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

Mary Hriick, MS; Eric Bowyer, BS; Angelica Goulbourne, MS; Dagny Noeth, MS; Katherine Goode, MS; Manya Warrior, PhD; Alexia Willis, PhD
Labcorp Genetics and Women’s Health, Laboratory Corporation of America®, Morrisville, NC

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 AMPP (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. 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 treatment, screening, and surgical recommendations made by their health care providers. 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. 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, BRCA2 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 reclassifications 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.

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 results 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 giving orders 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.

References


Table 1. Types of reclassifications

<table>
<thead>
<tr>
<th>Original classification</th>
<th>Reclassification</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VUS likely benign</td>
<td>Likely benign</td>
<td>249 (56.72%)</td>
</tr>
<tr>
<td>VUS possibly benign</td>
<td>Likely benign</td>
<td>151 (34.40%)</td>
</tr>
<tr>
<td>Likely pathogenic</td>
<td>Pathogenic</td>
<td>4 (0.09%)</td>
</tr>
<tr>
<td>Likely pathogenic</td>
<td>Likely pathogenic</td>
<td>151 (34.40%)</td>
</tr>
<tr>
<td>Likely pathogenic</td>
<td>Pathogenic</td>
<td>2 (0.04%)</td>
</tr>
</tbody>
</table>

* Clinically actionable reclassification

Figure 1. How are variants identified for reclassification?

Figure 2. Outcomes of Genetic Counselor outreach

384, 90%

44, 10%

Lab genetic counselors 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.