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Evaluating Trends in Re-classification of Variants in a Clinical Diagnostic Laboratory

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I. Abstract

Several recent studies have elevated the importance of variant re-classification in the management of patients and families with variants of uncertain clinical significance (VUS) identified in the setting of hereditary cancer testing. Two recent preliminary documents circulated by the ACMG on patient re-contact after revision and reanalysis of genomic test results have emphasized a shared responsibility among the ordering healthcare provider, the patient and the testing laboratory. Current ACMG guidelines for variant classification recommend that laboratories develop policies on variant re-analysis, encouraging them to consider proactively amending patient reports when variants move out of near-definitive (pathogenic or benign) classifications. The guidelines also suggest periodic inquiry by healthcare providers for updates pertaining to VUS and likely pathogenic variants. Additional guidance by ACMG addressing the protocol and resources for re-classification are currently under development. With a goal of understanding our laboratory's trends in variant re-classification, we evaluated a cross section of variants undergoing re-classification at our laboratory. We tracked 153 variants that underwent re-classification from VUS to benign/likely benign (B/LB) or pathogenic/likely pathogenic (P/LP) and vice-versa in an 18 month time frame. The distribution of variants was 75% for hereditary cancer testing (n=115), and 25% for hereditary cardiac disorders (n=38). No variants in our dataset underwent a re-classification from B/LB to P/LP or vice-versa. Ninety-six percent of variants (n=147) were re-classified from a VUS to LB/B/LP/P, while 4% (n=6) were re-classified from LB/LP/P to a VUS. One *BRCA1* variant was classified from Pathogenic to VUS. Re-classification from VUS to B/LB (n=137) constituted 90% of variant re-classifications in our dataset. Our trends in variant re-classification in hereditary cancer are consistent with reported findings across three recently published studies. The preliminary data presented here provide additional supportive insight into observed trends in variant re-classification for hereditary cancers, along with initial findings for cardiac disorders.

II. Study Plan

Time frame	18 months
Sources of variants ascertained	• Internal production • External client requests • ClinVar data sharing and discrepancy resolution efforts
Inclusion criteria	• Any variants that moved from or to a "VUS" classification • Variants that moved from LB/B ↔ LP/P
Exclusion criteria	Variants that moved from LB ↔ B and LP ↔ P

III. Results

Figure 1.
A total of 153 variants were re-classified, averaging to 8.5 variants/month

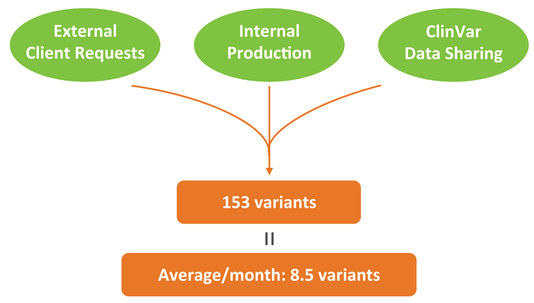
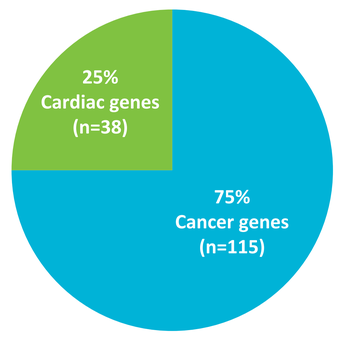
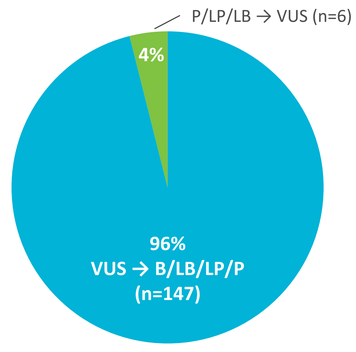


Figure 2.
The variant distribution was 75% hereditary cancer and 25% hereditary cardiac disorders



n=all re-classified variants

Figure 3.
Ninety-six percent of variants were re-classified from VUS → B/LB/LP/P, while 4% were re-classified from P/LP/LB → VUS



n=all re-classified variants

Figure 4.
Distribution of variant re-classification based on ACMG categories[1]

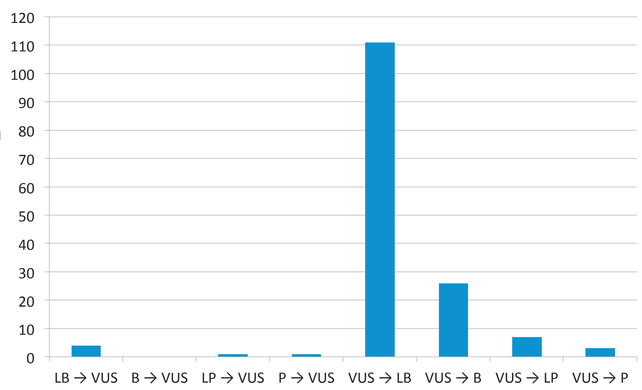
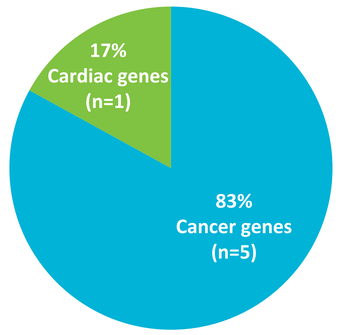
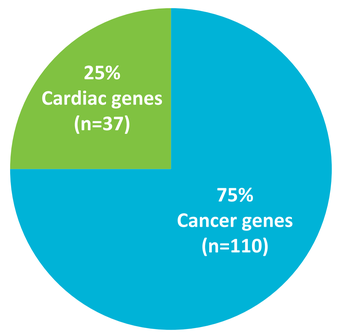


Figure 5.
One cardiac gene variant and five cancer gene variants were re-classified from P/LP/LB → VUS.



n=P/LP/LB → VUS

Figure 6.
A total of 147 variants were re-classified from VUS → P/LP/LB/B. Ninety-three percent of these variants were re-classified VUS → LB/B (n=137).



n=VUS → P/LP/LB/B Variants

Table 1. Our trends in variant re-classification for hereditary cancer are consistent with reported findings across three recently published studies.

	IG Cancer (LCA)	Turner, et al (2018)[2]	Macklin, et al (2018)[3]	Mersch, et al (2018)[4]
Variants	115	142	40	2139
Average/year	77	28	8	214
LP/P → VUS	0.9% (1)	4.2% (6)	5% (2)	3.6% (77)
LB/B → VUS	3.5% (4)	0%	2.5% (1)	0.70% (15)
VUS → LP/P	6.1% (7)	7.0% (10)	2.5% (1)	8.3% (178)
VUS → LB/B	89.6% (103)	81.7% (116)	72.5% (29)	87.3% (1867)

IV. Conclusions

- None of the variants evaluated in this dataset moved out of near-definitive (pathogenic to benign or vice-versa) classifications.
- Ninety-six percent of variants re-evaluated underwent a re-classification out of the VUS category.
- Four percent of variants re-evaluated underwent a re-classification into a VUS category.
- At 90%, VUS → LB/B transitions constituted the large majority of all variant re-classifications. A trend that was consistent across variant re-evaluations for cardiac disorders and hereditary cancers.
- Our trends in variant re-classifications for hereditary cancers are consistent with reported findings.

V. References

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