

Information about Variants of Uncertain Significance

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

A “variant of uncertain significance” 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 function of the gene or increase the cancer risk. Other genetic changes prevent the proper functioning of the gene and are therefore associated with increased cancer risks. In some cases, we do not have enough information to determine if a variant is a normal or disease-causing. These types of variants are classified as “variants of uncertain significance”.

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

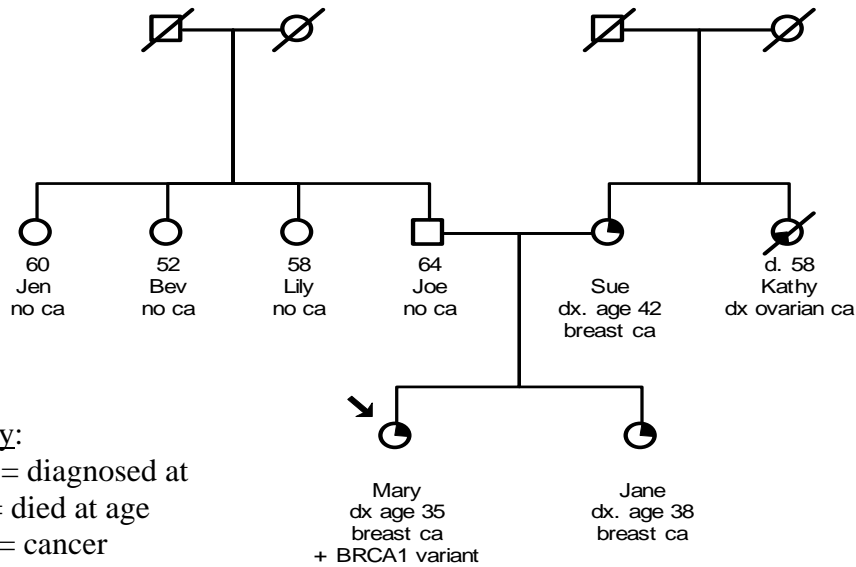
Since we do not understand the meaning of variants of uncertain significance, it would not be helpful to offer testing to other family members. Such testing would not clarify their cancer risks and therefore would not provide them with information that would be helpful for their medical management. *Their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

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 the gene and understand each part of its instructions, scientists may be able to determine if a variant increases cancer risks in the future.

We can also follow or track variants within families to see if the variants are found in the people in the family 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:



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 does carry 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 BRCA 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 the disease" in this family (i.e. those individuals in the family that have had breast cancer, Jane and Sue, also have the 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 “normal” after research studies reveal that numerous individuals without cancer carry the variant. In these cases, the variant is called a “polymorphism” meaning that it is a “normal variant” that is seen in many individuals in the general population. It is important to keep in mind that most of the information that is available about variants of uncertain significance is based on European populations. As individuals from more diverse ethnic backgrounds have testing, it is hoped that more information will be obtained about these variants.

Finally, some individuals who have genetic testing have been found to carry more than one change in the same gene. In some cases, one of these changes is a known “deleterious” mutation (i.e. it is known to be associated with increased cancer risks) and the other change(s) are variants of uncertain significance. Once a deleterious mutation is identified, it is unlikely that other genetic changes in the same gene are also deleterious. If a variant of uncertain significance is identified several times in unrelated individuals with a known deleterious mutation in the same gene, then the variant is less likely to be associated with increased cancer risks.

Sometimes individuals are found to have two or more variants, none of which have been classified as “deleterious” mutations. In these cases, it is likely that no more than one of the variants is associated increased cancer risks. It is also possible that future research may show that all of the variants are “normal” variants.

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

When a variant is reclassified, the laboratory that performed your testing will usually send a revised test report to your genetic counselor 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.