



Driven Reanalysis in Exome Sequencing

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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

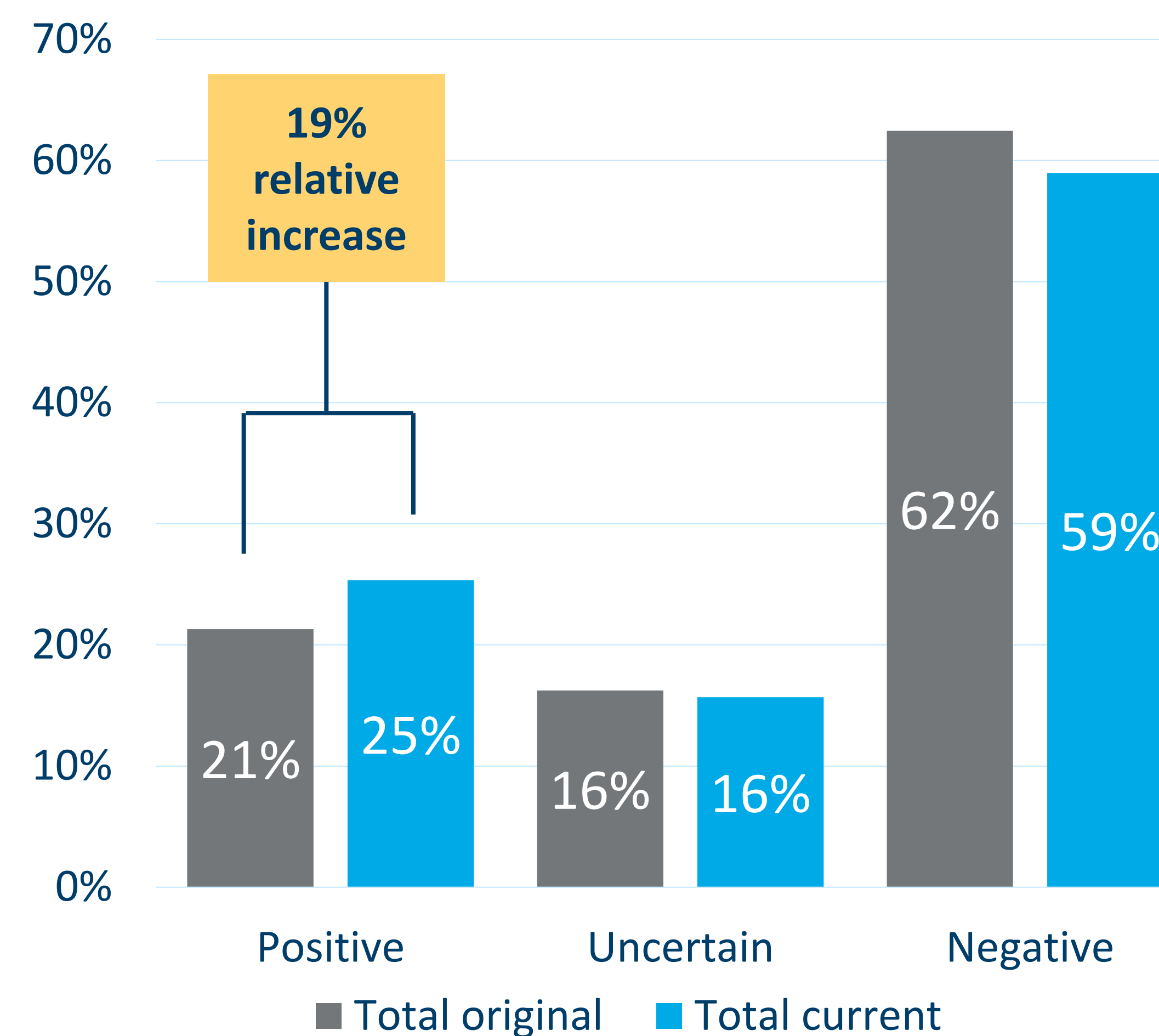
OBJECTIVES

- Present an evidence-driven reanalysis strategy, the **Patient for Life Program**
- Review outcomes >10 years of Patient for Life, identifying the types of evidence used to reclassify clinical ES cases

RESULTS

- 19% relative increase in diagnostic yield [FIGURE 1]
- 9% (963/10,921) of cases received a reclassification
 - 993 total reclassifications
 - 45% (449/993) had clinically significant upgrades (uncertain or negative to positive)
- New evidence related to genes was the most impactful category, accounting for 64% [FIGURE 2]
- Updated clinical phenotypes provided by clinicians accounted for 7%; this data would not have been available through other data sources
- 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%)

Figure 1: Impact on Diagnostic Yield



STUDY METHODS

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

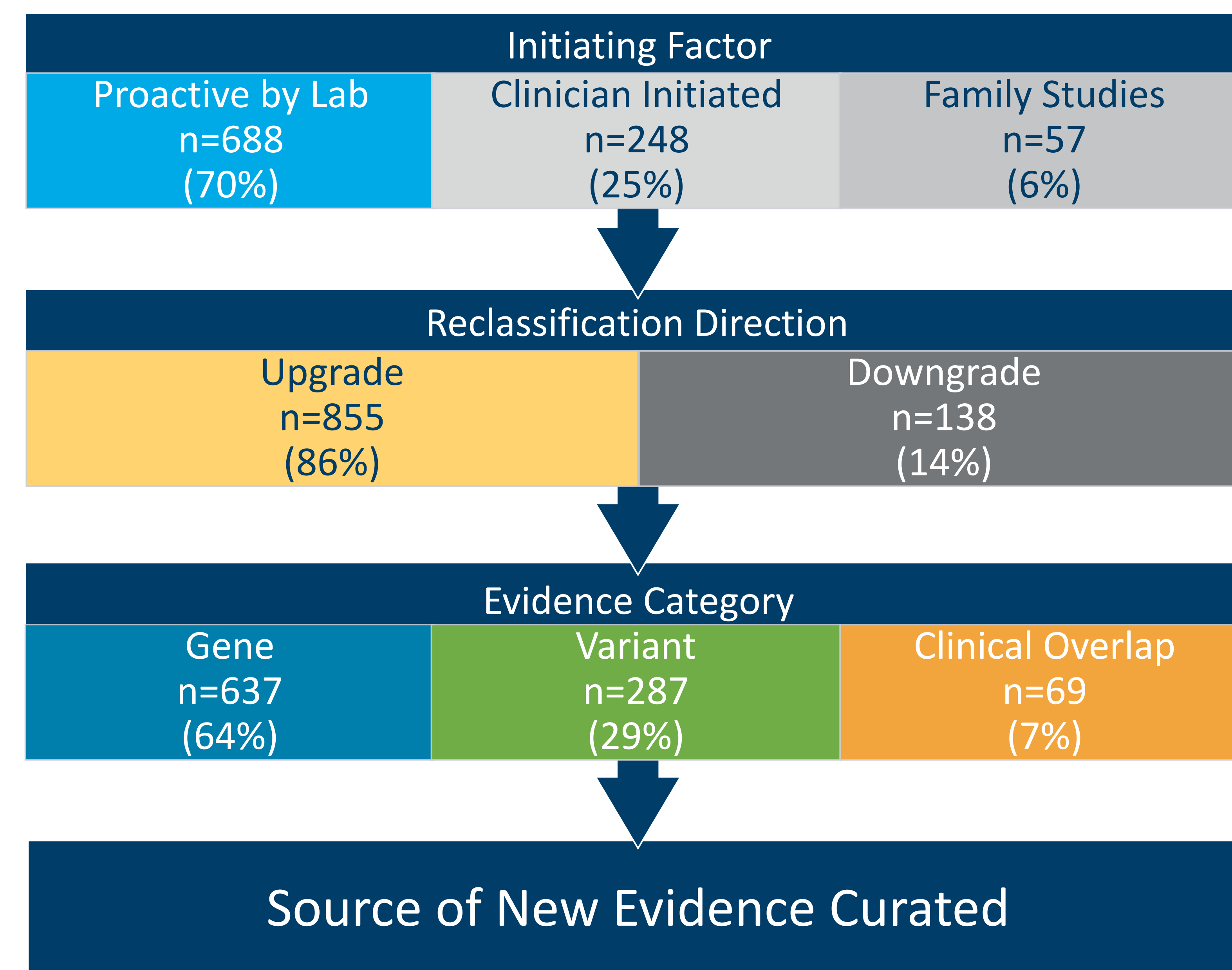


Figure 2: Evidence Categories

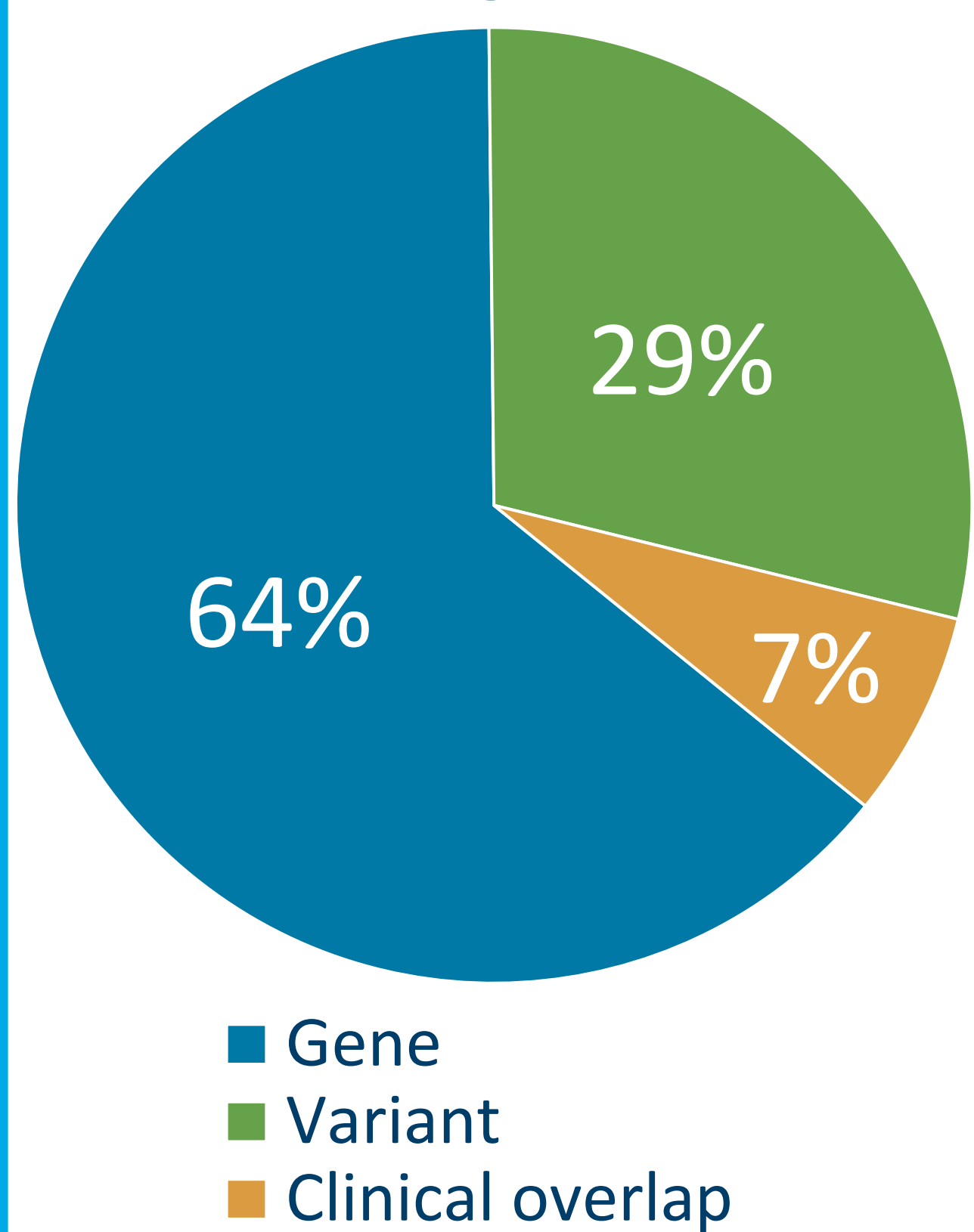
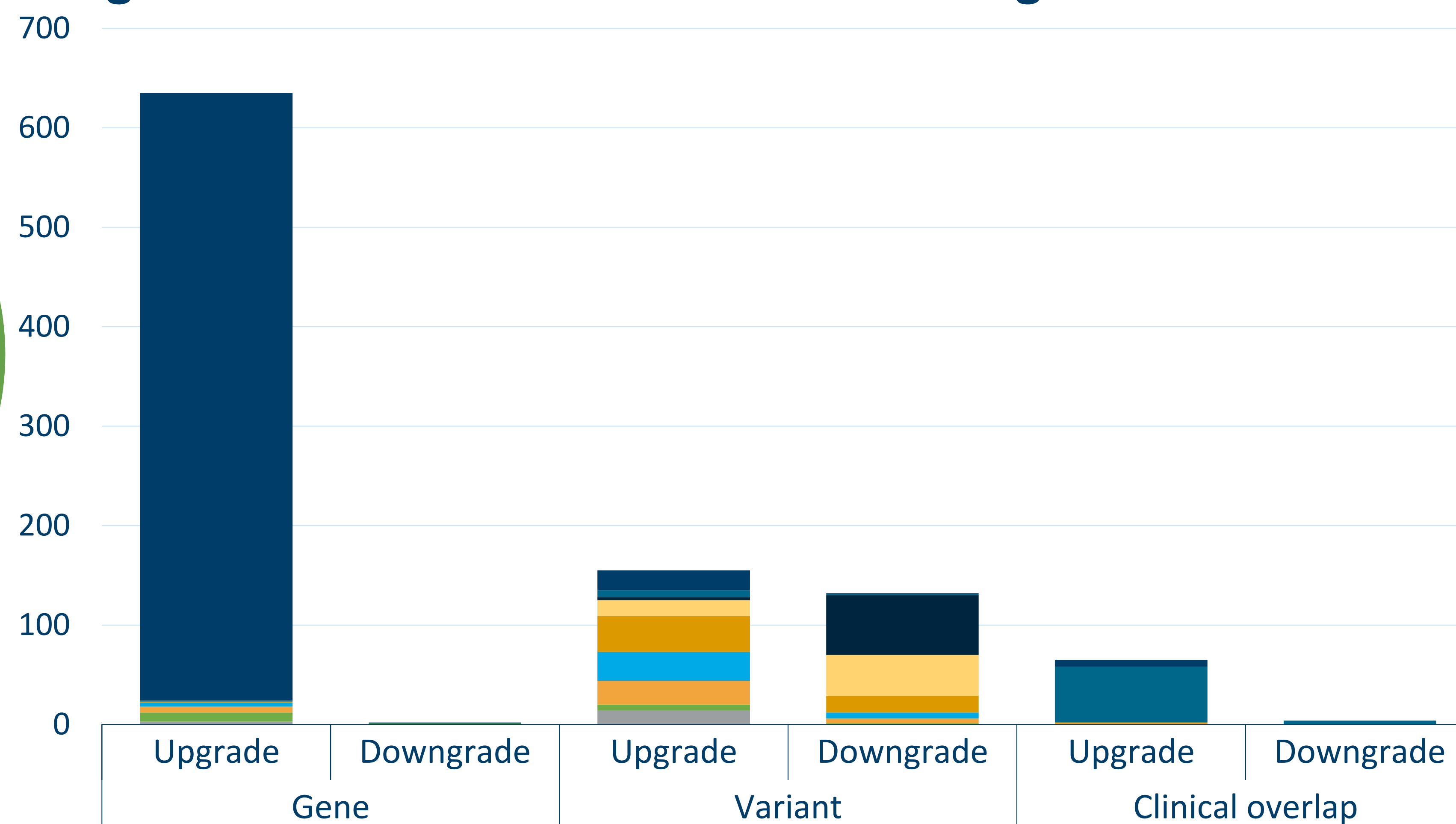


Figure 3: Source of New Evidence Resulting in Reclassification



*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, the vast majority were lab-initiated reclassifications
- Emerging GDRs and newly published data accounted for most reclassifications
- Clinician reanalysis requests in the setting of new phenotypic data are valuable
- Clinical labs should invest resources in proactive reclassification to reduce the burden on clinics to request reanalysis