

Title: Laboratory-driven Exome Reanalysis Increases Diagnostic Yield and Decreases Burden on Clinicians

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Objective: One advantage of exome sequencing (ES) is the ability to reanalyze data as our understanding of genetic contributions to human disease grows. We assessed the outcomes of a laboratory-driven ES reanalysis strategy, Patient for Life (PFL), which proactively incorporates new evidence into ES reports without requiring reanalysis requests by providers.

Methods: We reviewed individuals with neurological indications (neurodevelopmental, epilepsy, or neuromuscular) who underwent ES between 2012-2023. We categorized reanalysis type as PFL, provider-requested, or family studies. With PFL, when new information related to gene-disease relationships (GDR) and/or variant pathogenicity is identified, historical ES cases are reviewed, and reclassification reports are issued. We compared outcomes of the initial ES reports to current reports and determined the reasons for reclassification to assess the overall impact of PFL.

Results: 8472 individuals were included in the analysis, and 20% (n= 1685) underwent at least one reanalysis during the study period. Of these, 41% (n=694) received a reclassification report. 47% (n=327) of reclassifications resulted in diagnoses for initially unsolved cases (negative or uncertain), representing a new diagnosis for 5% of all originally unsolved cases and a 17% relative increase in diagnostic yield overall (21% vs 25%). 84% (n=273) of these diagnostic upgrades were through PFL, compared to 15% (n=50) provider-requested reanalyses, and 1% (n=4) family studies. The majority (88%) of provider-requested reanalyses resulted in a 'no change' notification, adding work for both the provider and laboratory with no clinical benefit.

Conclusions: PFL identifies more diagnostic reclassifications than the traditional provider-requested approach and reduces burden on laboratories and clinics.

Disclosures/Addendum

All authors of this work are salaried employees of Ambry Genetics.