Clinical Laboratories Implement the ACMG/AMP Guidelines to Resolve Differences in Variant Interpretations Submitted to ClinVar

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As part of a ClinGen initiative, four clinical laboratories, Ambry Genetics, GeneDx, Partners Laboratory for Molecular Medicine, and University of Chicago, have collaborated to resolve variant interpretation differences identified in ClinVar by reassessing variants and comparing American College of Medical Genetics and Genomics (ACMG) and Association for Molecular Pathology (AMP) variant interpretation guideline criteria. As of January 1, 2016, there are 6,169 variants in ClinVar interpreted by at least two of the participating labs. The majority of classifications were concordant (88%; 5445) while 8% (508) differed between uncertain significance vs likely benign/benign (VUS vs LB/B) and 4% (216) differed between pathogenic/likely pathogenic vs uncertain significance/likely benign/benign (P/LP vs VUS/LB/B). Labs reassessed 232 variants with interpretation differences (104 P/LP vs VUS/LB/B and 128 VUS vs LB/B) to determine if sharing internal data and applying the ACMG/AMP guidelines could resolve the differences. This process resulted in laboratories reaching consensus for 86% (200). Unresolved differences (23 P/LP vs VUS/LB/B and 10 VUS vs LB/B) were compared to determine the unique ACMG/AMP criteria applied by laboratories accounting for the differences. For persistent P/LP vs VUS/LB/B differences, the most frequently differentially applied ACMG/AMP criteria were functional studies showing a deleterious effect (PS3), mutation hotspot or functional domain (PM1), assertion from a reputable source (PP5), or the weight of additional benign criteria. For persistent VUS vs LB/B differences, the most frequently differentially applied ACMG/AMP criteria were population database information (BS1 and BS2) and variant found in a case with an alternative molecular cause (BP5). In conclusion, applying ACMG/AMP criteria and sharing internal evidence and classification rationales increased the overall concordance rate between these four labs from 88% to 91.5%, with 0.5% reassessed but unresolved and 8% still in need of reassessment. As variant interpretation requires expert opinion and subjective review of data, full consensus is unlikely to be reached; however, increased specification on how to apply ACMG/AMP criteria is critical to move toward more consistent variant interpretations which will improve the care of patients with genetic disorders.

[400 word max including authors & affiliations]