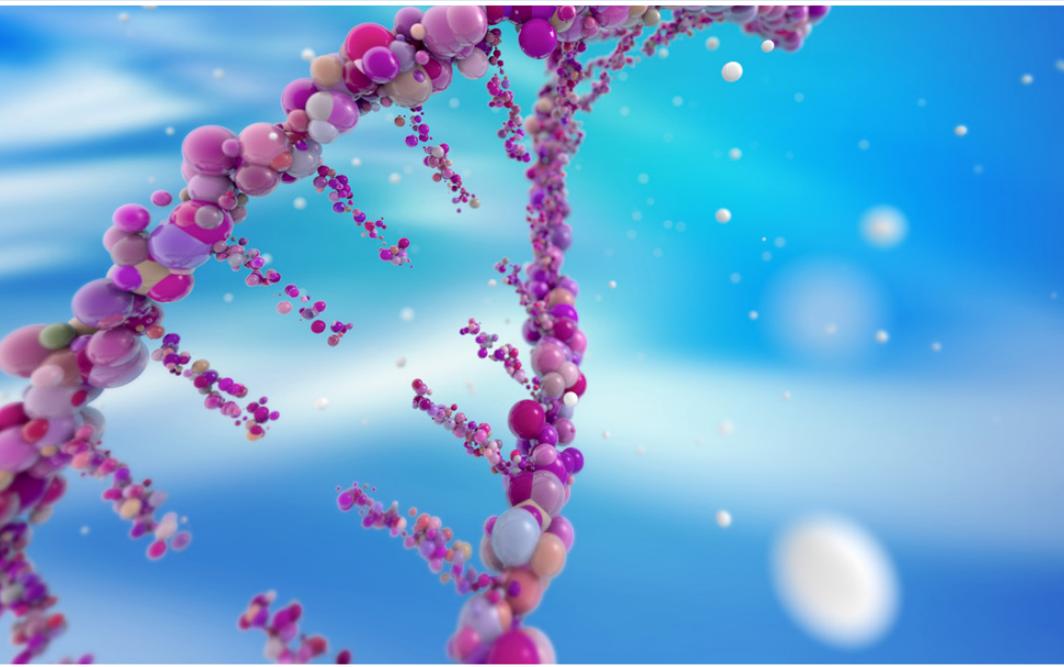




I have a VUS (Variant of Uncertain Significance) Now what?



This booklet was developed for individuals who had genetic testing and received a report of a VUS.

I have a VUS (Variant of Uncertain Significance)

When you agreed to have gene testing for gene mutations, you probably were expecting a “yes” or “no” answer. But the result of gene testing is not always a clean “yes” or “no”.

In your case, the test came up with an uncertain result called a **Variant of Uncertain Significance** or **VUS** for short.

A quick refresher on genetic testing for you:

Genetic testing is a read-out of your genetic code. DNA is the chemical that carries your genetic code, which can be thought of as a sequence of chemical letters. The diagram below is of DNA and the colored bars are the chemical letters. The genetic test analyzed your DNA to see if you have a change in the sequence of chemical letters. A genetic change of this kind may be called a mutation or a variant. Mutations or variants are often compared to misspelled words because the chemicals that make up the genetic code are not in the expected order.

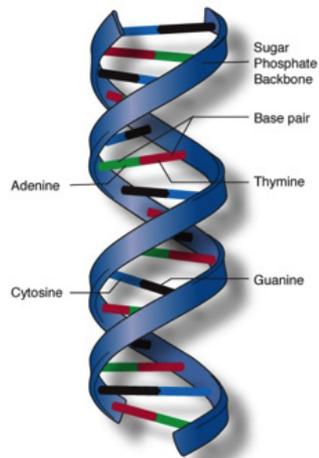
For example:

The expected spelling of part of a gene could be:

....A-G-C-T-A-G....

And a “misspelling” in that part of a gene might be:

....A-G-C-C-A-G.....



Meanings of genetic changes or variations:

Genetic changes have a range of outcomes, with some being significant and others not.

- Some people have a known [harmless](#) change in their genetic code. These changes are simply a part of the normal variations that makes us all a bit different from one another. Labs may not even report these types of changes.
- Some people have a genetic change that can be [harmful](#), often referred to as a disease causing mutation. When the changes are harmful, they may lead to medical problems. Genes tell our bodies how to work properly, and a harmful mutation may stop a gene from doing its job.
- Some people, like you, have a [Variant of Uncertain Significance \(VUS\)](#) which is a genetic change that the laboratory cannot interpret. VUS cannot be categorized as potentially disease causing or harmless because the meaning of this type of genetic change is not yet known.

Results you can get from genetic testing:

The official report you get from a laboratory may use 5 classes to score genetic test results:

- Class 1. Not a disease causing change or variant. Sometimes called neutral or benign or polymorphism.
- Class 2. Suspected not to be disease causing.
- Class 3. [Variants of Uncertain Significance \(VUS\)](#).
- Class 4. Suspected disease-causing. Sometimes called suspected pathogenic or deleterious.
- Class 5. Disease-causing mutation. Also called pathogenic or deleterious.



Why it is not possible to classify your result with certainty:

There is currently not enough data or information to interpret the exact meaning of your result. Yes, scientists can detect genetic changes, but they cannot always tell which of these changes are harmless or harmful. It will take much more research and further analysis to find answers. You cannot tell just by looking.

Some details: A variety of types of studies are needed to interpret a VUS. Sometimes researchers can learn more by studying DNA from your other family members to see if the genetic change went along with the medical conditions in your family. Your health care provider can help you figure out if this would be useful in your particular situation. Researchers can also try to find other people not related to you who have this VUS and compare them to people with the usual expected gene sequence. In the laboratory, researchers can try to see if a particular VUS affects the normal functions of that gene. These and other research methods are not without pitfalls. If a VUS is quite rare, meaning not a lot of people have it, then it can be very, very hard to figure out its significance. With further experience and new tools to draw from, many of the genetic changes now called VUS will be categorized as either neutral or disease causing even as new VUS may be discovered.

VUS are commonly found by genetic testing:

- Genetic changes are part of what makes us all different and unique, like fingerprints or snowflakes.
- Most genetic differences do not affect how cells function.
- All people have thousands and thousands of DNA changes that differ from the typical DNA code.
- The more genes tested, the more people tested, the more differences will be found.



You can't tell just by looking if it is harmful or harmless:

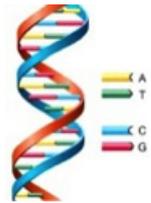
Mushrooms, for example:

- Imagine a new mushroom is discovered.
- Most mushrooms are not poisonous.
- But scientists cannot tell just by looking if this mushroom is or is not poisonous. The mushroom will have to be carefully studied to figure this out.



So it is with VUS:

- A new genetic misspelling or change is found in a gene of interest.
- Most genetic changes are harmless.
- But scientists can't tell just by comparison to the typical genetic code which genetic changes are harmless and which may be harmful. It takes more research to figure this out. And if a VUS is quite rare, then it can be very hard to determine its significance.



Thinking about your VUS Result:

- A VUS result should not be used for medical decision making because its meaning really is not known.
- A VUS is neither good nor bad in terms of your future health.
- Medical decisions should be based on your own medical findings and your family history, not on your VUS result.

Race, ethnicity, and VUS

Most genetic testing in the USA has been conducted on people of white European ancestry (Caucasian people), so more has been figured out on how to interpret DNA changes in this ethnic group.



As more people from other ethnic backgrounds have genetic testing, higher rates of VUS are being noted. This is partly because laboratories have less experience in figuring out harmful versus harmless DNA changes in these groups. It does not mean that other ethnic groups have higher genetic risks.

Important advice on your VUS:

- Do not assume the worst.
- Having a VUS and a medical diagnosis does NOT mean they go together.
- Remember, we all have thousands of DNA variants and most are entirely unrelated to our health situations.
- There may be more harm done in wrongly assuming a VUS is harmless or harmful.
- Your medical management and further testing of your family should still be based on your own medical history and on your family history.
- It may be reasonable to act as if a genetic test was never done at all, to avoid any temptation for interpreting what cannot be interpreted.

Quick answers are not likely:

For many people, their VUS may remain a big question mark for a long time. It is very difficult to gather enough information about any one VUS to be able to put it in a different category. Be prepared to live with the uncertainty for a while and focus on the things you can control regarding your health care.



Here are some suggestions and resources for you and your health care providers regarding VUS:

- Some laboratories will issue a revised report if they learn how to interpret your VUS. But don't count on this. Once a year or so you could ask your health care provider to check to see if there is any new information on your VUS.
- For some genes in some labs, testing of your relatives may be offered at no charge to help the scientists learn more about this gene. If interested, ask your health care provider about this.
- Participation in research could provide some answers by speeding the process of interpreting your VUS. Ask your health care provider if this is an option for you.
- There is a growing number of publicly available sources of information on VUS that you can consult. Your genetic specialist can help you find and interpret this information, which can be quite complicated.
- These websites have information on classification of many changes in many genes:

http://grenada.lumc.nl/LSDB_list/lstdbs

lists DNA variant databases that can be searched for any gene of interest

PROMPT (Prospective Registry of MultiPlex Testing) participation www.promptstudy.org

PROMPT (Prospective Registry of MultiPlex Testing) informational website www.promptstudy.info

ClinVar – Clinical relevance of BRCA1 variants - [http://ncbi.nlm.nih.gov/clinvar/?term=BRCA1\[gene\]](http://ncbi.nlm.nih.gov/clinvar/?term=BRCA1[gene])

ClinVar – Clinical relevance of BRCA2 variants - [http://ncbi.nlm.nih.gov/clinvar/?term=BRCA2\[gene\]](http://ncbi.nlm.nih.gov/clinvar/?term=BRCA2[gene])

BRCA1/2 variant databases - <http://databases.lovd.nl/shared/genes/BRCA1>

However, there may be better sources of information on your gene that your health care provider can point out.



Prepared by Mayo Clinic breast cancer researchers and patient advocates on behalf of the Mayo Breast Cancer SPORE

Feedback gratefully encouraged at nlindor@mayo.edu.





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