What are neurofibromas?
Neurofibromas are benign (not malignant) tumors/growths of nerves. They are basically overgrowth and disorganization of normal nerve tissue with the addition of inflammatory cells and blood vessels. Neurofibromas are made of nerve fibers, Schwann cells (cells that cover the nerve fibers), blood vessels, inflammatory white blood cells (mast cells), and connective tissue (fibroblasts and loose material called extracellular matrix). The mast cells can release histamine which causes the neurofibromas to itch or hurt.

Who gets neurofibromas?
Neurofibromas are a common tumor. Not everyone who has a neurofibroma has NF. People with NF1 usually get multiple neurofibromas. In neurofibromas, the nerve fibers run through the tumor. This means that removing the neurofibroma always means cutting the nerve (see treatment below). The diagram to the right shows a nerve that is swollen or ballooned out by a neurofibroma (in pink). It is compared to a Schwannoma which is a tumor of the covering of the nerve so that the tumor (in pink) simply lies on top of the nerve.

Types of neurofibromas in NF1
In NF1 we see: Diffuse neurofibromas
Cutaneous or Dermal neurofibromas
Intramuscular neurofibromas
Plexiform neurofibromas

Diffuse neurofibromas are tumors that involve the full thickness of the skin (from the surface all the way down to the base of the skin (fascia). Diffuse neurofibromas stop at the fascia and do not usually go any deeper. Diffuse neurofibromas are uncommon. They are often seen in the scalp and feel soft, almost squishy and they do not have clear margins (you can’t easily tell where the tumor stops). You can also see diffuse neurofibromas on the trunk (often protruding out – like a “love handle”) and they are usually associated with diffuse hyperpigmentation so that they look like a very large squishy café au lait spot. Diffuse neurofibromas are present in early childhood and can grow.
**Cutaneous or Dermal neurofibromas** are the most common type of neurofibroma. These are the bumps or lumps that occur on the skin. They usually start in teenage years or young adults and rarely start in childhood. They increase in size and number over the years. Sometimes they don’t start until middle age. They have clearly defined borders and can be removed if necessary. The number of skin tumors that someone has varies tremendously. Some patients have very few cutaneous neurofibromas. Some patients have very large numbers of cutaneous neurofibromas. It is less common to have a very large number and the tendency for very large numbers of them may run in families.

**Intramuscular neurofibromas** are tumors that occur in the muscle. They are usually growths along very small nerves. Sometimes they cause pain and usually they can be removed (although removing them leaves a scar). Sometimes intramuscular neurofibromas are actually plexiform neurofibromas that occur in a chain or network.

**Plexiform neurofibromas** are made up of the same cells as dermal or cutaneous neurofibromas and occur in about half of all people with NF1. Plexiform neurofibromas tend to be tumors of large nerves and are often internal, but they can also involve small nerves and the superficial skin. Plexiform neurofibromas differ from cutaneous neurofibromas in that they have more connective tissue (extracellular matrix) that separates the nerve fibers. Plexiform neurofibromas tend to be congenital – meaning we think patients are born with them, but they may not cause any problems and they may not be apparent for years, if ever. Plexiform neurofibromas can grow. They are more likely to grow in childhood but they can also grow in adult years. There is no evidence that they get worse with puberty. Plexiform neurofibromas have different subtypes.

**Types of Plexiform Tumors**

When plexiform neurofibromas involve the skin they usually extend through the skin and extend below the skin and fascia into the muscle. This type of plexiform neurofibroma may be referred to as a **diffuse plexiform neurofibroma** because it does not have clear margins and tends to have little “fingers” of tumor that invade the muscle or other tissue. When patients with diffuse plexiform neurofibromas are infants the tumors may not be easy to see or sometimes, if there is hyperpigmentation with it, it may just look like very large café au lait spots. However, slowly the skin may thicken and enlarge and distort the normal appearance of the part of the body that is affected.

To the right is a picture of a child with a **diffuse plexiform neurofibroma** of the face. You can see that one side of the face looks different than the other and is a little swollen. That is because the skin and some of the deep tissue of one side of the face has a **diffuse plexiform neurofibroma**. However, you can’t really see any “tumor” or a clear margin or point where the changes begin or stop.
Below is an MRI through the legs of a patient with a diffuse plexiform neurofibroma of one leg. You can see how one leg is bigger (the right side of the picture) compared to the other leg and how the muscle fibers (the light colored areas) are not as dense because they are teased apart by the plexiform neurofibroma, but there is no obvious tumor – no clear margins for what is normal and what is abnormal.

Plexiform neurofibromas often involve the nerves coming off the spinal cord. They can also involve large nerves like the sciatic nerve of the leg. They tend to enlarge or thicken the nerve that is affected and sometimes appear to produce little clusters of tumors along the nerve. We call this type of plexiform neurofibroma a **nodular plexiform neurofibroma**. The picture on the right shows the legs of a patient. There are a number of small white spots in the leg that are intramuscular plexiform neurofibromas and two long white cord like structures that are the sciatic nerves. The sciatic nerves are thick and have a cluster of tumors along them.

**What kinds of problems occur with Neurofibromas?**

Most neurofibromas grow and growth may or may not cause problems. Neurofibromas are often itchy (because the mast cells present in the neurofibromas release histamine) and they can hurt (as a sign of growth or when they are touched or injured). Neurofibromas can grow after trauma or a simple injury to the neurofibroma. The trauma or injury can damage the blood vessels associated with the neurofibroma and sometimes this results in very sudden swelling of the tumor.

**If neurofibromas hurt you should discuss that with your doctor.** Severe pain can also be a warning sign that a part of the tumor is becoming malignant (cancerous). Malignant deterioration of a plexiform neurofibroma happens in about 9% of patients with NF1. It is a very serious complication that requires immediate attention. If malignant deterioration of a plexiform neurofibroma occurs, it is usually in late teenage or adult years. Most neurofibromas, including plexiform neurofibromas don’t hurt.

Diffuse neurofibromas can also become malignant. Cutaneous neurofibromas never become malignant. You should also alert your doctor to growth of your cutaneous neurofibromas.

Sudden growth of tumors could be a sign of bleeding in the tumor and sometimes if the tumor is a plexiform neurofibroma or diffuse neurofibroma, the bleeding can be severe and needs to be dealt with emergently.
However, even though neurofibromas are tumors of nerves they usually do not cause weakness (unless the neurofibroma is along the spine and pushes on the spinal cord). The appearance of neurofibromas can be upsetting and diffuse plexiform neurofibromas can be disfiguring because they produce a change or distortion of normal appearance.

**Treatment of Neurofibromas**

Neurofibromas can potentially be removed surgically however the decision to do surgery to remove a neurofibroma must be carefully thought out. The approach to each patient depends on the location of the tumor/s, the patient’s age, whether they are causing problems such as pain, and whether the tumor is in a position that is easily injured. I also pay attention to whether the tumor is easily visible and makes people self-conscious or causes other people to pay attention to it. I try to remove *cutaneous or dermal tumors* when they become larger or are causing problems or are easily injured or people find them particularly embarrassing.

It is important to realize that when you remove a cutaneous neurofibroma surgically, there will be a scar. Also there is a tendency for cutaneous neurofibromas to come back in the general area where the tumor was removed, but this often does not happen for a long time. It is important to have a plastic surgeon or general surgeon experienced in NF remove the cutaneous neurofibromas because they are more likely to remove the tumor completely. Because removing the tumor cuts a nerve, it is important to have someone experienced with NF to determine whether removing the tumor and cutting the nerve can be done without any risk of injury or weakness. We often get MRIs to make sure the tumor is not attached to an important nerve. Removing large numbers of neurofibromas is difficult. There is a procedure often called “electrodessication” that can be used to remove large numbers of tumors. It is done with electrocautery and does not remove the tumor. Instead a cautery probe is inserted into the tumor and the cautery burns and shrinks the tumor producing a scar. Only a few centers do this procedure.

I often try to leave *diffuse neurofibromas* alone unless they are growing. It is impossible to completely remove diffuse neurofibromas so I often wait to see if they are going to grow or cause problems.

*Intramuscular neurofibromas* can usually be removed surgically if they are growing or causing pain. Remember that some intramuscular neurofibromas are actually plexiform neurofibromas (see the picture of the legs above).

*Plexiform neurofibromas* can also be treated surgically depending on their location and size and whether they are causing problems. The surgical approach to plexiform neurofibromas can be difficult. When you cut into a plexiform neurofibroma you are cutting into a nerve. Sometimes the plexiform neurofibromas are growths of small nerves or nerves that can be sacrificed. Also some spinal nerve roots can be removed without difficulty but that is not true of all the spinal nerves.

In some cases the plexiform neurofibroma involves a large area and can’t be removed without the use of skin grafts or expansion of the normal surrounding tissue. If the plexiform neurofibroma involves a large area then we need to very carefully assess the potential benefits of removing the tumor as well as the risks.

Plexiform neurofibromas of large nerves can sometimes be treated surgically by teasing apart the tumor and trying to remove parts of it without removing the entire nerve. This type of surgery however is very difficult and should only be done by very experienced surgeons and involves a team of a neurosurgeon and plastic/reconstructive surgeon.
Sometimes large tumors can also be shrunk using a technique to cut off the blood supply to a tumor. This is called embolization. It requires a very experienced team of interventional radiologists and plastic surgeons.

**Medical Treatment of Neurofibromas Are in the Future**

There is considerable hope for medical treatments for neurofibromas. Different medicines have been looked at to shrink neurofibromas. There have been some promising results recently with what are called MEK inhibitors. These are medicines that target a signaling pathway within the cells of nerves that are overstimulated because of NF. The MEK inhibitors decrease the stimulation/activity of the pathways that are involved in NF. At the time of writing this paper, the MEK inhibitors are still very experimental but I think it is very likely that we will be able to have medicines to shrink neurofibromas or prevent them from growing. It is important to keep that possibility in mind when we think about surgical treatments.

<table>
<thead>
<tr>
<th>Types of Neurofibromas</th>
<th>Characteristics/description</th>
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<tbody>
<tr>
<td>Cutaneous/Dermal</td>
<td>Most common; these are tumors on the skin;</td>
</tr>
<tr>
<td>Sub-Cutaneous</td>
<td>Common; these are tumors underneath the skin. They can be single tumors or chains. Subcutaneous neurofibromas are often a form of plexiform neurofibromas.</td>
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<tr>
<td>Diffuse (cutaneous?)</td>
<td>Uncommon; squishy; run the full thickness of the skin; edges difficult to define.</td>
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<tr>
<td>Intramuscular</td>
<td>Common, usually isolated tumors in the muscle; but sometimes they can occur in chains and are plexiform neurofibromas.</td>
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<tr>
<td>Plexiform</td>
<td>Usually on large nerves; they have more connective tissue that separates the nerve fibers; they are generally believed to be present at birth</td>
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<thead>
<tr>
<th>Sub-Types of Plexiforms</th>
<th>Characteristics/description</th>
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<tbody>
<tr>
<td>Diffuse Plexiform</td>
<td>Extends through the skin into the fascia and muscle; have “little fingers” that invade muscle or other tissue; they may have a large café au lait spot “above” them</td>
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<tr>
<td>Nodular Plexiform</td>
<td>Usually involve nerves coming off the spinal cord or off of larger nerves; they usually enlarge or thicken the nerve and look like little clusters of tumors along the nerve</td>
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