Clinical laboratories implement the ACMG/AMP guidelines to resolve differences in variant interpretations submitted to ClinVar

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In 2015, the American College of Medical Genetics and Genomics (ACMG) and the Association for Molecular Pathology (AMP) published a joint guideline for variant interpretation that provides a framework to classify variants. As part of a ClinGen initiative, four clinical laboratories, Ambry Genetics, GeneDx, Partners Laboratory for Molecular Medicine (LMM), and University of Chicago's Genetic Services Laboratory, have collaborated to resolve variant interpretation differences identified in ClinVar by reassessing variants and comparing ACMG/AMP guidelines criteria. As of June 1, 2015, these laboratories submitted a total of 35,507 unique variants to ClinVar with 4878 variants interpreted by at least two of the participating labs, of which 4253 (87%) had concordant interpretations, 375 (8%) had uncertain significance vs likely benign/benign discrepancies (VUS vs LB/B), and 250 (5%) had pathogenic/likely pathogenic vs uncertain significance/likely benign/benign (P/LP vs VUS/LB/B) discrepancies. As a pilot, the participating labs reassessed 115 variants with interpretation differences (80 P/LP vs VUS/LB/B differences and 35 VUS vs LB/B differences) to determine if sharing internal data and applying the ACMG/AMP criteria and classification rules could resolve the different interpretations. Collaboration and reassessment resulted in laboratories reaching consensus on 71% (82 variants) of the variants assessed in this pilot. 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 Out of date classifications accounted for 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 interpretation discrepancies as 23% were resolved by labs reassessing the variant with ACMG/AMP interpretation guidelines and 19% were reassessed prior to this pilot but the new interpretations had not yet been submitted to ClinVar. Labs were unable to reach consensus on 33 variants (23 P/LP vs VUS/LB/B discrepancies and 10 VUS vs LB/B discrepancies). Lab assessments for the remaining discrepancies were compared to determine the ACMG/AMP criteria applied by only one laboratory that accounted for the different clinical interpretations. For 8 of the 23 persistent P/LP vs VUS/LB/B discrepancies (35%), labs applied the same ACMG/AMP criteria for pathogenicity but one lab also applied criteria supporting a benign role resulting in a VUS interpretation. Of the remaining 15 P/LP vs VUS/LB/B discrepancies, the most frequently applied ACMG/AMP criteria by only one lab were functional studies showing a deleterious effect (PS3), mutation hot spot or functional domain (PM1), and a pathogenic assertion from a reputable source (PP5). For the 10 variants with unresolved VUS vs LB/B discrepancies, the most frequently applied ACMG/AMP criteria by only one lab were population database information (BS1 and BS2) and variant found in a case with an alternative molecular cause (BP5). These results show that clinical interpretations from these four clinical laboratories are in agreement for 87% of variants and collaboration and reassessment with the ACMG/AMP guidelines were able to resolve 71% of interpretation differences. Further specification regarding functional assays, hot spot and/or domain information, interpretations from reputable sources, thresholds for using allele frequency in public databases, and weighing conflicting pathogenic and benign criteria may further facilitate resolution of interpretation differences with ACMG/AMP guidelines. Given that the interpretation of variants for their role in disease requires expert opinion and subjective review of scientific evidence and medical data, it is unlikely that full consensus will ever be reached; however, increased training and guidance on the application of the ACMG/AMP criteria and ensuring the full sharing of evidence and classification rationales, is critical to move toward more consistent variant interpretations which will improve the care of patients with, or at risk for, genetic disorders.