Scaling the Resolution of Sequence Variant Classification Discrepancies in ClinVar

Steven M. Harrison[1,2], Jill S. Dolinksy[3], Wenjie Chen[4], Alison Coffey[5], Christin D. Collins[6,25], Soma Das[7], Joshua L. Deignan[8], Kathryn B. Garber[6], John Garcia[9], Olga Jarinova[10], Izabela Karbassi[22], Amy E. Knight Johnson[7], Juha W. Koskenvuo[11], Hane Lee[8], Rong Mao[12], Ales Maver[24], Rebecca Mar-Heyming[13], Andrew McFaddin[14], Krista Moyer[13], Narasimhan Nagan[4], Stefan Rentas[15], Avni B. Santani[15,16], Carol Saunders[23], Eija H. Seppälä[11], Brian Shirts[14], Timothy Tidwell[12], Scott Topper[9,17], Lisa M. Vincent[18], Kathy Vinette[19], and Heidi L. Rehm[1,2,20, 21]

Sharing data in ClinVar provides open access to variant classifications from many clinical laboratories. While most classifications are consistent across laboratories, classification differences exist. By aggregated submitted classifications, ClinVar provides an opportunity for submitters to collaborate on deriving the most accurate conclusions. A pilot project from ClinGen's Sequence Variant Inter-Laboratory Discrepancy Resolution team focusing on four clinical labs found that 53% of classification differences were resolved by either updating ClinVar with current internal classifications or reassessment of an older classification with current classification criteria (PMID: 28301460). With these findings in mind, our working group prioritized variants that reach a majority consensus (≥ ⅔ of submitters agree) with an outlier classification and expanded the scope to include more clinical labs. The first round compared classifications from 41 clinical labs and identified 24,445 variants classified by ≥2 clinical labs (April 2017). The majority of classifications were concordant (84.6%; 20,677 variants) and only 2.7% (650 variants) of variants were medically significant differences (MSDs) with potential to impact medical management. Labs with outlier classifications were sent a custom report and encouraged to reassess. Labs have returned results for 204 variants, of which 62.3% (127 variants) were resolved. **A second round of this expanded effort including classifications from all clinical labs submitting to ClinVar (108 submitters; April 2018) is underway and preliminary data shows 54.3% (150/276) resolution rate**. In total, 67.7% (488/721) of reassessed variants have been resolved through these rounds of discrepancy resolution and 22 clinical labs are now actively involved in this process. By comparison, within one year, 24.3% (106/437) of variants that previously had MSDs but did not reach a majority consensus are now concordant, showing that a subset of differences will be resolved over time by routine reassessment; however, notification of outlier classifications can serve as a prompt for reassessment and accelerate resolution. In conclusion, this process capitalizes on the value of data sharing within ClinVar and will help the community move toward more consistent variant classifications.

1-Laboratory for Molecular Medicine, Partners HealthCare Personalized Medicine, Cambridge, Massachusetts, USA;
2-Harvard Medical School, Boston, Massachusetts, USA;
3-Ambry Genetics, Aliso Viejo, California, USA;
4-Integrated Genetics, Laboratory Corporation of America® Holdings, Westborough, Massachusetts, USA;
5-Illumina Inc., San Diego, California, USA
6-EGL Genetics, Tucker, Georgia, USA;
7-Department of Human Genetics, The University of Chicago, Chicago, Illinois, USA;
8-Department of Pathology and Laboratory Medicine, David Geffen School of Medicine, University of California Los Angeles, Los Angeles, California, USA;
9-Invitae Corporation, San Francisco, California, USA;
10-Department of Genetics, Children's Hospital of Eastern Ontario, Ottawa, Ontario, Canada;
11-Blueprint Genetics, Helsinki, Finland;
12-ARUP Laboratories, Salt Lake City, Utah, USA;
13-Counsyl, South San Francisco, California, USA;
14-Department of Laboratory Medicine, University of Washington, Seattle, Washington, USA;
15-Division of Genomic Diagnostics, The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, USA;
16 - Department of Pathology and Laboratory Medicine, Perelman School of Medicine at The University of Pennsylvania, Philadelphia, Pennsylvania, USA;
17-Current: Color Genomics, South San Francisco, California, USA;
18-GeneDx, Gaithersburg, Maryland, USA;
19-Molecular Diagnostics Laboratory, A. I. duPont Hospital for Children, Wilmington, Delaware, USA;
20-Center for Genomic Medicine, Massachusetts General Hospital, Boston, USA
21-The Broad Institute of MIT and Harvard, Cambridge, Massachusetts, USA
22-Quest Diagnostics, Athena Diagnostics, Marlborough, Massachusetts, USA
23-Center for Pediatric Genomic Medicine, Children's Mercy Hospital, Kansas City, Missouri, USA
24-Clinical Institute of Medical Genetics, University Medical Centre Ljubljana, Ljubljana, Slovenia
25-Current: Global Laboratory Services, PerkinElmer Genomics, Branford, Connecticut, USA