

## ACMG cardio reclass abstract

Variant reclassification in a large cardiogenetic testing cohort: the importance of disease specific variant classification criteria

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### Introduction

Major cardiology societies have published guidelines supporting the use of multigene panel testing for patients with suspected inherited cardiovascular disease (CVD) including cardiomyopathies, arrhythmias, aortopathies, and lipid disorders. Although panels offer increased diagnostic yield, there is often a corresponding increase in variants of uncertain significance (VUS) rates. VUSs can be difficult to manage, especially for providers without the technical genetic knowledge to investigate the relevance for their patients. Changes in clinical management associated with pathogenic variants in cardiac genes can be life-changing (surgical, costly medications, lifelong screening), and as such, it is important to avoid unnecessary interventions based on an incomplete understanding of genetic test results. As more non-genetics providers order genetic testing for CVDs, there is an increased urgency to understand the ambiguity of a VUS for a patient's management. Reclassification rates from hereditary cancer cohorts show most VUS reclassifications are downgrades, but these rates have not been reported for CVD genetic testing cohorts.

### Methods

We performed a retrospective review of reported variants from 167 genes associated with genetic CVDs that were reclassified at our laboratory between July 2019 and November 2022. We compared the original and current classifications and calculated the number of unique variants reclassified by gene. Lastly, we looked at the reasons for reclassification.

### Results

A total of 1553 unique variants in 122 genes were reclassified during the study period. Reclassified variants began as 91% VUS (n=1406) and 9% likely pathogenic or pathogenic (LP/P; n=147). Following reclassification, 86% of variants were likely benign or benign (LB/B), 1% were VUS, and 14% were LP or P.

Of the variants initially reported as VUS, 95% (1330/1406) were downgraded to LB or B, and 5% were upgraded to LP or P (76/1406). *TTN* and *NF1* had the most unique variants reclassified (n=260 and 164, respectively). Most of the *TTN* reclassifications (238/260) were part of a bulk reclassification project downgrading missense variants from VUS to LB based on studies indicating that missense alterations in this gene are not independently causative for dilated cardiomyopathy. The reasons for the *NF1* reclassifications were more diverse and often due to internal data which is generated at a higher rate because of the presence of the *NF1* gene on some cancer panels.

Of the 147 variants that were initially reported as P or LP and then reclassified, the majority (93%) were LP reclassified to P. Ten variants were downgraded to VUS (n=7) or LB (n=3). These downgrades were largely the result of internal advancements in disease-specific variant classification guidelines. Specifically, 5 alterations were reclassified (4 VUS; 1 LB) due to new internal standards for interpreting

population frequency data based on penetrance, prevalence, and genetic contribution to disease. One alteration in *LMNA* was downgraded (VLP to VUS) after reassessment of the mechanism of disease for the cardiomyopathy phenotype. Of note, this alteration remains a VLP for the autosomal recessive neurological phenotype. Other reasons for these downgrades included newly published literature (n=1) and supplementary analysis including additional structural or *in silico* assessments (n=2) and RNA studies (n=1).

## Conclusions

95% of VUSs in this study were reclassified to LB/B, a rate even higher than what has previously been reported in hereditary cancer cohorts. This data further emphasizes that patient management decisions should not be made based on a reported VUS. As more non-genetics providers order genetic testing and the use of large multigene panels expands, the need for provider education is paramount. Many of the reclassifications were due to our laboratory's CVD tailored variant classification criteria. Clinical laboratories should continually improve variant classification tools and strive for gene-disease-specific classification criteria to optimize accurate variant classification and decrease VUS rates.