Sharing *BRCA1* and *BRCA2* data across Canada:

a case study from the Canadian Open Genetics Repository

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OntarioGenomicsInstitute

GenomeCanada

Overview

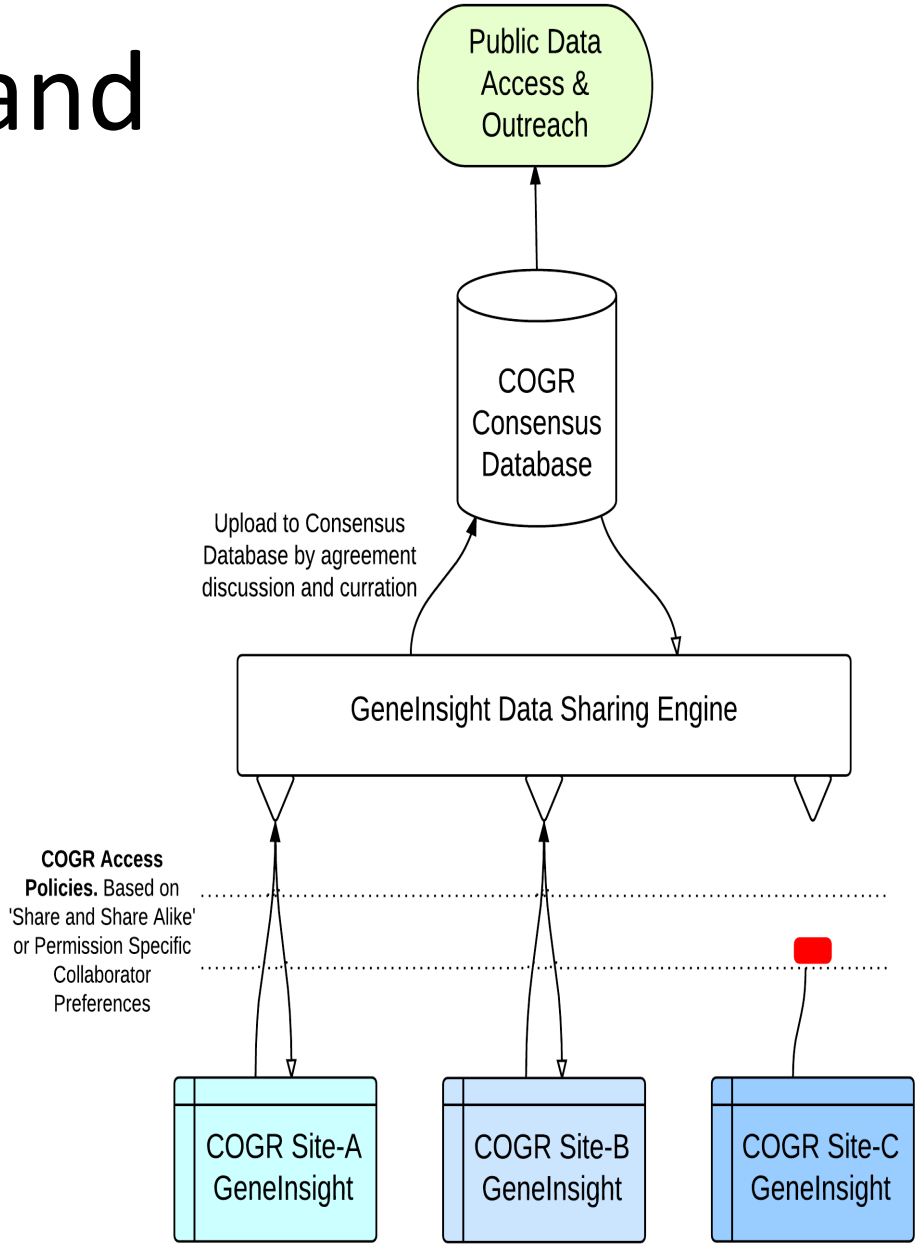
- Grant funded by Genome Canada
- Collaborative effort for the collection, sharing and analysis of variants reported by medical diagnostic laboratories across Canada
- Collaborate with other global initiatives including ClinVar, BRCA Challenge, Human Variome Project

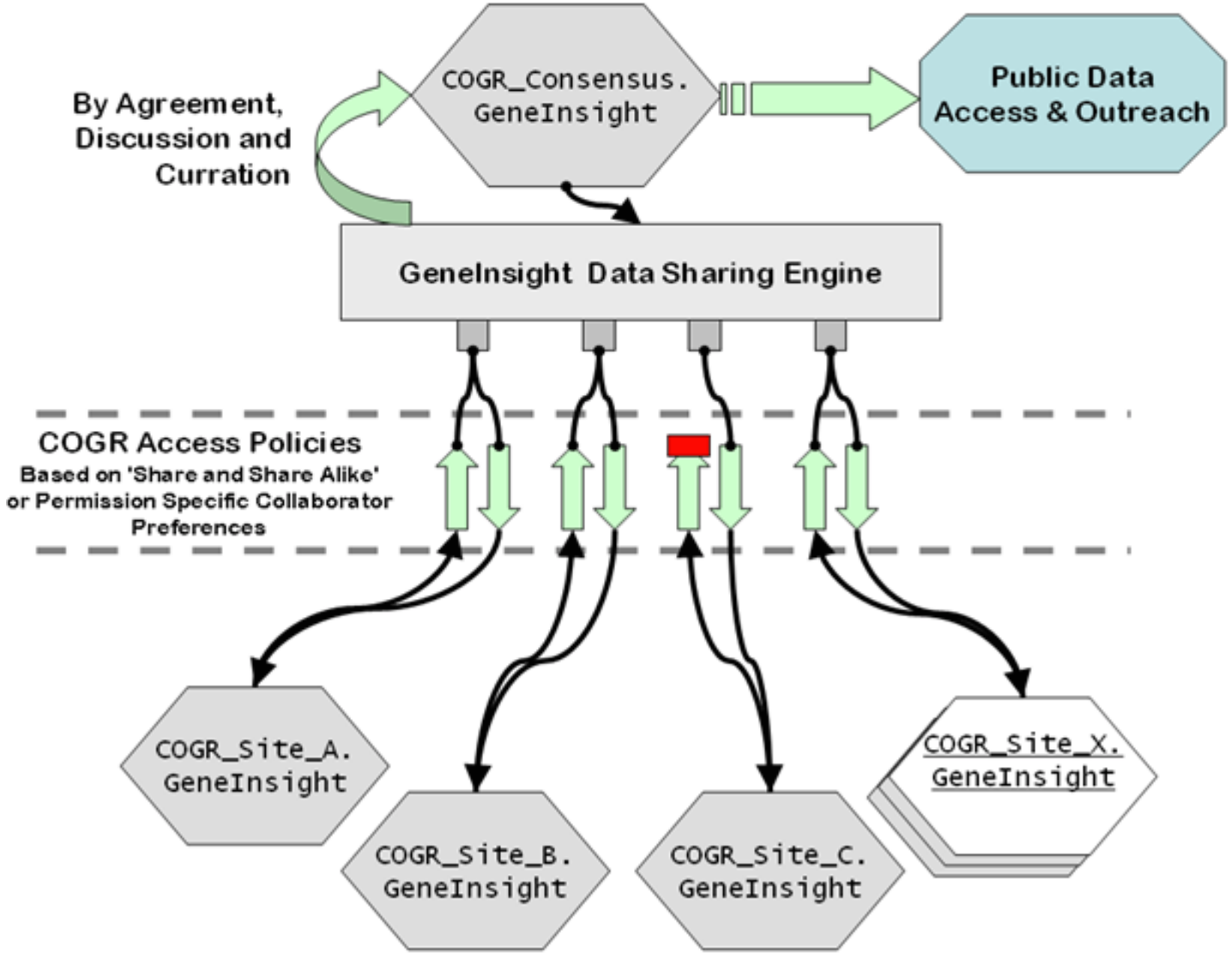
Objectives

- To create Canada's unified, open-access, clinical-grade genetic database using a commonly shared platform
- Standardize variant assessment procedures
- Data extraction and variant classification consensus building
- Data Access and Disseminate results to a large public repository

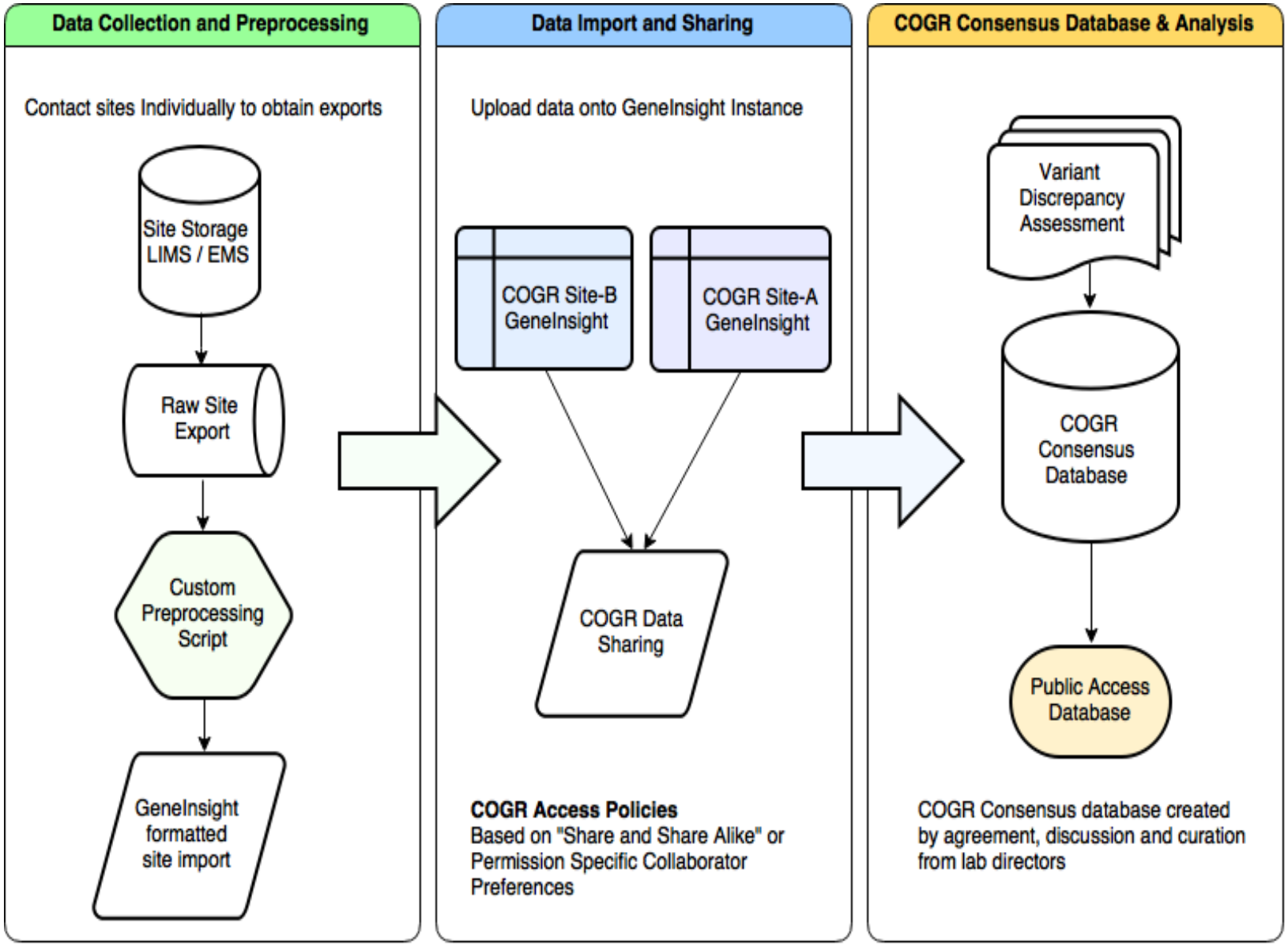
COGR storage and sharing

- The COGR Consensus Database holds variants with consensus classifications across labs
- Sharing is optional at the discretion of the lab and only enabled upon request




By Agreement, Discussion and Curration
COGR_Consensus. GeneInsight
Public Data Access & Outreach
GeneInsight Data Sharing Engine
COGR Access Policies
Based on 'Share and Share Alike' or Permission Specific Collaborator Preferences
COGR_Site_A. GeneInsight
COGR_Site_B. GeneInsight
COGR_Site_C. GeneInsight
COGR_Site_X. GeneInsight

Workflow Overview



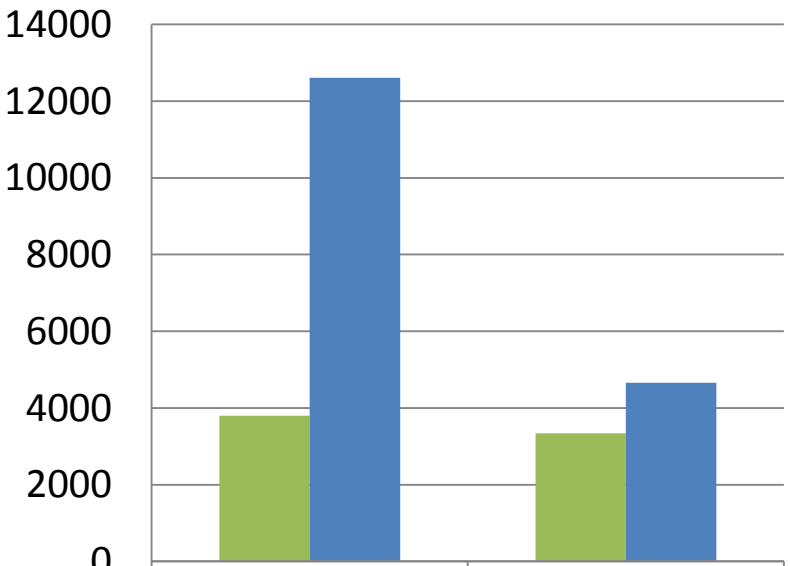
23 GeneInsight Instances Created

Organization	Upload Status	Sharing Status
Alberta Children's Hospital, Calgary AB	Uploaded	Sharing
Atlantic Cancer Research Institute, Moncton NB	Pending	-
British Columbia Cancer Agency, Vancouver BC	Uploaded	Sharing
Children's & Women's Health Centre of BC, Vancouver BC	Uploading	-
Children's Hospital of Eastern Ontario, Ottawa ON	Uploaded	Sharing*
Credit Valley Hospital, Trillium Health Centre, Mississauga ON	Uploaded	Sharing
Dept of Medical Genetics, University of Alberta, Edmonton AB	Uploading	-
Hamilton Health Sciences, McMaster University, Hamilton ON	Uploaded	-
Impact Genetics Inc., Bowmanville ON	Pending	-
Izaak Walton Killam Health Centre, Dalhousie University, Halifax NS	Uploading	-
Jewish General Hospital, Montréal QC	Uploading	
Kingston General Hospital, Queen's University, Kingston ON	Uploaded	Sharing
McGill University Health Complex, Montréal QC	Uploaded	-
Memorial Health University Medical Center, St. John's NL	Pending	-
Mount Sinai Hospital, University of Toronto, Toronto ON	Uploaded	Sharing*
North York General Hospital, Toronto ON	Uploaded	Sharing
Ontario Institute of Cancer Research (OICR), Toronto ON	Uploaded	Sharing
Regional Health Authority, University of Manitoba, Winnipeg MB	Uploading	Sharing
Sainte-Justine Hospital, University of Montreal, Montréal QC	Uploading	-
SickKids Hospital and McLaughlin Centre, Toronto ON	Uploaded	Sharing
University Hospital, Western University, London ON	Pending	-
Women's College Hospital, University of Toronto, Toronto ON	Uploaded	Sharing*

***Also sharing with VariantWire**

COGR Variant Numbers

COGR Comparison 2014/2015

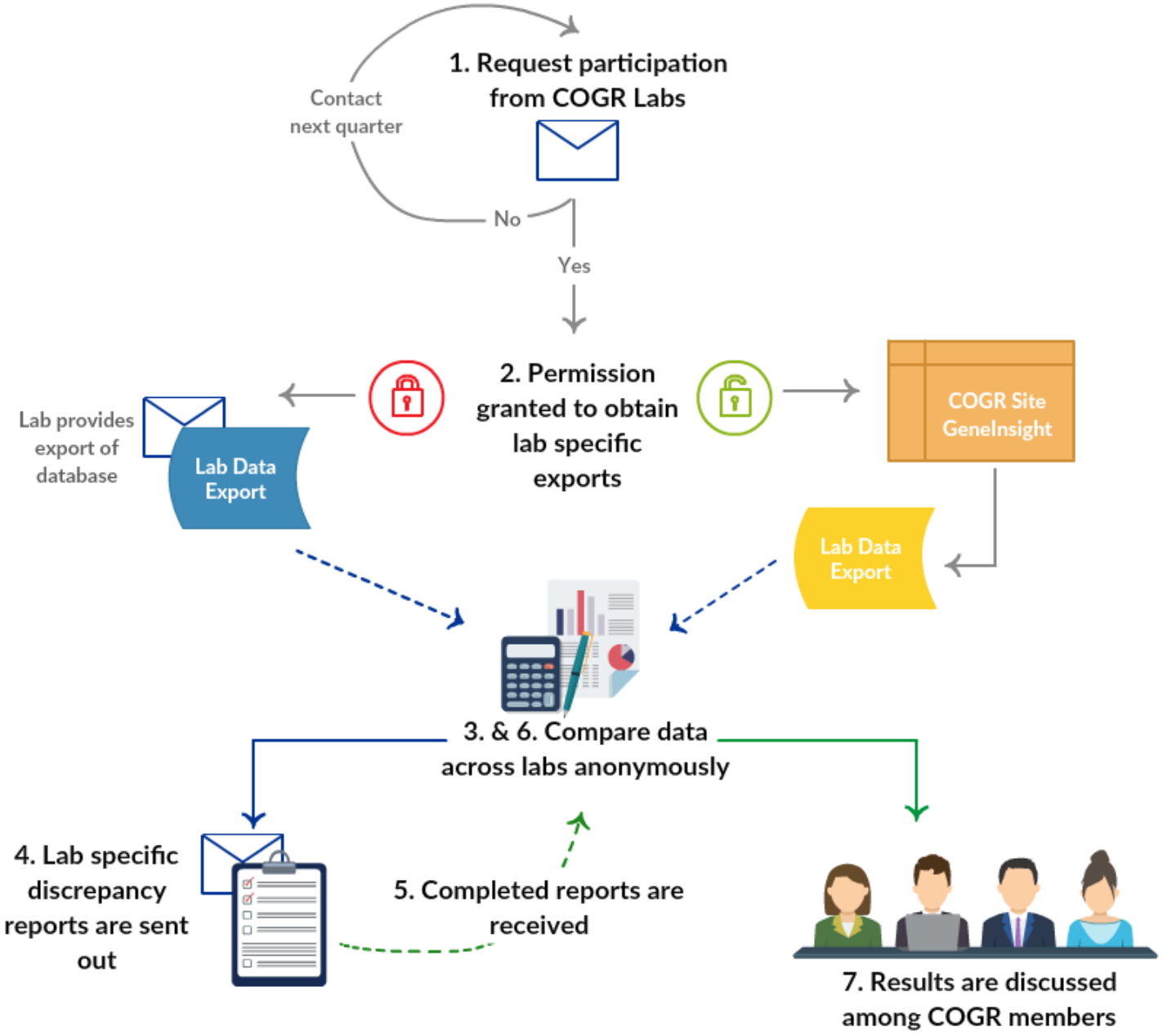


	Variants	Copy Number Variants
2014	3802	3339
2015	12607	4659

- >17,000 variants
- 1,266 genes
- 66 diseases

The COGR Recent Initiative

- 2016 marks the COGR's 4th year
  - Focus to make data holdings both extremely accurate and readily accessible
- Recent initiative to create and disperse lab specific discrepancy reports
  - Aim is to build clinical interpretation consensus on variants identified in Canadian clinical diagnostic laboratories and academic medical centers


1. Request participation from COGR Labs
Contact next quarter
No
Yes
2. Permission granted to obtain lab specific exports
Lab provides export of database
Lab Data Export
COGR Site GeneInsight
Lab Data Export
3. & 6. Compare data across labs anonymously
4. Lab specific discrepancy reports are sent out
5. Completed reports are received
7. Results are discussed among COGR members

COGR - BRCA Participating Institutions

A. Alberta Children's Hospital (Calgary, AB)
B. Atlantic Cancer Research Institute (Moncton, NB)
C. British Columbia Cancer Agency (Vancouver BC)
D. Children's & Women's Health Centre of BC (Vancouver BC)
E. Children's Hospital of Eastern Ontario (Ottawa ON)
F. Credit Valley Hospital, Trillium Health Centre (Mississauga ON)
G. Dept of Medical Genetics, University of Alberta (Edmonton, AB)
H. Hamilton Health Sciences, McMaster University (Hamilton, ON)
I. Impact Genetics Inc. (Bowmanville, ON)
J. Izaak Walton Killam Health Centre (Halifax, NS)
K. Kingston General Hospital, Queen's University (Kingston, ON)
L. McGill University Health Complex (Montréal, QC)
M. Memorial Health University Medical Center (St. John's, NL)
N. Mount Sinai Hospital, University of Toronto (Toronto, ON)
O. North York General Hospital (Toronto ON)
P. Ontario Institute of Cancer Research (OICR) (Toronto, ON)
Q. Regional Health Authority, University of Manitoba (Winnipeg, MB)
R. Sainte-Justine Hospital, University of Montreal (Montréal, QC)
S. SickKids Hospital and McLaughlin Centre (Toronto, ON)
T. University Hospital, Western University (London, ON)
U. Women's College Hospital, University of Toronto (Toronto, ON)
V. Jewish General Hospital, Montreal (Montréal, QC)

Discrepancy Report Results Overview

- **11** participating labs across 4 provinces
  - ON, BC, AB, MB
- Received total of **5,554** BRCA1/2 variants
  - 3014 unique variants
    - 1,148 seen in >2 labs
  - 110 to 1072 variants per lab (505 on average)

1. Overall discrepancy report results
2. Total changes in classifications and reasoning
3. Changes in discrepant variant classifications
4. Methods for reassessment

Submission Data - Before Issuing Discrepancy Reports

After data submission 1,148 unique variants were identified in more than one lab

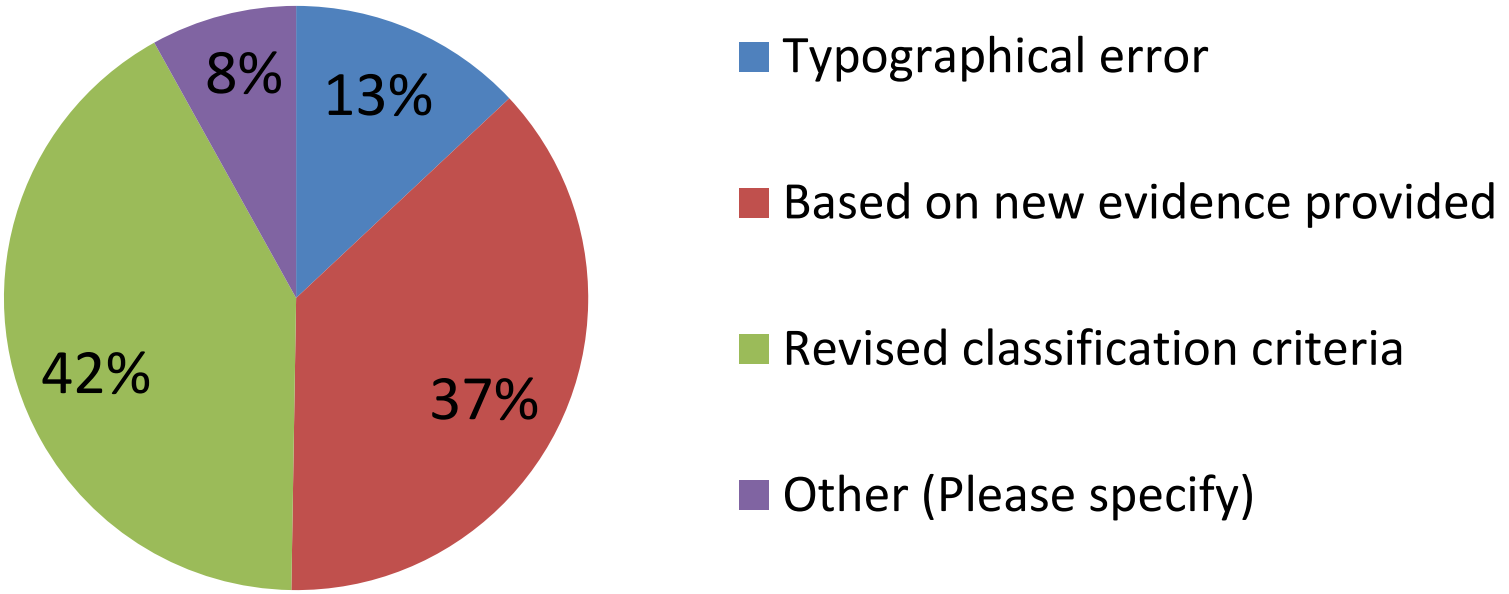
- 550 (48%) of variants had concordant classifications
- 350 (30%) were discordant
- 248 (22%) were unclassified

After Review of Discrepancy Report Results

- 42% of discordant variants changed classifications
- 28% did not change classifications
- 30% were not reassessed
- Only 18% of the discrepant variants reached a consensus
  - 3-tiered (LB/B, VUS, LP/P)
    - 65.7% concordant
    - 33.9% discordant

Reasoning For Reclassification

- 9 out of 11 labs on average specified reasoning
- 64% of reassessed variants provided reclassification reasoning:



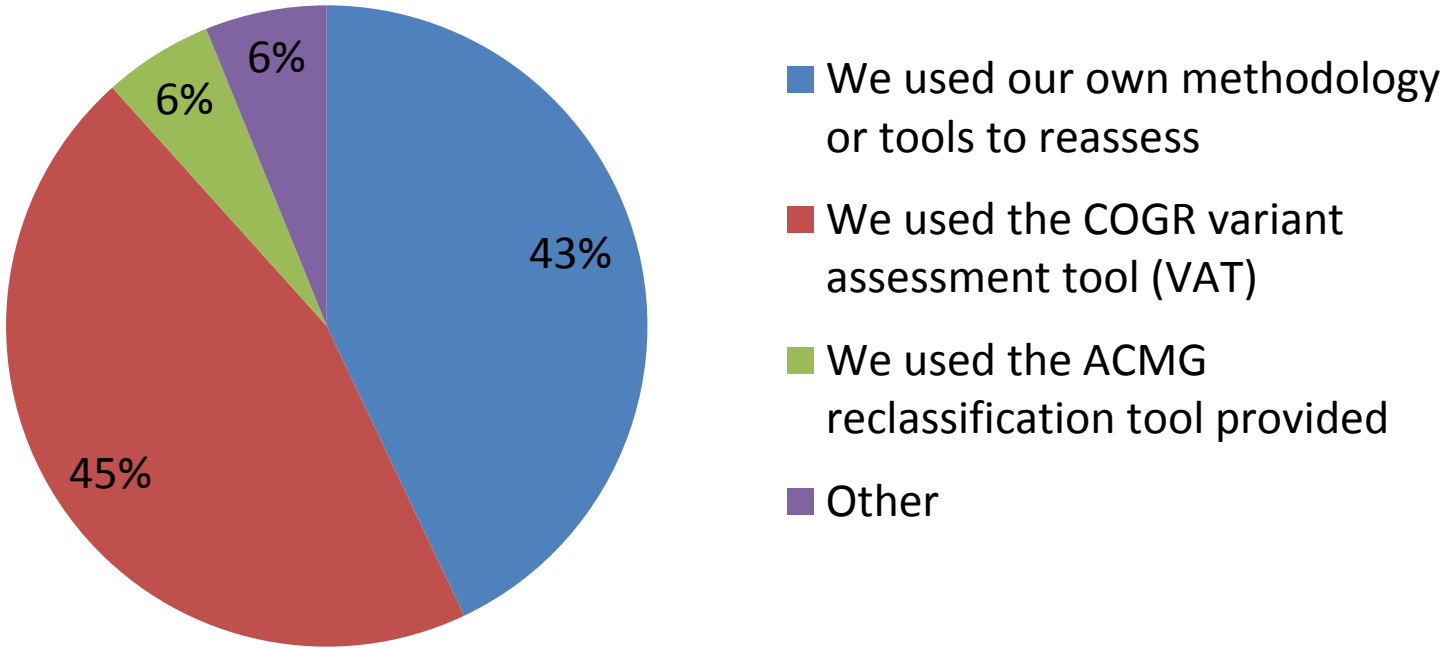
Changes in Discrepant Variant Classifications

- 42% changed from original classification
- 28% did not change classifications
- 30% were not reassessed

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%)

Methods Used for Reassessment

- Most labs did not review variants through the COGR network (GeneInsight)
- 8 out of 11 labs on average specified their reassessment methods
- 34% of variants had specified reassessment methods:



Summary

- Successful exercise with positive feedback within the COGR community
- Continuing initiatives:
  - releasing 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

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This work was funded by the Government of Canada through Genome Canada and the Ontario Genomics Institute (OGI-070)