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Variant reclassification in BRCA1/2: a snapshot of one laboratory's experience in reporting and client re-contact

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1. Introduction

The detection of variants of uncertain significance (VUS) in hereditary cancer genetic testing poses challenges for clinical laboratories, health care providers, and patients. The ACMG (American College of Medical Genetics) and AMP (Association for Molecular Pathology) have put forward standards and guidelines for the interpretation of sequence variants that incorporate all current evidence for classification including variant type, population frequency, functional studies, relevant literature, and *in silico* prediction models.[1] As additional research is done and technology improves, variant classification is subject to change and laboratories must have procedures in place for communicating these changes to clients. Reclassification of hereditary cancer variants has important implications in clinical management for patients and their families and can alter the screening, treatment, and surgical recommendations made by their health care providers.[2] ACMG has outlined considerations for clinical laboratories when developing procedures for variant reclassification that emphasize the shared responsibility of the laboratory, health care provider, and patient in this process.[3] Here, we review the experience of one large, commercial laboratory with reclassification reporting over a 37 month period.

2. Methods

In this study, 441 consecutive reclassifications between January 2019 and February 2021 were assessed. The analysis was limited to reclassification reports issued for the laboratory's *BRCA1/2* comprehensive, *BRCA1* known familial variant, and *BRCA2* known familial variant tests. Variants were identified for reclassification as outlined in **Figure 1**.

Initial results reported over a span of 7 years (2014-2020). Lab methodology over that period of time included Sanger sequencing, MLPA (multiplex ligation dependent probe amplification), and next generation sequencing (NGS) for detection and confirmation of both sequence variants and deletions/duplications. Retrospective case review was performed to analyze trends in the reclassification cases.

3. Results

A total of 441 reclassifications, including 134 unique variants, were reviewed. 13 patients had more than one variant on a report, therefore the total number of reclassification reports issued was 428. **Table 1** summarizes the types of reclassifications observed in the cohort.

In summary, any type of VUS was reclassified to likely benign or benign in 426 of the cases and to likely pathogenic or pathogenic in 12 cases. **Variants were reclassified to give the patient a more definitive result 99.8% of the time.** In only one case, a pathogenic variant was reclassified to VUS. All clinically actionable reclassification cases (13) were prioritized for reporting and client contact. Reclassified variants are routinely submitted to ClinVar.

Lab genetic counselors (GCs) reach out to laboratory clients to discuss reclassification results in an effort to assist in education about the reclassification process and encourage patient re-contact. **Figure 2** highlights the outcome of these efforts for the cohort.

GCs made 428 phone calls to discuss reclassification results during the given timeframe. GCs were able to reach clients and provide a full discussion of the reclassification 90% of the time. In the remaining 10% of cases, GCs were unable to reach the client, the client declined discussion of the results, or the client no longer had a relationship with the patient.

4. Conclusions

Employing clear policies and procedures for variant reclassification in a clinical laboratory is necessary to keep clients and patients up to date on the actionability of hereditary cancer test results. In nearly all cases in this study, variant reclassification clarified uncertain results. These reclassified reports are important tools in reducing ambiguity about screening, treatment, and surgical management. GC outreach proved to be successful in the majority of cases in this study as well and gave ordering providers the chance to review the reclassification process and updated results with a certified genetic counselor. However, in 10% of cases, GCs were unable to discuss reclassification results. In some of these cases, reclassification results may have been communicated to the patient successfully without GC contact, but it is still important to emphasize the collaboration needed between the laboratory and health care provider in the reclassification process. Appropriate expectations regarding the possibility of variant reclassification and plans for future re-contact should be discussed with patients in pre-test and post-test counseling to support published guidelines and informed consent.

Tables + Figures

Figure 1. How are variants identified for reclassification?

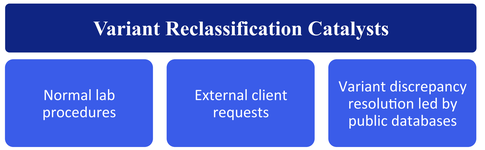
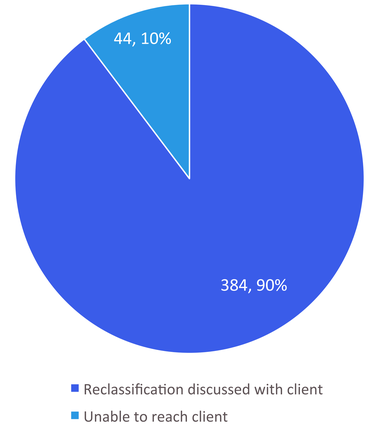


Table 1. Types of reclassifications

Original classification	Reclassification	n (%)
VUS possibly benign	Benign	24 (5.46%)
	Likely benign	249 (56.72%)
VUS	Benign	2 (0.46%)
	Likely benign	151 (34.40%)
	Likely pathogenic	3 (0.68%)*
	Pathogenic	4 (0.91%)*
VUS possibly pathogenic	Likely pathogenic	4 (0.91%)*
	Pathogenic	1 (0.23%)*
Pathogenic	VUS possibly pathogenic	1 (0.23%)*

*Clinically actionable reclassification

Figure 2. Outcomes of Genetic Counselor outreach



References

1. Li MM, Datto M, Duncavage EJ, et al. Standards and Guidelines for the Interpretation and Reporting of Sequence Variants in Cancer: A Joint Consensus Recommendation of the Association for Molecular Pathology, American Society of Clinical Oncology, and College of American Pathologists. *J Mol Diagn*. 2017;19(1):4-23. doi:10.1016/j.jmoldx.2016.10.002
2. Daly M, Pilarski R, Berry M, at el. Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic (version 1.2022). https://www.nccn.org/professionals/physician_gls/pdf/genetics_bop.pdf. Accessed August 24, 2021.
3. Deignan JL, Chung WK, Kearney HM, et al. Points to consider in the reevaluation and reanalysis of genomic test results: a statement of the American College of Medical Genetics and Genomics (ACMG). *Genet Med*. 2019;21(6):1267-1270. doi:10.1038/s41436-019-0478-1

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