Resolving Variant Interpretation Differences in ClinVar between 43 Clinical Laboratories

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Sharing data in ClinVar provides open access to variant classifications from many clinical laboratories. While the majority of classifications agree, ClinVar has shed light on the important issue of interpretation differences between laboratories, providing a valuable opportunity to resolve differences and positively impact patient care. Recent work with four clinical laboratories found that 53% of interpretation differences were resolved by either updating ClinVar with current internal classifications or reassessment of an older interpretation with current classification criteria (PMID: 28301460). With this finding in mind, ClinGen's Sequence Variant Inter-Laboratory Discrepancy Resolution team will encourage clinical laboratories with outlier interpretations to update ClinVar with current classifications and reassess remaining conflicts using current guidelines. To identify variants that could be resolved by this outlier strategy, interpretations from 43 clinical laboratories in ClinVar were compared, identifying 26,421 variants interpreted by ≥2 clinical laboratories. The majority of classifications were concordant (85.7%; 22,637 variants). Only 2.5% (667 variants) of all shared variants were medically significant differences (MSDs) with potential to impact medical management [pathogenic (P/LP) versus other (VUS/LB/B]. These differences were investigated to determine if submitted interpretations could reach a majority consensus (agreement in classification of at least 2/3 of clinical laboratory submitters). Of the MSDs with ≥3 interpretations (249 variants), 87.6% (218 variants) reached a majority consensus, thus allowing for identification of outlier submissions most in need of reassessment. Outlier submitters on variants with majority consensus will be contacted with a custom report and be encouraged to update ClinVar, if the classification has already changed internally, and reassess remaining outlier interpretations. If the discrepancy remains, other clinical laboratories will be encourage to share internal evidence to facilitate resolution. Based on our initial study results, it is anticipated that this process will resolve at least 79% of MSDs, reducing total MSDs to 0.5%. This process adds to the value of ClinVar and will help the community move toward more consistent variant interpretations which will improve the care of patients with, or at risk for, genetic disorders.