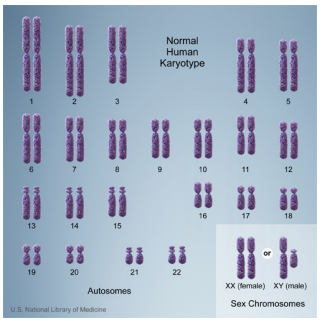
CHILDREN'S TUMOR FOUNDATION
ENDING NF THROUGH RESEARCH

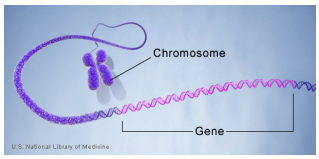
A GUIDE TO GENETIC TESTING

in Neurofibromatosis and Schwannomatosis

This resource reviews the option of genetic testing for all types of NF, including neurofibromatosis type 1 (NF1), and all types of schwannomatosis (SWN) including *NF2*-related schwannomatosis (*NF2*-SWN), formerly known as NF2. This is to provide information only and should not be considered medical advice. One should make genetic testing decisions with a genetic counselor or other knowledgeable healthcare provider.

To begin to understand genetic testing, some background knowledge is needed.





WHAT ARE CHROMOSOMES, GENES, AND VARIANTS?

Chromosomes are the packages of our genetic information. Each cell of the body typically contains 46 chromosomes arranged in 23 pairs. One chromosome in each pair is inherited from the mother, and the other from the father. The pairs are numbered by size. The first chromosome pair is the largest and the 22nd pair is the smallest. The last pair of chromosomes (sex chromosomes) determine whether an individual is a male or a female.

Genes are small segments along the chromosomes, and are the body's blueprints or instructions. We have approximately 20,000 genes that control how we develop, what we look like, and how we grow. Each gene can be thought of as a sentence made up of four letters (A, T, C and G). ***Variants*** (previously called mutations), are changes in a gene's letters that may disrupt a gene's instructions. There are several different types of variants within genes such as, deletions (removing letters), duplications (adding duplicate letters), or substitutions (changing letters).

WHAT IS GENETIC TESTING?

Condition	Gene(s)	Chromosome
NF1	*NF1*	17
NF2-SWN	*NF2*	22
Other types of SWN	*LZTR1* or *SMARCB1*	22

Genetic testing is also called molecular or DNA testing. Genetic testing involves evaluating the gene(s) involved in a condition to look for variants, similar to a spellcheck on the computer. Sometimes these variants disrupt the instructions of the gene and are considered *pathogenic variants*. A pathogenic variant in a gene changes the function of the product, which in turn changes a component in our bodies often leading to disease. Other times, the variants do not impact the instructions of the gene and are called *benign variants*. There are times when it is not clear if a sequence change is either benign or pathogenic, and these are called *variants of uncertain significance* (VUS).

The different types of NF1 and SWN are caused by different genes (see the chart above). Individuals with one of these conditions have a pathogenic variant in one of their two gene copies. Therefore, they have one working copy of the gene and one non-working. These genes are important in regulating cell growth and activity. Although not all of the functions of these genes are known, they are thought to be tumor suppressor genes, which means that the protein produced by the genes stops the growth of tumors when it is working normally. In these conditions, if the gene product/protein is not fully functioning, tumor growth goes unchecked.

In some situations, healthcare providers may choose to test more than one gene (called a gene panel). This could be because the individual's symptoms overlap with more than one condition or when there are several conditions that have similar symptoms. A condition called Legius syndrome has some of the same physical features as NF1. Therefore, healthcare providers often order testing for both *NF1* and *SPRED1*, the gene that causes Legius syndrome. Similarly, the different types of schwannomatosis cause similar manifestations. Therefore, the evaluation of multiple genes (a gene panel) may be recommended.

WHO SHOULD HAVE GENETIC TESTING?

Genetic testing can be helpful in the following situations:

- To confirm a diagnosis of NF in a person who does not meet the diagnostic criteria any type of NF, or is difficult to diagnose by clinical exam.
- To identify a variant in an individual with NF so that other family members can be tested.
- To determine whether an individual with a family history of NF the condition themselves (a familial variant must be previously known).
- To identify a variant to allow a couple to consider prenatal diagnosis or preimplantation genetic testing (PGT) in a current or future pregnancy. (See CTF resource: "Family Planning and Reproductive Options in NF" for more information).
- To provide insight into the severity or likelihood of the development of specific features (in some cases).

WHAT IS INVOLVED IN GENETIC TESTING?

Sample

Most genetic testing is performed on either blood or saliva. Since DNA is found in every cell in our bodies, it does not matter which cells are sampled, but blood and saliva are the easiest cells to access. The sample is often obtained in a clinic or lab, but a saliva kit may be available for home collection. In some situations, testing of skin or a tumor specimen is required. It is important to review the details of these collection procedures with your medical provider.

Lab

Once the specimen is obtained, it is sent to a genetics laboratory for testing of the appropriate gene(s). There are many different laboratories offering genetic testing for NF. Laboratories vary by experience, costs, sensitivity, and service. Not all laboratories provide the same level of testing. Your NF care providers will determine the best testing location.

Costs

Most genetic tests are expensive. Prior to initiating genetic testing, a request is usually made to the family's insurance plan as part of a preauthorization process. This is typically initiated by the healthcare provider by submitting a letter of medical necessity explaining the importance of the testing. This process often takes 30 business days. The billing codes (called CPT codes) are sent to the insurance company to determine if the testing is eligible for coverage. Even when coverage is confirmed, families are often responsible for deductibles and co-pays as determined by their health insurance plan(s). Some families choose to pay for the testing themselves instead of going through their insurance company. This is referred to as a self-pay, or out of pocket, option and is helpful when insurance denies coverage for testing. There is often a reduction in the cost of testing if a family elects the self-pay option.

Consent

Genetic testing is voluntary and a family should be informed of benefits and risks of testing, and provide their consent prior to testing. Because testing has limitations as well as benefits, the decision about whether to be tested is a complex and personal one. A genetic counselor or other healthcare provider can help by providing information about the pros and cons of the test and discussing the social and emotional aspects of their decision.

Time

Genetic testing takes longer than most labs performed through primary care providers. It is a time-intensive process using specialized laboratory techniques and requires complex interpretation. Depending on how many genes are being tested, results may be available in as few as 4 weeks to as many as 16 weeks. Ask your healthcare provider or genetic counselor how long your test will likely take.

WHAT TYPES OF RESULTS CAN YOU EXPECT FROM A GENETIC TEST?

There are three possible test results from genetic testing.

1) **The test detects a pathogenic variant in an NF gene**

An informative (also called a "positive") test result means a pathogenic variant in an NF gene was identified and the individual is confirmed to have either NF1 or SWN, or *NF2*-SWN. This result typically cannot determine how severe the condition will be. Knowing the pathogenic variant allows for targeted genetic testing of family members or for future pregnancies. However, even in the same family, individuals can have different and variable features of either NF1 or SWN, or *NF2*-SWN.

2) **The test does not detect a pathogenic variant in an NF gene**

When a genetic test does not identify a pathogenic variant in the NF gene, it should be interpreted carefully by a provider experienced with the nuances of genetic tests. There are two situations:

- **Testing in a family with no previous NF genetic testing:** Genetic testing does not completely rule out an NF diagnosis. Because of existing technology and other limitations, a small number of individuals with a clinical diagnosis of NF1 and many individuals with a clinical diagnosis of *NF2*-SWN and other types of SWN have testing that does not identify a pathogenic variant. The individual could still have NF and often should continue to be seen by an NF provider for care. Additional testing might be recommended. As an individual gets older, if they continue to have few signs of NF, these results may help a healthcare provider eventually rule out NF with no additional need for monitoring. This is not a "negative" result because of the possibility that the individual may still have NF.
- **Testing in a family with a known pathogenic NF variant:** When one individual in the family has previously been identified with a pathogenic NF gene variant, testing can be done on others in the family. In this case, if an individual does not have the same pathogenic variant, the testing is conclusive and the family member without the variant does not have NF. This is also called a "negative" result.

3) **The test detects a variant of uncertain significance (VUS)**

A test result that reports a variant in the NF gene that has not been reported previously and/or is not clearly associated with NF is referred to as a variant of uncertain significance (VUS). Your providers and the laboratory may not be able to determine whether the variant causes a disruption of the NF gene or is a normal variation in the gene. With this result, the laboratory may request blood samples and clinical information from other members of the family to help interpret the results. As genetic testing technology

continues to improve and we learn more about genetic variants, our ability to identify and classify variants will likely improve. Over time, an inconclusive result may be reclassified as either pathogenic (causing NF) or benign (not causing NF).

WHAT ARE THE LIMITATIONS OF GENETIC TESTING?

Although genetic testing may be helpful in many situations, there are some limitations to testing.

- If a pathogenic variant is identified, genetic testing does not often predict the severity of the condition or determine with certainty how an individual will be impacted.
- A negative result does not definitively exclude the condition.
  - Additional testing might be recommended by different lab techniques or in a different body tissue.
  - If someone is highly suspected of having a condition, a negative genetic test might not change the medical screening recommendations.
  - If a diagnosis is known based on clinical features, a negative genetic test does not change the diagnosis.
- If a VUS is identified, additional testing of family members is often requested, but may not help in the final interpretation of the result.

QUESTIONS TO ASK YOUR PROVIDER

There are many things to think about when considering genetic testing. You may want to ask your healthcare provider the following questions about genetic testing:

How will testing help me/my child?

Will the testing change medical recommendations?

What genes will be evaluated?

Will insurance cover the testing?

What is the total amount billed to insurance for the test?

What is the chance that the testing will find a variant in the NF gene?

When and how will I be notified of the results?

For more information, talk with a genetic counselor or other knowledgeable healthcare provider. To locate an NF Clinic in your area, go to **ctf.org/doctor** or to find a genetic counselor, go to **https://www.nsgc.org/page/find-a-genetic-counselor**.

For more resources on the genetics of NF, please visit **ctf.org/genetics**.

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