What FA Families Should Know About Variants of Uncertain Significance (VUS)

WHAT IS A VARIANT OF UNCERTAIN SIGNIFICANCE (VUS)?

When genetic testing identifies a **Variant of Uncertain Significance (VUS)**, it means there's a change in the DNA—but it's unclear whether it's harmful (pathogenic) or harmless (benign). This is common, especially in rare genetic conditions like Fanconi anemia (FA), where research is still catching up with the complexity of the genes involved.

Some VUS may be considered likely harmful if paired with clinical signs and a known pathogenic variant. Other isolated VUS in a gene on a broader panel may be less concerning. Making medical decisions or changing treatment plans based on a VUS should only be done with careful consideration with your medical team.

Can a VUS be part of an FA diagnosis?

Yes. This often happens when one of the two FA-related gene changes is clearly disease-causing (pathogenic), while the second gene change is uncertain. In these cases, the diagnosis may be based on a combination of genetic and clinical evidence. Over time, that uncertain variant may be reclassified.

WHY DOES THIS MATTER FOR PEOPLE WITH FA?

If you or your child has FA, you've likely had genetic testing to confirm the diagnosis or learn more about related health risks, and a VUS result may have shown up on that test. These uncertain results can be frustrating or confusing. The good news is that more information will likely become available about the VUS over time.

WHY SHOULD I TRACK A VUS?

Tracking your VUS helps ensure that you're working with the most current information. As more data becomes available, a VUS may be reclassified. If that happens, it could affect your:

- Eligibility for and access to certain screenings, therapies, or clinical trials
- Insurance coverage for treatments, screenings, family planning and reproductive counseling, genetic testing for relatives, etc.
- Ability to make informed medical, family planning, or care decisions based on the latest science

QUESTIONS OR NEED SUPPORT?

1-888-326-2664 | 541-687-4658
communitysupport@fanconi.org
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WHAT IF I'M A CARRIER OF A VUS?

If you are a **carrier** of a VUS in an FA gene, it can be difficult to know if it's possible to pass on FA. This is especially important for reproductive planning, partner testing, and decisions around preimplantation or prenatal testing. A genetic counselor familiar with FA can help clarify what this means and whether additional testing in your partner or family members might help.

IMPACT OF A VUS ON CAREGIVERS

If you're a **caregiver** to someone with FA, you may encounter VUS results while managing genetic or cancer risk testing. Checking in regularly for updates and navigating uncertainty can be emotionally and practically burdensome to an already complex care journey. You are not alone. Resources like FCF, your care team, or VUS tracking services, like Citizen Genetics, can help you stay informed and supported.

WHEN A VUS IS FOUND IN A HIGH-RISK FA GENE

Some FA genes, like ***BRCA2 (FANCD1)*** and ***FANCD2***, are linked to more severe symptoms, earlier cancer risks, and transplant needs for the person with FA. Some high-risk FA genes also have cancer risks for carriers. If your test result includes a VUS in one of these genes, it's especially important to:

- Follow up with your genetics team annually for updates, possible reclassification, and interpretation of your specific variant(s), and to consider participating in research studies assessing pathogenicity.
- Ask whether clinical care should be adjusted while waiting for clarification.
- Talk with your FA care team about family planning, cancer surveillance, and transplant implications.
- Talk with your care team about any recommended cancer screening for carriers of variants in your gene. Screening plans are complicated when someone carries a VUS. Cancer screening may, or may not, be recommended based on your family's unique situation.

In these cases, the stakes of uncertainty are higher—don't hesitate to advocate for regular re-evaluation, second opinions, or targeted testing in family members.

HOW CAN I TRACK CHANGES TO MY VUS?

- **Check annually with your genetics team** or testing lab for updates.
- **Stay connected with your FA care team** to help make sense of VUS updates in the context of living with FA.
- **Explore ClinVar** (www.ncbi.nlm.nih.gov/clinvar/), a public database, where researchers and labs share genetic variant information. Note: can be challenging to interpret without a genetics background.
- **Use a tracking service**: For a real-time, patient-friendly experience, you can subscribe to Citizen Genetics (www.citizengenetics.co/, code FANCONI for a discount), a service that tracks your VUS for you. Citizen Genetics monitors ClinicalTrials.gov amongst other sources, and sends you updates when new information becomes available about your variant.

This resource was co-developed by the Fanconi Cancer Foundation (FCF) and Citizen Genetics, and reviewed by clinical genetics experts with experience in Fanconi anemia. For more information about FA genetics and diagnosis, refer to Chapter 2 of the FA Clinical Care Guidelines or contact FCF directly at communitysupport@fanconi.org.