Getting to the Source of the Matter: Evidence-Driven Reanalysis in Exome Sequencing

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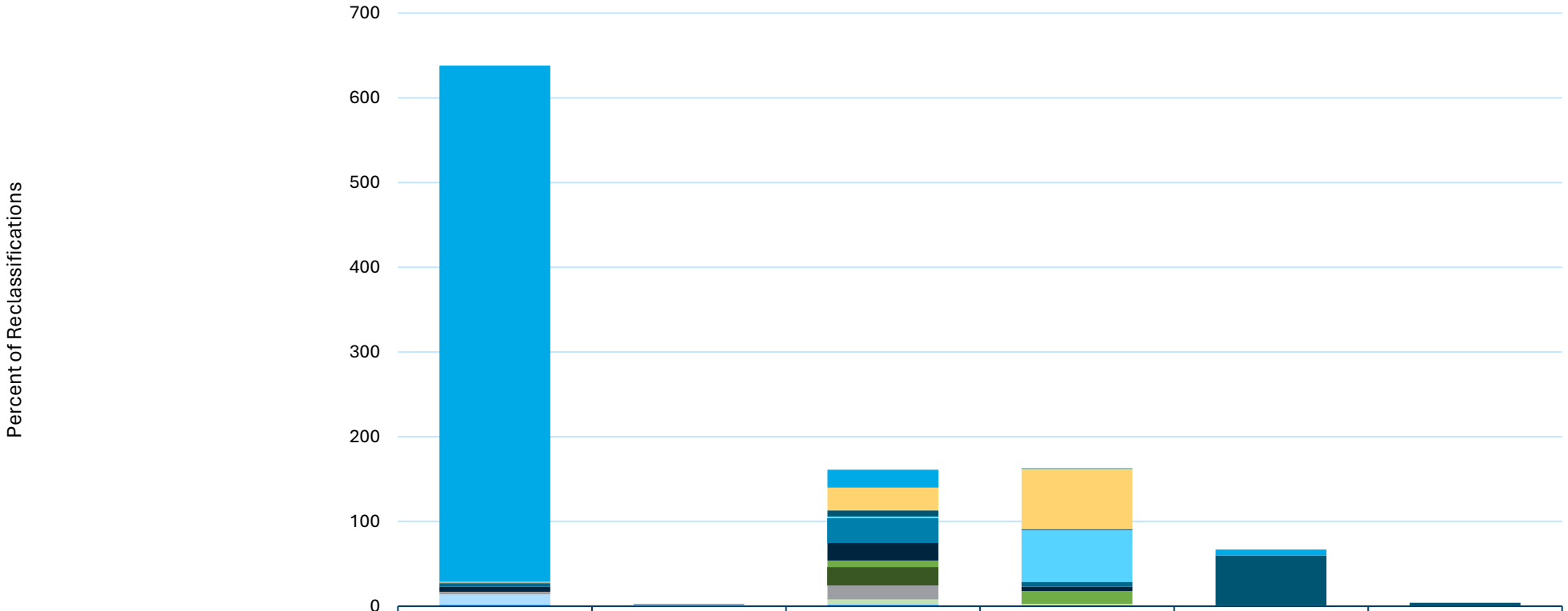
As evidence on gene-disease relationships (GDR) and variant pathogenicity grows, reanalysis of exome sequencing (ES) data is critical to optimize diagnostic yield. Recommendations for periodic reanalysis exist, typically every 2 years and driven by clinician request. However, this approach may delay the return of relevant diagnostic updates. We present an evidence-driven reanalysis strategy, the Patient for Life Program, in which scientists monitor literature and other data sources for new information. Historical ES cases are reviewed, and reclassification reports are issued when appropriate.

We retrospectively reviewed cases at a clinical lab with ES between 2011- 2021 and subsequent reclassifications through 2023. Reanalysis may be initiated by the lab as evidence is identified, requested by the clinician, or due to family co-segregation studies after initial report. We identified the evidence category resulting in reclassification (gene, variant, or clinical overlap) and directionality (upgrade v. downgrade). Within each evidence category we grouped the evidence source (ex. literature describing new patients).

There was a 19% relative increase in diagnostic yield (21% vs. 25%). Overall, 9% (963/10,921) of cases received a reclassification report; 61% of these cases, or 5.4% of the total cohort (595/10921), received an upgraded lab-initiated reclassification. Some cases underwent multiple reclassifications, totaling 993. Notably, 45% (449/993) had clinically significant upgrades, moving from uncertain or negative to positive. New evidence related to genes was the most impactful category, 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 patient phenotypes (7%), updated MAF data from population databases (6%), family co-segregation studies (6%), and improvements to lab classifications and reporting procedures (5%).

This underscores the importance of implementing an evidence-driven reanalysis program to proactively incorporate new evidence, improving ES accuracy, clinical utility, and diagnostic yield. The greatest impact on upgrades was from establishing new GDR, while downgrades were largely due to variant reclassifications following family studies or availability of new population databases. Clinical labs should invest resources in proactive reclassification based on new evidence, reducing the burden on clinics to request reanalysis.



	Gene upgrade	Gene downgrade	Variant upgrade	Variant Downgrade	Clinical overlap upgrade	Clinical overlap downgrade
New literature described new patients	609	1	21	1	7	0
Family studies	1	0	27	71	0	0
New patient clinical information	1	0	7	1	59	4
New MAF data from population databases	0	0	2	61	0	0
Additional patients (unpublished)	4	0	29	6	0	0
Follow up analysis	6	0	21	5	0	0
Updated lab procedures	0	0	8	15	1	0
Pipeline Upgrade	0	0	21	0	0	0
Client inquiry based on external testing	3	0	17	0	0	0
New information on mechanism of disease	11	2	0	0	0	0
Periodic review of previous cases	1	0	6	2	0	0
Gene functional data and/or animal models	2	0	2	1	0	0