The Power of Data Sharing in Canada: A Case Study from the Canadian Open Genetics Repository (COGR) using *BRCA1* and *BRCA2*

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Background

We present preliminarily findings from a large, cross-laboratory case study in sharing clinical variant interpretations through the COGR.

The COGR is a collaborative effort for the collection, storage, sharing and analysis of variants reported by 23 medical diagnostics laboratories across Canada.

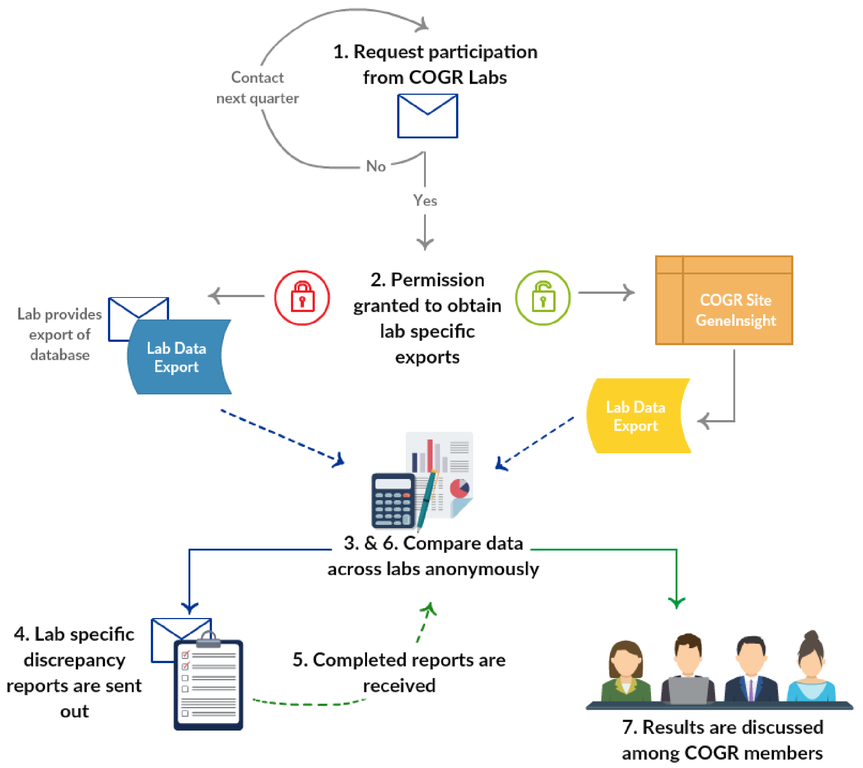
The inherent collaborative structure of the COGR promotes real-time sharing between geographically distant laboratories and enhances the exchange of information about DNA variants within the expert community.

The COGR currently has 11 out of the 23 participating laboratories actively sharing data. The platform has over 17,000 variants uploaded encompassing 1,266 genes and 66 diseases.

One of the main objectives of the COGR is to make data holdings both extremely accurate and readily accessible.

The COGR started an initiative to create and disperse lab specific discrepancy reports to build consensus on variants identified in Canadian clinical laboratories.

Consensus Building Workflow



Discrepancy Reports

The discrepancy reports were broken down into three main sections:

i. **Concordant Variants** - variants seen in at least two laboratories with variant interpretations in agreement

ii. **Variant unique to a lab** – variants only seen in one laboratory

iii. **Discrepancy reports** – variants seen in at least two laboratories with variant interpretations in disagreement

For each variant, laboratories were provided variant details and their current variant interpretation. For discrepant variants laboratories were also provided with anonymized data showing how their variant classification compared to other laboratories.

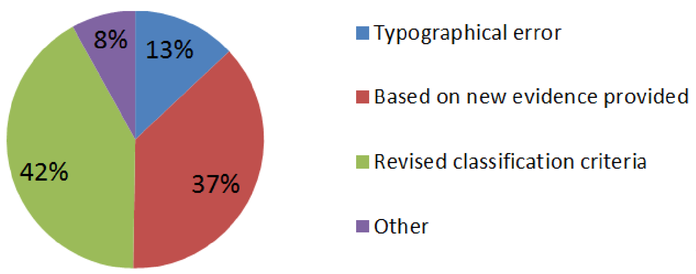
Evidence was provided for each variant if available and laboratories used either a variant assessment tool provided by the COGR or proprietary methods combined with ACMG 2015 guidelines for interpreting variants.

Results & Discussion

There were a total of 5,554 *BRCA1* and *BRCA2* variants submitted from the 11 participating laboratories across four provinces (ON, BC, AB, MB). This represents 3,014 unique variants. 1,148 unique variants were seen in two or more laboratories.

For unique variants observed in more than one laboratory, before discrepancy reports were issued 550 (48%) of variants had concordant classifications; 350 (30%) were discordant and 248 (22%) were unclassified.

After review, 42% of discordant variants changed classifications, 28% did not change classifications and 30% were not reassessed. However, only 18% of the discrepant variants reached a consensus and 82% remained discordant. The reason for changes in variant classification are shown below.



Overall Changes in Discrepant Variant Classifications

	Submitted		*After Completion of Reports*		
	# Variants	%	# Variants	%	Overall Change
Benign	526	37.23%	635	45.04%	↑ 109 (7.81%)
Likely Benign	271	19.18%	321	22.77%	↑ 50 (3.59%)
VUS	342	24.20%	211	14.96%	↓ 131 (9.24%)
Likely Pathogenic	60	4.25%	64	4.54%	↓ 4 (0.29%)
Pathogenic	136	9.62%	170	12.06%	↑ 34 (2.44%)
Unclassified	75	5.52%	9	0.64%	↓ 66 (4.88%)
Total	1410		1410		394 (27.9%)

Overall, the percent of variants of uncertain significance (VUS) decreased by ~9% and similarly the number of unclassified variants decreased by ~5%.

Further investigation is being performed to determine what evidence led to a change in classifications. Additionally, some laboratories did not consider likely benign ↔ benign and likely pathogenic ↔ pathogenic as significant differences and in some cases these variants were not reassessed. Further analyses are being conducted to using a 3-tier system instead of a 5-teir classification system.

Future Directions

The COGR project was designed to help overcome obstacles including the lack of standardized resources and protocols for interpreting the ever-increasing volumes of patient data being generated by clinical labs.

Continuing initiatives include:

- Release quarterly discrepancy reports.
- Making consensus variant interpretations publically available to other stakeholder groups with appropriate levels of summary.
- To collaborate with other international data-sharing efforts including ClinVar, the HVP and the GA4GH.

In summary, the COGR serves as a focal point for the collaboration of Canadian laboratories with each other and with other countries in the development of tools and methods that take full advantage of laboratory data in diagnosing and managing genetic diseases. As a continuing effort, the COGR endeavors to increase genetic knowledge and standardization through data sharing and consensus building, ultimately improving our ability to diagnose and treat genetic diseases.

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