Melanoma and the BRAF D594E Mutation

This material will help you understand:

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

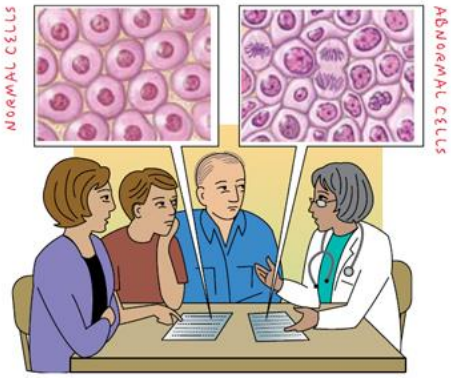
Melanoma usually starts on areas of the skin exposed to the sun. But melanoma can also show up in other parts of your body like the eye, the bottom of the feet, under the nails, or inside the mouth.

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 BRAF?
BRAF (pronounced "B-răf") is the name of both a gene and a protein. The BRAF gene contains the instructions for making the BRAF protein. BRAF is a member of the RAF family of proteins. Their main job is to help control cell growth. RAF proteins are part of a pathway. Proteins in pathways work together to do specific jobs within the cell. Some of the other proteins in this pathway include RAS, MAP2K1 and ERK. This is shown in the healthy cell image below (Figure 1). This pathway is a signaling pathway. It passes 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. These are all normal cell functions. The body turns the signals on and off as needed.

What is BRAF's role in the 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. BRAF receives the signal via RAS. BRAF passes it on to MAP2K1, and MAP2K1 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.

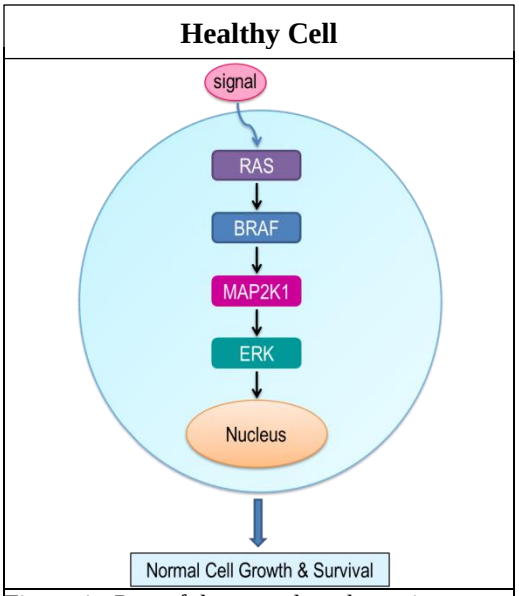
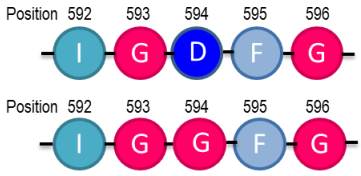


Figure 1: Part of the growth pathway in a healthy cell. The proteins pass the signal to the nucleus, which leads to normal cell growth.

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 BRAF mutations in melanoma?
About half of all melanomas have a mutation in the BRAF gene that changes the BRAF protein. BRAF mutations are most common in melanomas found on skin without long-term sun damage. But these mutations can occur in all types of melanoma.

What is the BRAF D594E mutation?
D594E is a specific variation in the BRAF protein. Proteins are long chains of amino acids. The BRAF protein has 766 amino acids. BRAF with no mutation at amino acid position 594 has an aspartic acid, or D for short. The amino acid at position 594 in BRAF with the D594E mutation is a glycine, or G for short.



BRAF without mutation

BRAF with mutation

What is the effect of this mutation?
The D594E mutation is in the part of BRAF that passes along the cell growth signal. In cells with this mutation, BRAF can no longer pass along the signal. So, the cell tries to find another way to turn this pathway back on. BRAF D594E mutation does not cause cancer by itself. Mutations can occur in the RAS gene that could keep the pathway turned on. Since BRAF cannot pass along the growth signal, the mutated RAS protein works with CRAF, another RAF protein (Figure 2). Cancer may develop in cells that have both a BRAF D594 mutation and a RAS mutation that keep the pathway on.

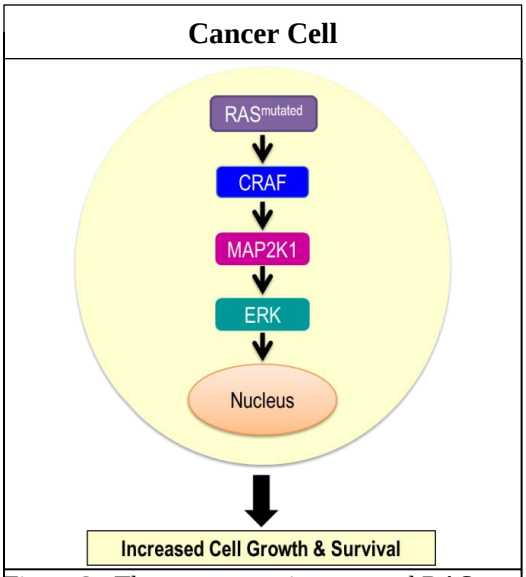


Figure 2: The cancer-causing mutated RAS protein works with CRAF to increase cell growth. BRAF with D594 mutation is not shown, since it cannot pass the signal.

Are there targeted therapies for BRAF D594E?
At this time, it is unclear if any drugs target the BRAF D594E mutation. But, there are targeted therapy drugs that inhibit MAP2K1. MAP2K1 is another protein in this cell growth pathway. Cells with this BRAF mutation use CRAF to turn on MAP2K1. If we block MAP2K1, we can stop this pathway. Trametinib and selumetinib are two common MAP2K1 inhibitors. These drugs inhibit the growth of cells and may lead to cell death (Figure 3). But, you should talk to your doctor about your treatment options.

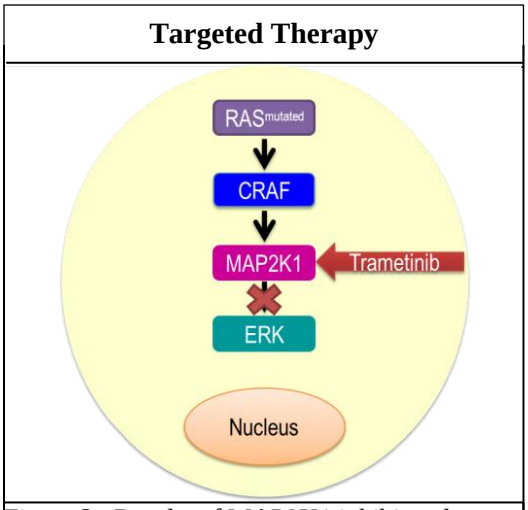


Figure 3: Results of MAP2K1 inhibitor drugs. These stop the MAP2K1 protein from turning on the rest of the cell growth pathway.

What if I have a different mutation in BRAF or "no mutation"?
Your cancer cells might have 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.