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

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BACKGROUND

- Reanalysis of exome sequencing (ES) data improves diagnostic yield as new evidence clarifies gene-disease relationships (GDR) and variant pathogenicity
- Recommendations for reanalysis exist, typically every 2 years and driven by clinician request
  - This approach may delay the return of relevant diagnostic updates

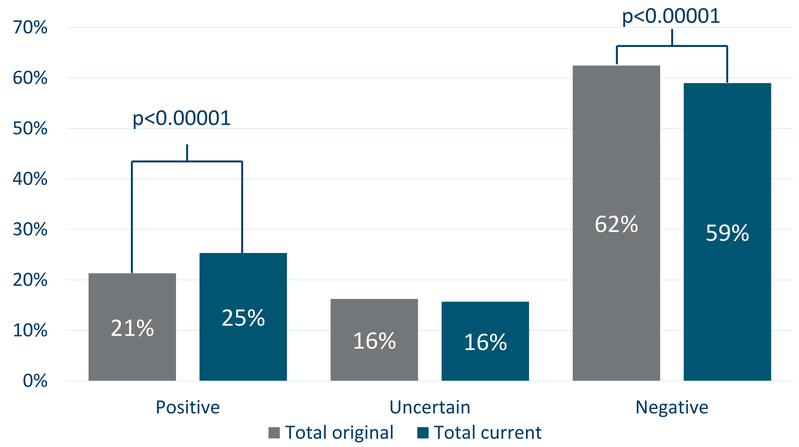
RESULTS

- There was a 19% relative increase in diagnostic yield (21% v. 25%) **[Figure 1]**
  - 5% of the total cohort (595/10921) received an upgraded lab-initiated reclassification
- 9% (963/10,921) of cases received a reclassification; 993 total reclassifications
  - 45% (449/993) had clinically significant upgrades (uncertain or negative to positive)
- Gene-related evidence was the most impactful category, accounting for 64% **[Figure 2a]**
  - Updated clinical phenotypes provided by clinicians accounted for 7%; this data would not have been available through other data sources
- While most new evidence came from external sources, 18% was generated through internal laboratory work **[Figure 2b]**
- Literature describing new patients was the largest contributing factor **[Figure 3]**
  - Other sources: new patient phenotypes (7%), updated population databases (6%), co-segregation studies (6%), and improvements to lab procedures (5%)

OBJECTIVES

- Review outcomes >10 years of Patient for Life, an evidence-driven reanalysis strategy
- Identify the sources and categories of evidence used to reclassify clinical ES data

Figure 1: Exome Reanalysis Impact on Diagnostic Yield



STUDY METHODS

Retrospective review of cases at a clinical lab with ES between 2011- 2021 and subsequent reclassifications through 2023

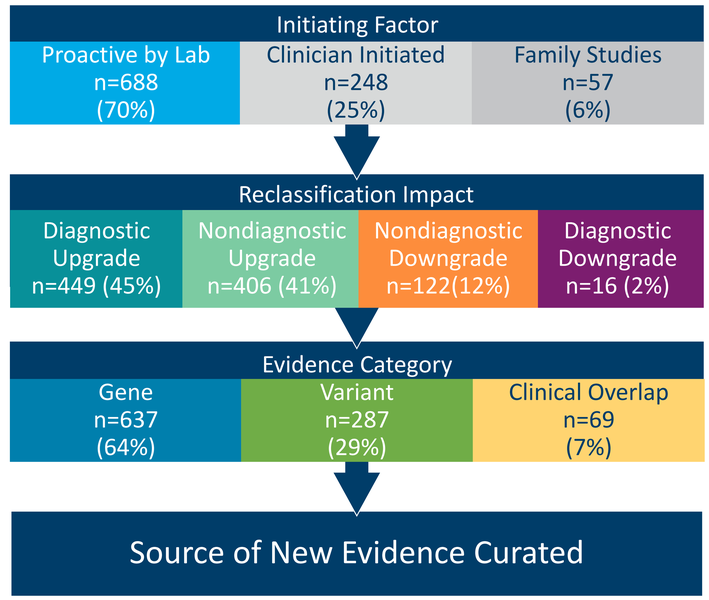


Figure 2a: Evidence Categories

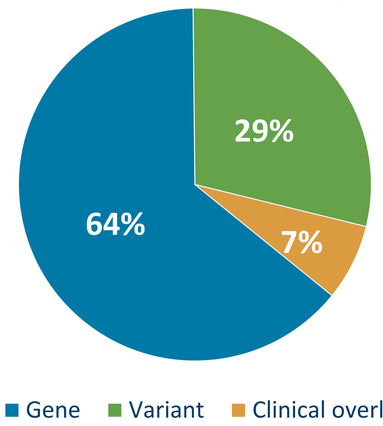


Figure 2b: Source of Evidence

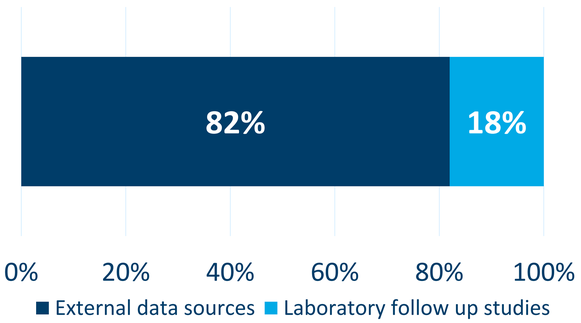
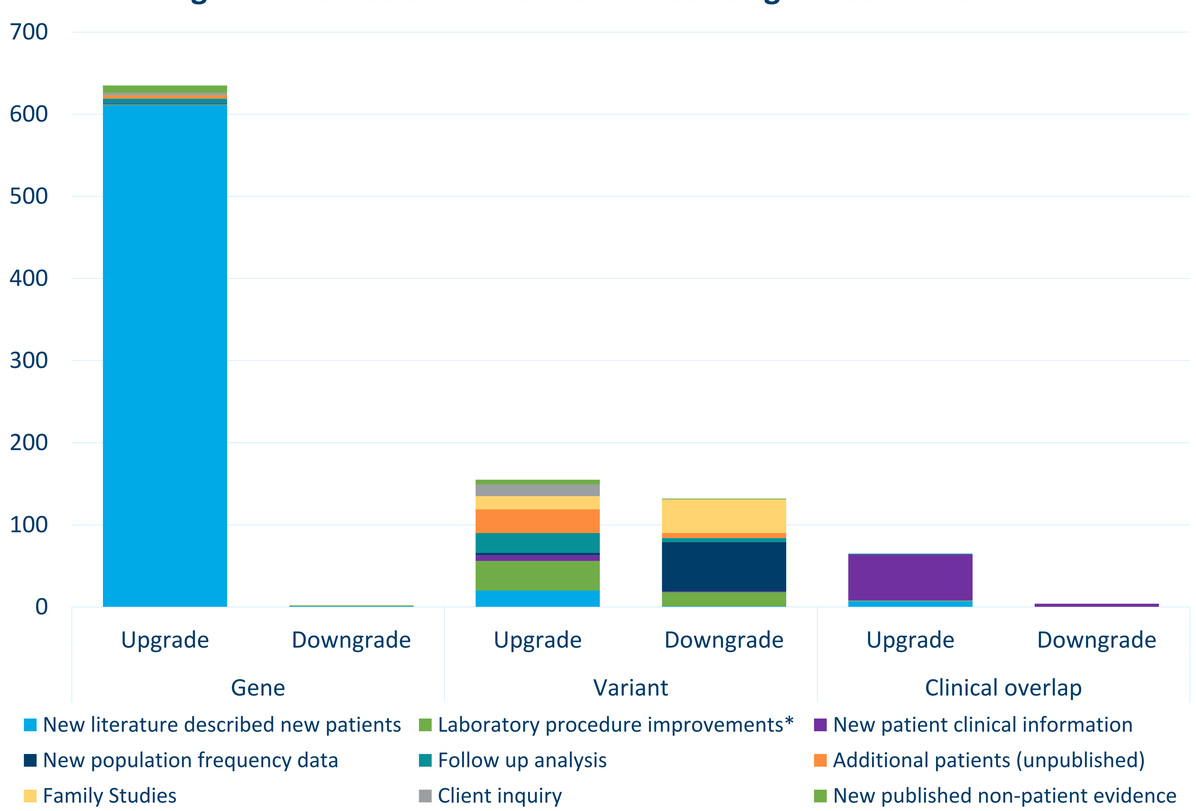


Figure 3: Source of New Evidence Resulting in Reclassification



*Laboratory procedure improvements = Pipeline upgrades, Updated lab classification/reporting procedures, and Periodic review of previous cases

TAKE HOME POINTS

- Exome reanalysis resulted in a 19% relative increase in diagnostic yield
- Most reclassifications (70%) were lab-initiated, including upgraded reports for 5% of the total cohort
- Published data, especially related to new GDRs, accounted for most reclassifications
- Laboratory-generated data drove nearly 1 out of 5 reclassifications
- Clinical labs should invest in comprehensive approaches to proactive reclassification to maximize the clinical utility of ES