

ASHG 2024 Abstract

Title: Integrating emerging data into genomic testing: Outcomes from an evidence-based reanalysis initiative

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As evidence on gene-disease relationships (GDR) and variant pathogenicity grows, incorporating new data into variant interpretation requires a comprehensive approach. Sources of evidence can vary and include reports in the literature which may define new GDRs or expand phenotypic spectrums, public databases with more diverse representation, and variant-level functional data, such as RNA analysis.

We reviewed exome sequencing (ES) reported at a clinical lab between 2011- 2021 and subsequent reclassifications through 2023. All cases were involved in the Patient for Life Program, an evidence-driven reanalysis initiative that incorporates emerging evidence into clinical testing. A team of scientists proactively monitor scientific literature and other data sources. As new information is identified, historical ES cases are reviewed, and reclassifications are issued when appropriate. We identified the outcome (negative, uncertain, positive [pathogenic/likely pathogenic]), evidence category resulting in reclassification (gene, variant, or clinical overlap) and directionality (upgrade v. downgrade). Within each evidence category we grouped evidence source. There was a 19% relative increase in diagnostic yield (21% vs. 25%). Overall, 9% (963/10,921) of cases received a reclassification report; some underwent multiple reclassifications, totaling 993.

New evidence related to genes was the most impactful, accounting for 64% (637/993), followed by variant (29%; 285/993) and clinical overlap (7%; 71/993). The most vital source of evidence (64% of reclassifications) was literature describing new patients, often establishing new GDRs. Other common sources of evidence were new proband phenotypes (7%), updated MAF data from population databases (6%), family cosegregation studies (6%), and improvements to lab classifications and reporting procedures (5%). Most reclassifications (82%; 811/993) were triggered from evidence from external sources, such as publications and updated proband phenotypes, while 18% (182/993) were the result of a laboratory follow-up studies including family cosegregation studies, RNA analysis, and additional structural assessment. Collectively, 45% (449/993) had clinically significant upgrades, moving from uncertain or negative to positive, underscoring the impact of new

evidence. Implementing evidence-driven reanalysis to proactively monitor, create, and incorporate emerging data improves ES accuracy, clinical utility, and diagnostic yield. Clinical laboratories should invest resources in proactive reclassification based on new evidence to maximize the diagnostic yield of genomic-based testing.