Benefits of Sharing Variant Classifications and Evidence with ClinVar

Given the rarity of most variants of clinical relevance, it is imperative that genomic variant classifications and supporting evidence are shared in a public, centralized database such as ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/) to improve both our understanding of genomic variation and patient care that relies on this information.

Improved Variant Classification

Sharing variant classifications with ClinVar allows laboratories to identify classification differences with other ClinVar submitters and work towards consensus, providing more accurate and consistent results to patients.

- ClinVar provides a broader set of clinical classifications than users may have assessed in their own clinical laboratory. Data can be retrieved programmatically via APIs, which allows users to incorporate the information into their own workflows (https://www.ncbi.nlm.nih.gov/clinvar/docs/maintenance_use/#api).
- ClinVar provides a monthly report of conflicting classifications which submitters can use to prioritize reassessment (https://ftp.ncbi.nlm.nih.gov/pub/clinvar/).
- Studies of clinical laboratory ClinVar submitters have shown data sharing is a successful approach to prioritizing variant reassessment and resolving classification differences.[1, 2, 3]

Keep Providers Up-to-Date with Variant Knowledge

- Classifications change over time and providers, patients and scientists in the community need to be kept up-to-date. Directing inquiries to ClinVar for current knowledge can reduce resources needed to respond to inquiries on current variant classifications.

Adds Value through Standardization and Quality Control

ClinVar adds value to submitted classifications by standardizing descriptions of variants, conditions, and terms for clinical significance.

- Variants are mapped to reference sequences and reported in HGVS. This provides a quality control check for accurate nomenclature.
- Clinical significance terms for Mendelian disorders are converted to standard ACMG-AMP categories (Pathogenic, Likely pathogenic, Uncertain significance, Likely benign, Benign), enabling comparison across laboratories.
- As many variants identified in Mendelian disease testing are extremely rare and thus unlikely to be re-observed, sharing variant interpretations in ClinVar is can serve as an ongoing quality assurance measure for laboratory reassessment of rare variants

Publicity as a Lab that Shares Data

- ClinGen recognizes submitters meeting minimum requirements for data sharing to support quality assurance (https://www.clinicalgenome.org/lablist/).
- Submitters receive recognition by ClinGen at meetings and conferences for sharing data.
- Submitters are displayed on the ClinVar website (https://www.ncbi.nlm.nih.gov/clinvar/docs/submitter_list/).

- The Genetic Testing Registry (GTR) indicates whether a particular laboratory shares their data under each registered test.

Position Your Lab with Evolving Regulatory and Medical Standards

- The National Institutes of Health (NIH), the American Medical Association (AMA), the American College of Medical Genetics and Genomics (ACMG), and the National Society of Genetic Counselors (NSGC) have all released statements testifying to the importance of publicly available databases on genomic variants and their clinical significance.[4-7]
- The Food and Drug Administration (FDA) is recognizing shared variant data in publicly accessible databases as valid scientific evidence to support the clinical validity of genotype-phenotype relations, see FDA's guidance "Use of Public Human Genetic Variant Databases to Support Clinical Validity for Genetic and Genomic-Based In Vitro Diagnostics."[8]

Data Sharing as a Business Strategy

- Medical institutions and healthcare providers are increasingly adopting policies to preferentially order genomic testing from laboratories that publicly share data.[9]
- There are increasing pressures from payers to selectively reimburse tests from companies that share their data.[10]

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[1]Harrison SM, Dolinsky JS, Knight Johnson AE, et al. Clinical Laboratories Collaborate to Resolve Differences in Variant Interpretations Submitted to ClinVar. Genetics in Medicine: Official journal of the American College of Medical Genetics. 2017;19(10):1096-1104. doi:10.1038/gim.2017.14.

[2]Harrison SM, Dolinsky JS, Chen W, et al. Scaling resolution of variant classification differences in ClinVar between 41 clinical laboratories through an outlier approach. Human Mutation. 2018;39:1641–1649.

[3]Riggs ER, Nelson T, Merz A, et al. Copy number variant discrepancy resolution using the ClinGen dosage sensitivity map results in updated clinical interpretations in ClinVar. Human Mutation. 2018;39:1650–1659.

[4]American Medical Association. 2013. Genome Analysis and Variant Identification Policy D-460.971.

[5]National Institutes of Health. 2014. Genomic Data Sharing 79 FR 51345.

[6]National Society of Genetic Counselors. 2015. Clinical Data Sharing.

[7]ACMG Board of Directors. 2017. Laboratory and clinical genomic data sharing is crucial to improving genetic health care: a position statement of the American College of Medical Genetics and Genomics. Genet Med 19: 721–722.

[8]Use of Public Human Genetic Variant Databases to Support Clinical Validity for Genetic and Genomic-Based In Vitro Diagnostics. 2018. https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm509837.pdf

[9]https://www.geisinger.edu/research/departments-and-centers/gmi

[10]https://www.genomeweb.com/informatics/genomic-variant-data-sharing-gains-support-collaboration-seen-key-interpretation#.W2IQhtIzpXg

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