

Melanoma and the NRAS G12D Mutation

This material will help you understand:

- the basics of melanoma
- the role of the NRAS gene in melanoma
- if there are any drugs that might work better if you have certain changes in the NRAS gene

What is melanoma?

Melanoma is a type of skin cancer. It starts in the cells that make melanin, the substance that gives skin its color.

What causes melanoma?

Cancer is caused by changes in our genes. Genes contain the instructions for making proteins. Changes in genes, called mutations, may result in changes in proteins. These changes may cause cells to grow out of control which could lead to cancer.

Melanoma usually starts on areas of the skin exposed to the sun. But melanoma can also show up in other parts of your body like the eye, the bottom of the feet, under the nails, or inside the mouth.



What are the most common current treatments for melanoma?

Doctors may treat melanoma using one or more of these options:

- **Surgery** – operation that removes as much of a cancer tumor as possible.
- **Traditional chemotherapy** – drugs that kill growing cells. All cells grow, but cancer cells grow faster than healthy cells. So, these drugs kill more of the cancer cells. But because these drugs kill healthy cells too, this can cause unwanted side effects.
- **Precision medicine therapy** – treatments that target proteins involved in cancer.

These therapies mainly kill cancer cells and not healthy cells. This also means you may have fewer side effects. Two types of precision medicine therapies are:

- **Small molecule therapy** – mainly acts on cells with specific protein changes. Small molecule therapy uses drugs to target those proteins. Genetic testing can tell if your cancer cells have protein changes that can be targeted. Small molecule therapy is a type of targeted therapy.
- **Immune-based therapy** – works with your body's defense system to fight cancer. These can mark cancer cells so they are easier for your immune system to find.



Can I pass on mutations found in my cancer cells to my children?

You cannot pass on mutations found only in your cancer cells to your children.

How well does cancer drug treatment work?

After a while, your cancer cells may stop responding to the drug(s). This means your cancer may start to grow again. Your doctor will do regular checkups to watch for this. If the cancer starts to come back, your doctor can try another drug or treatment.



What is NRAS?

NRAS (pronounced “N-ras”) is the name of both a gene and a protein. The NRAS gene contains the instructions for making the NRAS protein. NRAS is a member of the RAS family of proteins. RAS proteins are part of at least six pathways. Proteins in pathways work together to do specific jobs within the cell. Some pathways help the cell survive. Other pathways help the cell grow. Some of the other proteins in one of the growth pathways include RAF, MEK and ERK. These are shown in the healthy cell image on the right (Figure 1). These pathways relay signals from outside the cell to the cell’s nucleus. The nucleus is the control center of the cell. These signals may tell the cell to grow, divide, or die. The body turns the signals on and off as needed

What is NRAS’s role in this growth pathway?

In healthy cells, the growth signal turns proteins “on.” As the signal reaches each protein in the pathway, it turns on the protein. When the NRAS protein receives the signal, it passes it on to a RAF protein. RAF passes it on to MEK, and MEK passes it on to ERK. ERK is the last protein in the pathway. When ERK is on, it turns on genes in the nucleus that help cells grow. When the signal stops, the proteins turn off.

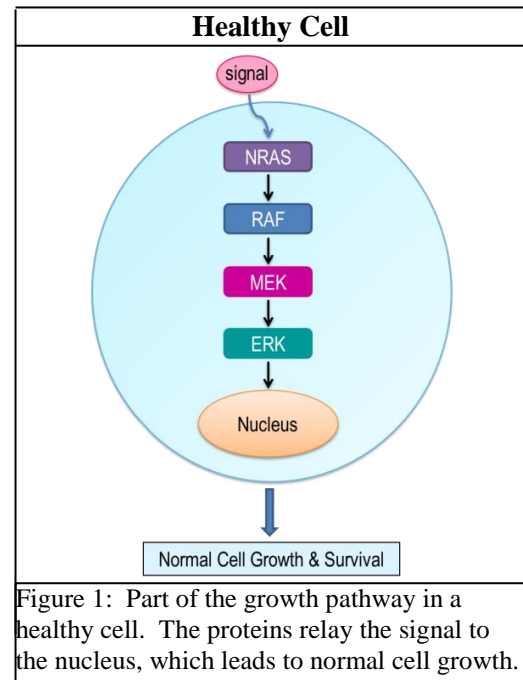


Figure 1: Part of the growth pathway in a healthy cell. The proteins relay the signal to the nucleus, which leads to normal cell growth.

How do mutations in proteins affect pathways?

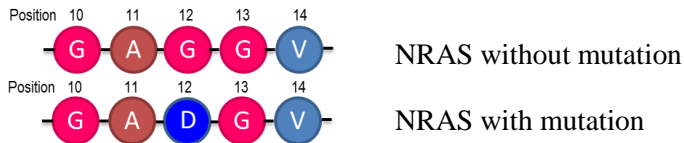
If a mutation affects one or more proteins in a pathway, the proteins may not be able to be turned on or off as expected. This can cause cells to grow out of control and lead to cancer.

How common are NRAS mutations in melanoma?

About 1 in 5 melanomas have a mutation in the NRAS gene that changes the NRAS protein. NRAS mutations are a little more common in melanomas found on skin damaged by the sun. But these mutations can occur in all types of melanoma.

What is the NRAS G12D mutation?

NRAS G12D is a specific variation in the NRAS protein. Proteins are long chains of amino acids. The NRAS protein has 189 amino acids. NRAS with no mutation at amino acid position 12 has a glycine, or G for short. The amino acid at position 12 in NRAS with the G12D mutation is an aspartic acid, or D for short.



What is the effect of this mutation?

The most common mutations in NRAS occur at positions 12, 13, and 61. All three of these amino acid positions are important in turning on the protein. When a mutation occurs at any one of these positions, the growth pathway cannot be turned off. This can cause cells to grow out of control and lead to cancer (Figure 2).

Are there targeted therapies for NRAS G12D?

At this time, it is unclear if any drugs target NRAS with this specific mutation. But, you should talk to your doctor about your treatment options.

What if I have a different mutation in NRAS or “no mutation”?

You might still have other mutations in this gene or in other genes that were not tested. Your genetic test results will still help your doctor determine the best treatment for you.

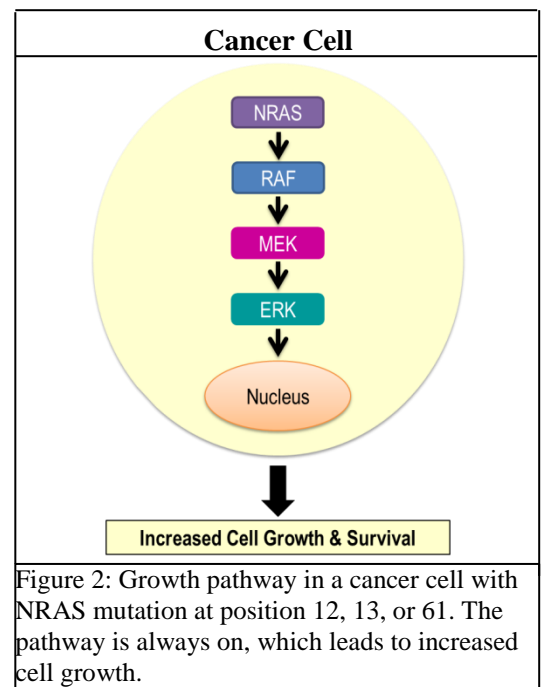


Figure 2: Growth pathway in a cancer cell with NRAS mutation at position 12, 13, or 61. The pathway is always on, which leads to increased cell growth.