

Variants of Uncertain Significance

Updated November 2019

1. My test result indicated that a “variant of uncertain significance” was identified. What does this result mean?

A “variant of uncertain significance” (VUS) is a genetic change whose impact on the individual’s cancer risk is not yet known. Everyone’s genes are slightly different. Some genetic changes (variants) do not affect the gene’s function and therefore do not increase cancer risk. Other genetic changes prevent proper functioning of the gene and are associated with increased risks for certain cancers. In some cases, we do not have enough information to determine if a variant is normal or disease-causing. These types of variants are classified as “variants of uncertain significance.”

Of note, variants that are identified in genes that do not correspond with a patient’s medical and/or family history are less likely to be associated with disease and are more likely to be benign (e.g., a variant in a gene associated with colon polyposis identified in a patient with breast cancer).

2. Should my family members be tested for the “variant of uncertain significance” that was identified?

In general, because we do not understand the meaning of variants of uncertain significance it would not be helpful to offer testing to most family members. Such testing would not clarify their cancer risks and therefore would not provide them with information that would be helpful for their medical management. *Their medical management should be based on their personal and/or family history of cancer.*

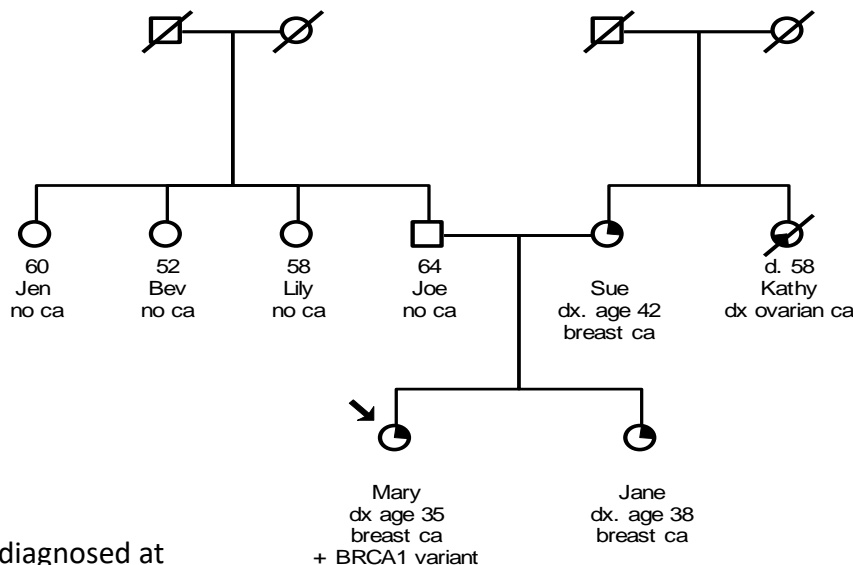
However, testing particular family members for a variant of uncertain significance is sometimes suggested to help determine the significance of the variant (i.e. whether the variant is tracking with the cancers in the family). Please see the example below (question 3) for additional information about when testing other family members for a VUS may be warranted.

3. How can scientists learn more about these “variants of uncertain significance”?

There are several ways of gathering more information about genetic variants. One way is for scientists to study the gene in the laboratory. As we learn more about the gene, scientists may be able to determine if a variant increases cancer risk or is benign.

We can also follow or track variants within families to see if the variants are found in the family members who have cancer. These methods cannot prove or disprove that a variant is disease-causing, but they may provide more information about the chance that a variant in a certain family is disease-causing.

Here is an example:



Key:

dx = diagnosed at
 d = died at age
 ca = cancer

Mary was diagnosed with breast cancer at age 35. She had genetic testing and was found to carry a variant of uncertain significance in the *BRCA1* gene (breast cancer 1 gene, associated with an increased risk of breast and ovarian cancer). Her sister, Jane, was diagnosed with breast cancer at age 38 and her mother, Sue, was diagnosed with breast cancer at age 42. Her maternal aunt, Kathy, died of ovarian cancer at age 58. Her father, Joe, has a large family including 3 sisters, Jen, Bev, and Lily, and has no known family history of cancer. Both of Mary's parents agree to have testing to determine if they also carry this *BRCA1* variant. Let's say in this case that her father carries this *BRCA1* variant and her mother does not. Since Mary inherited this variant from her father, who has a large family with no history of breast or ovarian cancer, and not from her mother, who has a significant history of breast and ovarian cancers, it is less likely that Mary's *BRCA1* variant is associated with increased risks for cancer.

Using Mary's family history again, let's now say instead that Mary's mother and sister chose to have testing for this *BRCA1* variant and they were both found to also have this variant. In this

case, the variant is “tracking with disease” in this family (i.e. those individuals in the family that have had breast cancer, Jane and Sue, also have the *BRCA1* variant). This finding could be a coincidence, but it could also mean that the variant is associated with the cancers seen in this family. If a variant is found to track with breast and/or ovarian cancers in several families (and is not found in individuals without these cancers) then it increases the likelihood that the variant could be associated with increased cancer risks.

In some cases, variants are reclassified as “benign” after research studies reveal that numerous individuals without cancer carry the variant. In these cases, the variant is called a “benign variant” or a “normal variant,” meaning that it is seen in many individuals in the general population and is not associated with increased risk of disease.

4. How would my genetic counselor or I know when more information has been obtained about the variant that was identified in my DNA?

When a variant is reclassified, the laboratory that performed your testing will usually send a revised test report to your genetic counselor (or whomever ordered your genetic testing) explaining how and why the variant was reclassified. If this happens, you will receive a letter and/or phone call from your genetic counselor explaining the revised interpretation of your test results and what it means for you and your family. For this reason, it is very important that you notify us of any changes in your address or phone number and of any changes in your personal or family history of cancer. You can also check back with us periodically for updates at 203-200-4362.