may or may not be cancerous) can develop. Researchers believe this is why people with Neurofibromatosis type 1, have a higher risk of developing tumors than people who do not have the disorder.

How are people with Neurofibromatosis type 1, screened for tumors?

People with Neurofibromatosis type 1, should be managed by a health care provider who is familiar this condition. There are clinics throughout the country that specialize in taking care of people with Neurofibromatosis type 1. For more information, please see the “Resources” section below. Although most of the tumors related to Neurofibromatosis type 1, are not cancerous, people with the condition should be monitored for the development of these tumors. Some non-cancerous tumors cause problems, such as loss of vision with optic pathway gliomas or nerve damage with neurofibromas. It is also important to carefully monitor neurofibromas for signs that

might show that they have become cancerous. The goal of screening is to find and treat tumors early to allow the best outcome for patients.

Recommended screenings for children with Neurofibromatosis type 1:

- **Yearly physical exams** that include blood pressure monitoring by a health care provider who knows this condition well.
- **Annual vision screening** by an ophthalmologist in early childhood, which can become less frequent as the child gets older.
- **Regular assessments of development and school progress**, as deemed necessary by health care providers caring for the child.
- **Regular monitoring of any abnormal problems** of the central nervous system, skeletal system, or heart and blood vessels, as deemed necessary by a specialist in one of these areas.

It is possible that recommendations may change over time as health care providers learn more about Neurofibromatosis type 1. Parents should discuss all screening options for their child with a health care provider who knows this condition well. Because Neurofibromatosis type 1, is a complex condition, it is important that parents seek out an experienced health care provider for their child.

How is genetic testing for Neurofibromatosis type 1, done?

The health care provider may suspect Neurofibromatosis type 1, after looking at a person's medical or family history. In most cases, a health care provider or genetic counselor will ask questions about a person's health and the health of other family members.

The genetic counselor or health care provider will record which family members have developed tumors, what types of tumors, and at what ages tumors occurred. From this information they will create a family tree. Health care providers and genetic counselors will look at the family tree to find out:

- If there are more cancers than normal,
- If cancers occurred at younger-than-expected ages,
- If the types of tumors match up with what might be seen in those with Neurofibromatosis type 1, and
- If there are family members who have clinical signs of Neurofibromatosis type 1.

If Neurofibromatosis type 1, is suspected in a child or other family members, the health care provider or genetic counselor will likely recommend genetic testing of the *NF1* gene.

Diagnostic genetic testing

If the health care provider or genetic counselor suspects that a person has Neurofibromatosis type 1, diagnostic testing may take place as follows:

- A blood sample is collected.
- DNA is isolated from the cells in the sample. A person's genes are made of DNA.
- Both copies of the person's *NFI* gene are checked for possible changes. A genetic specialist compares the two copies of the patient's gene to a normal *NFI* gene. If there are differences, the specialist decides if these changes point to a Neurofibromatosis type 1, diagnosis.
- If an *NFI* mutation is found, the genetic counselor will work with the family in the following ways:
 - To help the family understand the cancer risks of Neurofibromatosis type 1
 - To find out if other family members should consider testing for the mutation
 - To help with decisions about prenatal genetic testing.

If a person has an *NFI* mutation, they have a 50% chance (1 in 2) of passing it on to future children.

It is important to remember that genetic testing only finds a mutation in the *NFI* gene for about 90% to 95% of people with a clinical diagnosis of Neurofibromatosis type 1.

Some people with a clinical diagnosis of Neurofibromatosis type 1, may not have a mutation in *NFI* in their blood cells, but they could be “mosaic” Neurofibromatosis type 1. “Mosaic” means a mixture.

A person who has mosaic Neurofibromatosis type 1, has two populations of cells that make up the body. One population contains two working copies of the *NFI* gene and the second population contains one working copy of *NFI* and one copy with a mutation. Patients with mosaic Neurofibromatosis type 1, may show signs of the disease only in parts of the body that contain cells with the *NFI* mutation. Because it is hard to know which cells of the body are affected, it is not possible to predict a person's exact risk of developing tumors or passing the *NFI* mutation on to future children.

Prenatal genetic testing

Parents may undergo prenatal testing to find out if the pregnancy is affected with a known *NFI* mutation in the family. Testing may take place either before pregnancy occurs or during pregnancy.

People considering prenatal testing should work with a genetic counselor to review the pros and cons of the testing. The genetic counselor can also help parents consider how they wish to handle the results of the testing.

Testing that occurs before pregnancy—Testing that happens before pregnancy is called preimplantation genetic testing (PGT). This type of genetic testing is done along with in vitro fertilization (IVF). PGT offers a way to test embryos for a known *NFI* mutation before placing them into the uterus.

Testing that occurs during pregnancy—Testing can be used to see if a pregnancy is affected with a known *NFI* mutation. A doctor gathers cells from the pregnancy in one of two ways:

- **Chorionic villus sampling (CVS)**—during the first trimester (first three months)
- **Amniocentesis**—during the second trimester or later (last six months)

Collected tissue can be checked for the presence of the *NFI* mutation identified in the family.

Both of these tests carry minor risks and should be discussed with an experienced doctor or genetic counselor.

Special concerns

Genetic testing for Neurofibromatosis type 1, is a complex process. Those thinking about testing should take time to consider the benefits and risks. They should discuss the process with a genetic counselor before testing is done. If they choose testing, they should review the test results with the health care provider or genetic counselor to be sure they understand the meaning of the results.

Sometimes children or adults with Neurofibromatosis type 1, feel sad, anxious, or angry. Parents who pass on an *NFI* mutation to one or more of their children can feel guilty. Some people with an *NFI* mutation could have trouble getting disability coverage, life insurance, or long-term care insurance in some states. More information about genetic discrimination can be found at www.ginahelp.org.

Are there other special health care needs for children with Neurofibromatosis type 1?

People of any age with Neurofibromatosis type 1, have a higher risk of cancer. They should monitor their health and adopt healthy habits. It is important to continue to have regular physical check-ups and screenings. That way, any cancer can be found early at the most treatable stage.

Other ideas to reduce the risk of cancer include the following:

- Eat a healthy diet with lots of fruits and vegetables
- Avoid excess sun exposure and always wear sunscreen, hat and protective clothing when out in the sun
- Get regular exercise
- Avoid smoking or using tobacco products
- Avoid secondhand smoke

People with Neurofibromatosis type 1, should watch closely for general signs or symptoms that could signal cancer, such as:

- Unexplained weight loss,

- Loss of appetite,
- Pain in the abdomen,
- Blood in the stool or changes in bowel habits,
- Aches, pains, lumps, or swelling that cannot be explained, and
- Headaches or changes in vision or nerve function that don't go away.

It is important to seek medical help if anything unusual appears.

What other information and resources are there for children with Neurofibromatosis type 1, and their families?

Resources about Neurofibromatosis type 1:

- Genetics Home Reference (ghr.nlm.nih.gov/condition/neurofibromatosis-type-1)
- Health Supervision for Children with NF1 (<https://pediatrics.aappublications.org/content/143/5/e20190660#sec-2>)
- Neurofibromatosis Network (www.nfnetwork.org)
- Children's Tumor Foundation (www.ctf.org)

Additional resources:

- Making Sense of Your Genes: A Guide to Genetic Counseling (www.ncbi.nlm.nih.gov/books/NBK115508/)
- Young People with Cancer: A Parent's Guide (www.cancer.gov/publications/patient-education/young-people)

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