Data sharing to improve concordance in variant interpretation across laboratories: Results from the Canadian Open Genetics Repository

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COGR
Canadian Open Genetics Repository

Background

Accurate variant interpretation is essential for the benefits of clinical genetic testing to be realized. In variant interpretation, multiple lines of evidence are considered to evaluate a variant's pathogenicity. Despite guidelines from the American College of Medical Genetics and Genomics (ACMG) and the Association of Molecular Pathology (AMP), discordant variant classifications exist between laboratories. Data sharing may improve concordance in variant interpretation. The Canadian Open Genetics Repository (COGR) is a collaborative effort for sharing and reinterpreting variants reported by diagnostics laboratories, using an online platform. Previously, we found that COGR was effective at improving concordance in *BRCA1* and *BRCA2* variant interpretation across 13 laboratories. We now expand our efforts to all genes tested at the participating laboratories.

Aim: To identify and resolve discordant variant interpretations across participating diagnostic laboratories.

Methods

Figure 1. Variants were classified using ACMG/AMP guidelines. Three tiered models were used to evaluate variant concordance across laboratories.

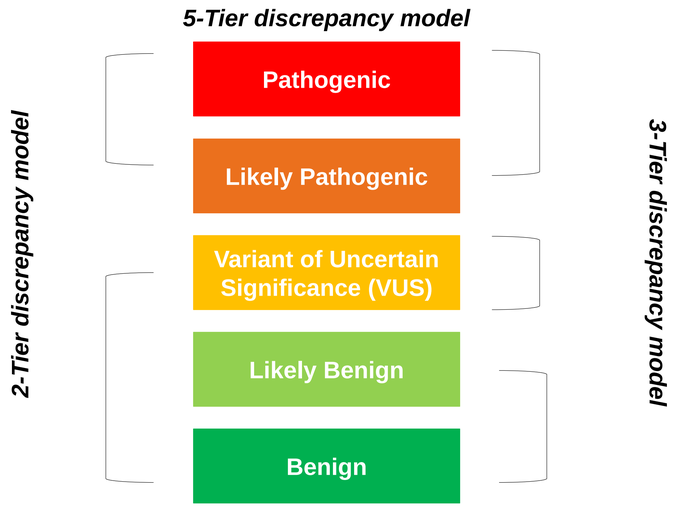
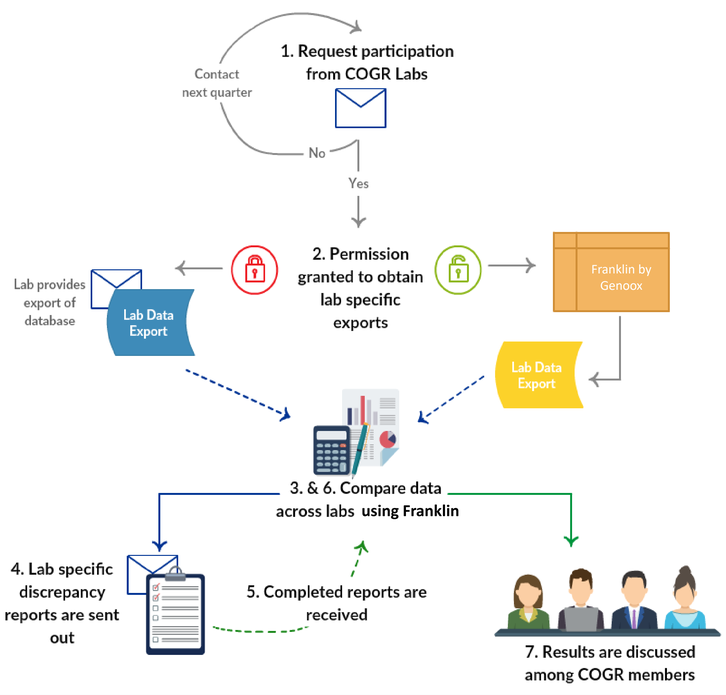


Figure 2. Workflow used to build a consensus on variants identified in clinical laboratories. Franklin by Genoox (franklin.genoox.com) was used for discordance analysis. Franklin is an online variant interpretation tool that assimilates evidence from curated data sources and the literature and provides classification, annotations, and evidence associated with the variant, as well as an online interface for community members to discuss variants.



Results

At baseline, 43 871 variants from 986 genes were uploaded by 10 laboratories. Of these variants, 2227 (5.1%) were reported by two or more laboratories. These are preliminary results from the first 8 laboratories that have reassessed variants.

Figure 3. Number of discordant variants at baseline and after data sharing and reassessment, based on each of the tiered models.

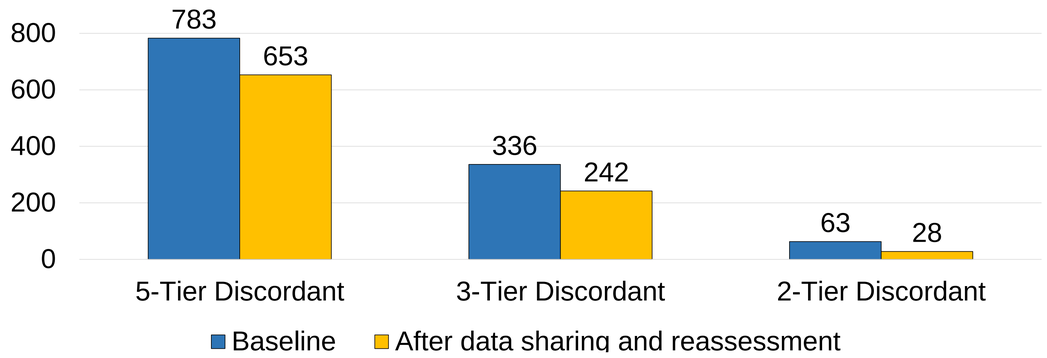


Figure 4. Reasons for variant reclassifications (data from 7 laboratories).

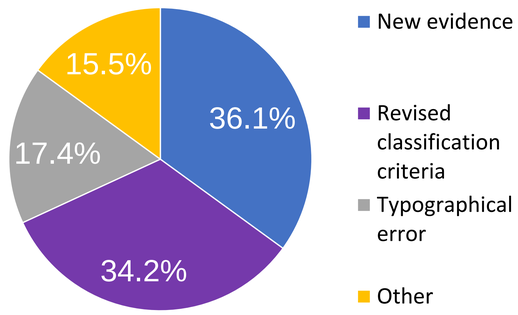


Table 1. A break down of how classifications differed between laboratories for variants that were discordant based on the 5-tier model, and the proportion of discordant variants with these conflicting classifications at baseline (n=736) and after data sharing and reassessment (n=653).

Conflicting classifications from different laboratories	Baseline (n=736)	After data sharing and reassessment (n=653)
Benign | Likely Benign	44.7% (329)	51.8% (338)
Likely Benign | VUS	25.1% (185)	22.2% (145)
Pathogenic | Likely Pathogenic	9.6% (71)	11.3% (74)
Benign | VUS	5.8% (43)	4.3% (28)
Pathogenic | VUS	4.1% (30)	1.7% (11)
VUS | Likely Pathogenic	3.7% (27)	2.4% (16)
VUS | Likely Benign | Benign	6.1% (45)	6.1% (40)
VUS | Likely Pathogenic | Pathogenic	0.5% (4)	0% (0)
Likely Pathogenic | Likely Benign	0.1% (1)	0% (0)
Likely Benign | Pathogenic	0.1% (1)	0% (0)
Likely Benign |VUS |Likely Pathogenic	0% (0)	0.2% (1)

Conclusions

- The COGR provides a standardized mechanism for Canadian public hospital laboratories to identify differences in variant interpretations.
- Data sharing and variant reassessment through COGR resulted in improved concordance in variant classification between laboratories, but not all discrepancies were resolved.
- A challenge was that laboratories were not able to reassess all variants due to resource constraints (e.g. time, personnel).
- Data sharing and periodic reassessment are important to ensure the quality of variant interpretation.