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

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BACKGROUND

- Exome sequencing (ES) data can be reanalyzed as understanding of genetic contributions to disease grows
- Reanalysis increases ES diagnostic yield over time
  - Mostly due to gene-disease relationships (GDR)

OBJECTIVE: Assess the outcomes of proactive vs. reactive ES reanalysis processes

STUDY METHODS

- Reviewed 10 years of ES for neurological indications (n=8539)

Neurodevelopmental 74% of cohort

Epilepsy 9% of cohort

Neuromuscular 17% of cohort

- Compared reanalysis outcomes and evidence used for reclassifications based on the reanalysis initiation factor

METHODS FOR EXOME REANALYSIS

Provider requested

Clinicians determine when and under what circumstances they want a reanalysis

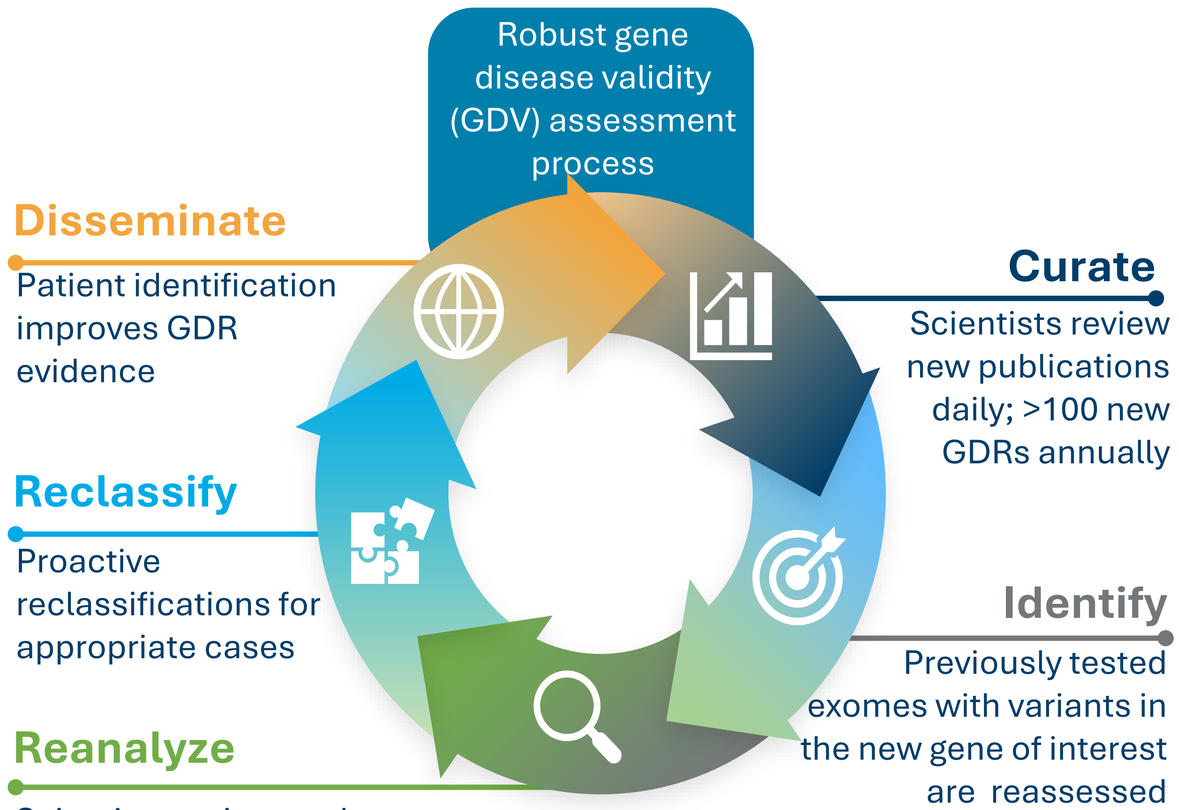
Reanalysis is requested from the lab

- Labs may have differing criteria, costs, and timeline for reanalysis

Updated report documenting reanalysis issued

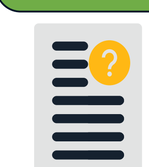
- Time-based
- Requires laboratory and clinician resources
- Comprehensive review of data at time of reanalysis

Patient for Life



- Ongoing assessment
- Requires no clinician resources
- Comprehensive, consistent review of data as evidence is published

Family Studies



Variant of Unknown Significance reported on testing

Review likelihood that co-segregation studies in available family members would reclassify a variant

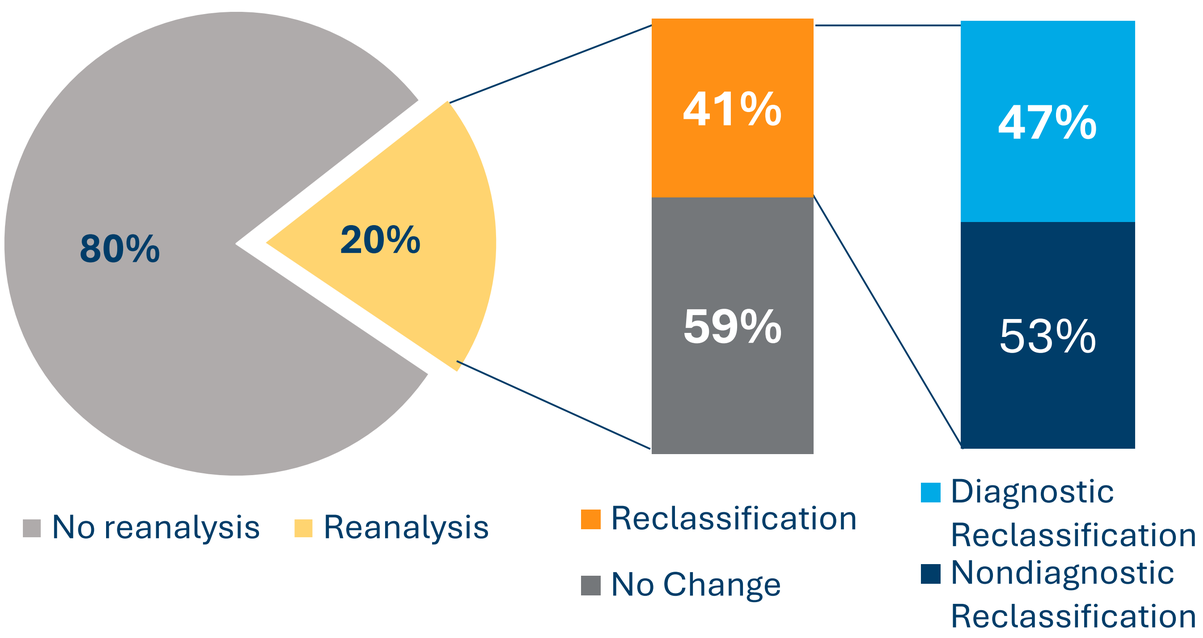
New sample collected from family member(s) with single variant analyzed

Results incorporated into variant classification and updated report issued

- Limited by available/informative family member(s)
- Requires laboratory and clinician resources
- Limited to just variant in question

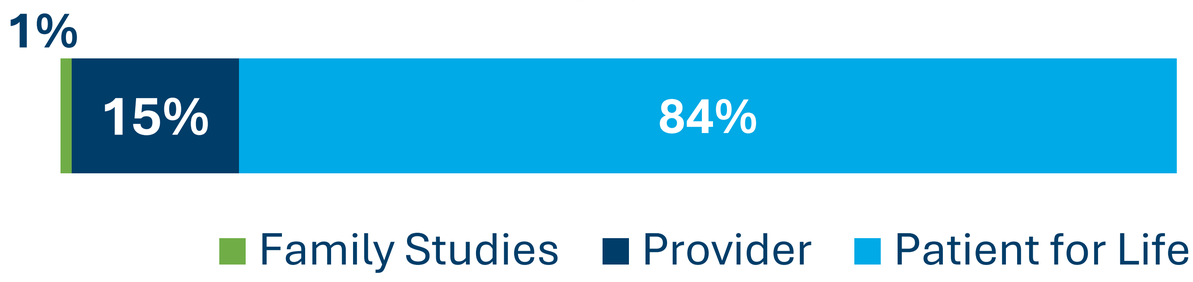
RESULTS

FIGURE 1: COHORT REANALYSIS AND RECLASSIFICATION



- 20% of cases (n= 1685) underwent at least one reanalysis during the study period **[Figure 1]**
  - Of these, 41% (n=694) received a reclassification report
- Increase in overall diagnostic yield (21% vs 25%)
  - **5% of all originally unsolved ES received a diagnostic finding**

FIGURE 2: DIAGNOSTIC RECLASSIFICATIONS BY INITIATING FACTOR



- 327 total diagnostic reclassifications (4% of all cases)
- 84% of diagnostic upgrades were through PFL, compared to 15% provider-requested reanalyses, and 1% family studies **[Figure 2]**

TAKE HOME POINTS

- ES reanalysis increases the diagnostic yield over time
- Patient for Life resulted in higher rates of diagnostic reclassification and initiates when new relevant data is available
- Majority of provider-requested reanalyses resulted in a 'no change' notification, adding work for the provider and laboratory with no clinical benefit