Clinical laboratories collaborate to resolve variant interpretation differences in ClinVar

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Background and Methods

- The ClinVar database allows labs to share variant interpretations that previously had been unpublished or unavailable to the larger community.
- ACMG published guidelines for variant interpretation providing a framework to classify variants; however, given the complexity of variant interpretation, application of the guidelines still require subjective interpretation
- Through a ClinGen initiative, 4 clinical labs, Ambry Genetics, GeneDx, Laboratory for Molecular Medicine (LMM), and University of Chicago, identified variants with interpretation differences in ClinVar and collaborated to:
  - Categorize the reason for interpretation differences
  - Resolve interpretation differences
- Laboratories collaborated on 115 variants:
  - 80 with medically significant differences (P/LP vs. VUS/LB/B)
  - 35 with VUS vs. LB/B differences

Initial Data

- As of June 1st 2015, a total of **35,507** unique variants had been submitted to ClinVar by at least one of the four participating labs.
- **4878 (14%)** variants had been submitted by ≥2 of the participating labs and **625** had one or two-step differences between the three major categories: P/LP, VUS, and LB/B

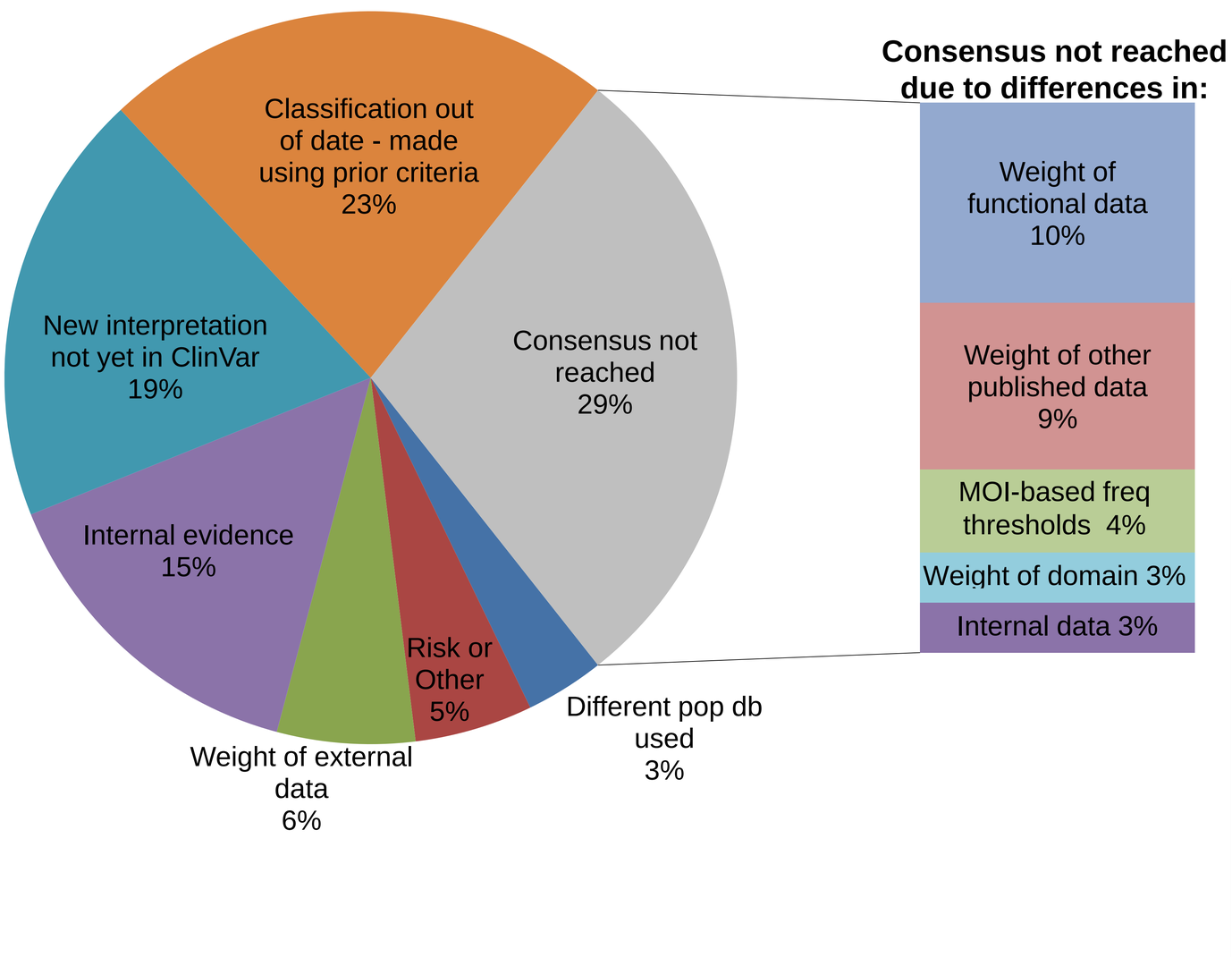
Table 1: Interpretation differences in ClinVar from participating labs

Submitted by	# shared variants	# Agreed (%)	# VUS vs. LB/B differences	# medically significant differences
Ambry/GeneDx	2246	1993 (89%)	**207 (9%)**	**46 (2%)**
GeneDx/LMM	1793	1534 (86%)	**61 (3%)**	**197 (11%)**
Chicago/LMM	463	422 (91%)	**36 (8%)**	**5 (1%)**
Ambry/Chicago	43	41 (95%)	**2 (5%)**	**0**
Ambry/LMM	63	60 (95%)	**2 (35%)**	**1 (2%)**
GeneDx/Chicago	914	835 (91%)	**79 (95%)**	**0**
All 4 Labs	**4878**	**4253 (87%)**	**375 (8%)**	**250 (5%)**

Table 2: Outcome of resolution attempts for 115 variants with interpretation differences

Type of interp. difference	# diff	# resolved interpretation:				# not resolved
		P/LP	VUS	LB/B	Risk / Other	
P/LP vs. VUS	73	13	31	0	6	23
P/LP vs. B/LB	7	2	2	1	2	0
VUS vs. B/LB	35	-	0	25	0	10

Figure 1: Reasons for interpretation differences for 115 variants interpreted by ≥2 labs



Resolution Results for 115 variants

- Collaboration and reassessment resulted in laboratories reaching consensus on 71% (82 variants) of variants with interpretation differences
  - 62% of the resolved P/LP to VUS interpretation differences were resolved to VUS
  - 5 of the Risk/Other resolved variants represent variants classified with non-standard pathogenicity terms that are conflicting in ClinVar due to translation to standard pathogenicity terms
- Sharing internal evidence, such as segregations, co-occurrences, and de novo observations, resolved 15% of interpretation differences.
- Out of date classifications accounted for >40% of differences as,
  - 23% were resolved by labs reassessing the variant with current interpretation criteria
  - 19% were concordant but the new interpretations had not yet been submitted or posted in ClinVar
- Labs did not reach consensus for 33 variants (29%), most due to differences in the weight of functional data or other published data.

Conclusions

- Interpretations agree for 87% of variants shared in ClinVar by ≥2 of the four participating labs.
- Sharing internal evidence resolved 15% of differences (13% of medically significant differences; 23% of VUS vs. LB/B differences)
- Persistent interpretation differences are largely due to differences in the weight of external evidence, suggesting further specification or guidance on interpreting and weighting external data, such as functional assays, is needed to reach consensus
- Sharing internal evidence allowed 18% of medically significant differences to be classified as pathogenic or likely pathogenic, strengthening the interpretation of variants used in patient care.