DCM beat
Precision Medicine Study
Newsletter of the Dilated Cardiomyopathy Project at The Ohio State University
dcmproject.com
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# Navigating uncertain genetic results:

## What they mean and how to solve them

Welcome to the Winter 2019 edition of the DCM Beat! The Precision Medicine study is very busy! While continuing to enroll families throughout the country, we are returning genetic results to families who have previously enrolled. In the last edition, we discussed the different types of genetic test results. In this newsletter, we focus on one of those types of results: Variants of Uncertain Significance (VUS). We will review how a variant is determined to be a VUS, what having a VUS means, and how your family can help resolve uncertainty.

***The DNA of individuals with DCM is analyzed for differences in the DNA code, known as variants, in genes known to be associated with DCM.***

DNA is the unique code that controls what cells do. If there is a difference in the code from what we expect to see for a gene to function properly, this is called a "variant." The term "mutation" is used to describe a variant in a gene that is known to cause a disease. Genetic variants can determine simple features, such as eye or hair color, or can cause diseases, such as a heart condition like DCM.

Individuals with DCM undergo genetic testing as a part of their participation in the DCM Precision Medicine Study. If a variant is found in one of the genes known to be associated with DCM, it is further investigated to determine if it impacts the gene's ability to function properly and therefore causes DCM.

***Every variant is investigated by variant interpretation experts using published guidelines.***

In the previous newsletter, we outlined the process of applying guidelines published by the American College of Medical Genetics (ACMG) and adapted by the Clinical Genome Resource (ClinGen) Cardiovascular Working Group to review variants. Variant interpretation experts carefully review available evidence for each variant identified in DCM-associated genes. Once all available evidence is analyzed, variants are placed into one of the five categories: Benign, Likely Benign, Variant of Uncertain Significance, Likely Pathogenic, or Pathogenic. Each of these categories have different meanings for clinical care.

***When the meaning of a variant is unknown, it is classified as a Variant of Uncertain Significance (VUS).***

Everyone has a unique DNA code. Therefore, it often occurs that an individual is found to have a variant that has never been seen before or has only been seen in a few other individuals. When a variant is unique or rare, and no clinical case information from other individuals or families is available, it is difficult to predict if the variant causes DCM or not. When we are unable to predict whether a variant causes DCM or not, it is classified as a VUS. For these reasons, a VUS result is considered an inconclusive genetic result.

***Family members are not tested for a VUS found in the proband of their family.***

Because we do not know if a VUS causes DCM or not, we do not test relatives of the proband (the first individual with DCM enrolled in the study), as we do not know the clinical meaning of the VUS. Family members of probands with inconclusive results are recommended to continue clinical screening (echocardiogram and EKG) for DCM. Probands with a VUS/inconclusive result receive a lab report, a letter, and a phone call from a genetic counselor. Participating family members receive a letter explaining the inconclusive test result found in the proband of their family.

(CONTINUED ON PAGE 2)

Please review your results letter carefully. If you have any questions, you can call the DCM Precision Medicine Study at 877-800-3430.

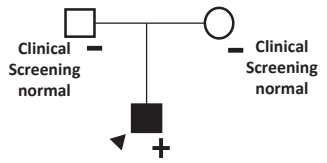
***The interpretation of a VUS can change over time - enrolling family members helps solve VUS results!***

When a proband is found to have a VUS, enrollment of their family is the first step to better understand the VUS. The combination of clinical screening results and genetic testing in family members can help clarify the clinical meaning of a variant. ***Clinical and genetic information of family members with and without DCM is informative!*** Examples of how family members, with or without DCM, can contribute to the understanding of a variant are shown in the figure below.

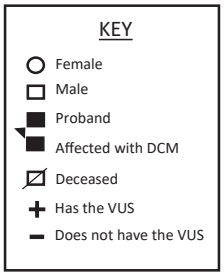
We only perform genetic testing in family members when the proband enrolled in the study is found to have a variant that is shown to cause DCM, known as a likely pathogenic or pathogenic variant. As discussed, we do not know if a VUS causes DCM. Therefore, we do not test family members for a VUS because it is not possible to make clinical recommendations for family members based on the presence or absence of a VUS. When enough evidence is collected for a particular VUS, the classification may be changed. If reclassification of the VUS occurs, you will be notified.

***Please help the DCM Precision Medicine study solve inconclusive results by helping us enroll your family members!***

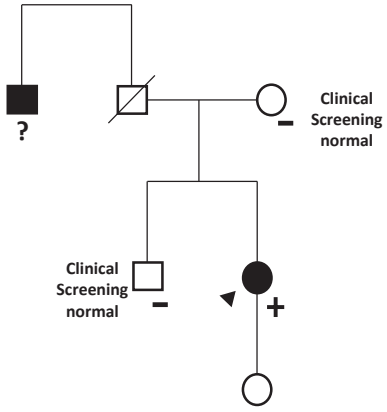
**Example 1**: New DNA change in proband not found in parents




In **Example 1**, the proband has a VUS that neither of her parents have. This means that the variant most likely was a new DNA sequence change in him. This is called a *de novo* variant. When we can prove that a variant is *de novo* by genetic testing of the parents of a proband, it may further the suspicion that a VUS is more likely to be clinically relevant (likely pathogenic or pathogenic) and is very meaningful to the family.

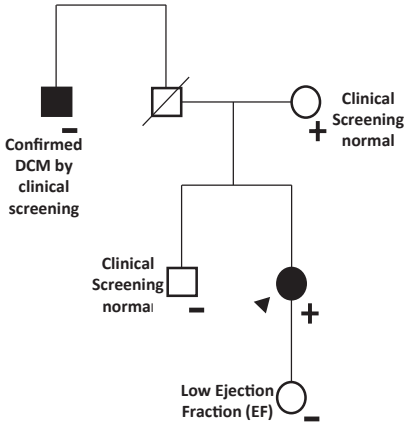



**Example 2**: Variant found in other family members with DCM




In **Example 2**, the proband reports that her father's brother (paternal uncle) also has DCM. Currently, the proband's mother and brother, who do not have DCM found on clinical screening, do not have the same VUS that the proband has. However, if we were able to prove through clinical screening that her paternal uncle does have DCM and that he has the same VUS as the proband through genetic testing, it would add supporting evidence that in her family this VUS is tracking with DCM. This type of family information could support that this VUS has a clinical impact in her family.

**Example 3**: Variant not found in other family members with DCM




In **Example 3**, the proband's paternal uncle who is affected with DCM does not have the VUS found in the proband. However, the proband's mother, who had normal clinical screening, was found to have the VUS. In addition, the proband's daughter was found to have a low ejection fraction through clinical screening, which may be an early sign of DCM, but she also does not have the VUS. Therefore, in this family, it was very helpful to test both the affected and unaffected individuals in order to show that individuals with the VUS do not have DCM and those with DCM or possible early signs of DCM do not have this VUS in common. In this case, there could be an unidentified genetic variant that is causing DCM in the family.

## Why Should Family Members Enroll?

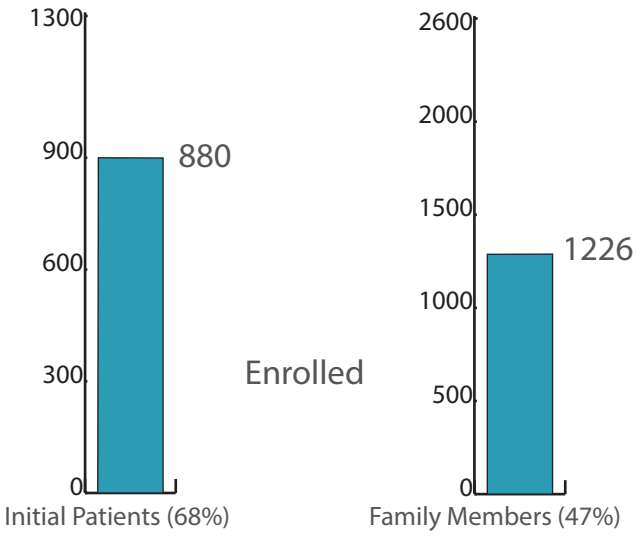
- DCM runs in families.
- DCM can be silent - for months or years! When silent, DCM can only be found with a Heart Check.
- A Heart Check (echocardiogram, ECG) is provided at no cost to family members of patients with DCM.

## What to Expect?

- It's a family based study, so ALL first-degree family members are welcome to participate!
- Easy enrollment - one clinic visit!
- One blood draw and questionnaires.
- Follow up only once each year with a phone survey.
- A Heart Check is provided at no cost at any of our consortium sites (see our map on page 3).
- If family members do not live near a site, the study provides clinical screening instructions to their own provider, including diagnosis codes.

## Study Enrollment Progress

June 7, 2016 - January 30, 2019



# DCM Consortium– Precision Medicine Sites Map


Map Data as of February 1, 2019

## DCM Precision Medicine Study: Key Points to Remember

1. ***OSU is the coordinating site for the DCM Precision Medicine Study.*** For any study related questions, you may contact our study personnel at OSU (877-800-3430) or at the site where you were consented.

2. ***We need all family members to participate.*** Family members will help us best determine how much of DCM runs in families. Participation of family members is also important as we evaluate if a gene change is responsible for DCM in the family.

3. ***Every individual enrolled will receive an annual follow up phone call for the duration of the Precision Medicine study.*** This phone call is to complete a survey to learn more about how you communicate with family members about the genetics of DCM.

4. ***One year after enrollment, we will inform participants of their genetic testing result.*** If results are negative, we will also inform participating family members.

5. ***Medical guidelines recommend cardiovascular screening (Heart Check) of first-degree family members of individuals with DCM.*** This screening consists of an echocardiogram and an ECG. These are simple and painless procedures that can be accomplished by your physician or, at no cost, through the Precision Medicine study at any of our active sites on the above map.

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## CLINICAL GENETIC TESTING?

While our research continues even after a research result is identified in a family, we recommend that all individuals with DCM consider undergoing clinical genetic testing. Clinical genetic testing is done similarly to any other blood test that is ordered by your doctor and sent out to a laboratory. Your results would be provided to your doctor. According to medical guidelines for the evaluation of cardiomyopathy, clinical genetic testing can be a complex process. Therefore, referral to a center expert in genetic evaluation should be considered. We can help you identify a clinic that offers genetic counseling and testing for DCM.

***If you have undergone clinical genetic testing outside of this study and have results, please provide us with a copy of your results for our database.***

This information will help us in our approach to identifying the gene or genes that may be causing DCM as well as how these mutations lead to DCM. Please contact us (toll-free) at **877-800-3430** or email Ana Morales, MS, LGC at **ana.morales@osumc.edu**.

## MEDICAL UPDATES

If anyone in your family is newly diagnosed with heart problems, please let us know. Similarly, if you or anyone in your family has had heart or genetic tests performed, regardless of results, we would be interested in receiving copies. Please contact us and we will send you a medical records release form. If we have already sent you medical record release form(s), please send us the completed form(s) as soon as possible.

## CONTACT INFORMATION UPDATES

If you have moved or have a new phone number or email address, please let us know. Call **877-800-3430** or email us through the "Contact Us" page on our website: **www.dcmproject.com.** This way we can get in touch with you for any follow-up and continue to send you our newsletter.

## GO PAPERLESS!

If you would like to receive our newsletter by email, please contact us with your email address, and we will be pleased to add you to our email mailing list. You may also opt out of receiving a paper copy of this newsletter.



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**DCM BEAT NEWSLETTER**

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