Evidence contributing to reclassification of a subset of hereditary cancer variants at a commercial laboratory

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1. Introduction

Variant classification incorporates the evaluation of several types of evidence, including a variant's functional impact, evidence of deleterious impact, prevalence, genotype-phenotype correlation and other considerations. Evidence incorporated into variant classifications can be obtained from peer-reviewed literature, computational and prediction tools, public databases, as well as other sources.[1] Evidence evaluated at the time of initial variant classification can change over time. As variant evidence evolves, laboratories must incorporate updated information into their weighted variant assessments, which may lead to variant reclassifications. Although most variants in hereditary cancer genes reclassified by Labcorp are classification downgrades, a small subset of variants are upgraded from variant of uncertain significance (VUS) to likely pathogenic (LP) or pathogenic (P), often leading to changes in clinical management for patients with these variants.[2] This study evaluates the lines of evidence contributing to Labcorp's reclassification of hereditary cancer variants from VUS to LP/P that led to issuance of reclassification reports for impacted patients.

2. Methods

This study includes all hereditary cancer variants reclassified by Labcorp from VUS to LP/P between August 2016 to May 2021. Variants included were initially reported for a Labcorp hereditary cancer test, with test types ranging from familial testing to multi-gene panels. Variants were classified by an in-house variant classification protocol in accordance with guidelines set forth by the American College of Medical Genetics and Genomics and as described in Labcorp's Variant Classification Specifications.[1] Triggers for variant re-evaluation included detection of the variant in a new patient, external client requests for re-review, and variant discrepancy resolution initiated by data sharing into Clinvar and/or another external consortia.

To identify evidence leading to reclassification, variant classification histories were reviewed in detail and evidence types supporting reclassification were categorized.

3. Results

From August 2016 to May 2021, 29 unique variants were reclassified by Labcorp from VUS to LP/P. Variant reclassifications resulted in updated reports for 48 patients. These variants were in 10 genes, as shown in **Figure 1**, with most variant upgrades occurring in the *BRCA1* and *BRCA2* genes. **Figure 2** demonstrates the types of genetic variants among this data set.

Functional studies and clinical data (genotyped affected cohorts), from literature, were the only evidence types that contributed to reclassification. **Figure 3** outlines the types of evidence that led to reclassification. Nearly half (48%, n=14) of reclassified variants had multiple evidence types contribute to reclassification. New clinical evidence contributed to 79% (n=23) of all reclassifications and new functional evidence contributed to 45% (n=13) of all reclassifications. A combination of both new clinical and new functional evidence contributed to 34% (n=10) of all variant reclassifications. Re-evaluation of existing clinical data and re-evaluation of existing functional studies contributed to 28% (n=8) and 7% (n=2) of all reclassifications, respectively. Of the eight variants involving re-evaluation of existing clinical evidence, 75% (n= 5) of these re-evaluations were triggered by the emergence of new clinical data and functional studies.

4. Conclusions

Periodic re-evaluation of variant classifications is essential for optimal patient care in patients with VUS findings. In considering reclassification of a variant, not only is it important to evaluate newly reported clinical and functional evidence, but it is also important to re-evaluate previously curated evidence to understand the overall evolution of variant literature over time. Newly emerging evidence may add reliability to prior studies, with a combination of both the new and previously curated evidence leading to variant reclassification.

References

1. Labcorp. (2022). Variant Classification Specifications [White paper]. Retrieved from https://womenshealth.labcorp.com/providers/hereditary-cancer-testing.
2. Weymouth KS, Gardner SA, Chen W, et al. Evaluating trends in reclassification of variants in a clinical diagnostic laboratory. Poster presented at: America College of Medical Genetics and Genomics Annual Clinical Genetics Meeting; April 2-6, 2019; Seattle, Washington.

Tables + Figures

Figure 1. Variants reclassifed per gene

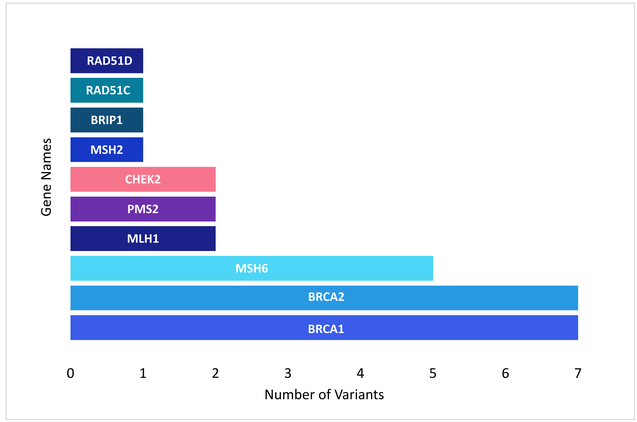


Figure 2. Types of variants reclassified

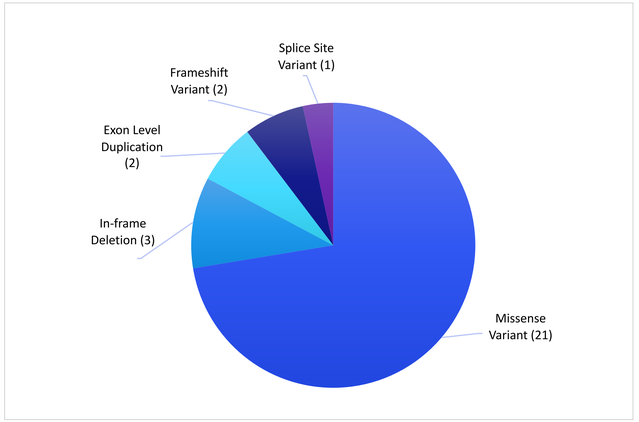
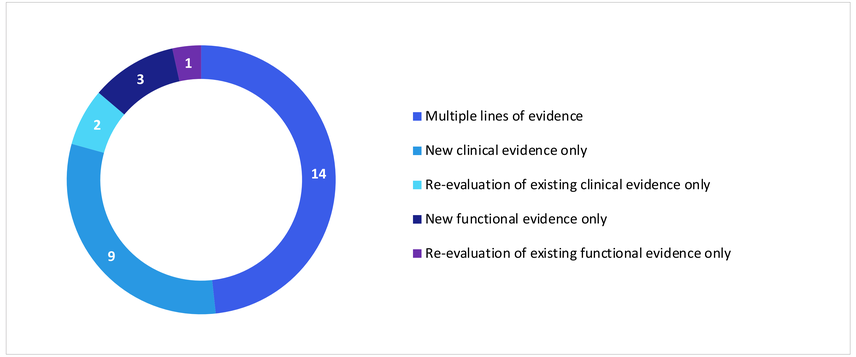


Figure 3. Evidence types contributing to re-classification



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