Genome and Exome Sequencing Reanalysis: Improvement to Diagnostic Yield and Classification of Variants Over Time

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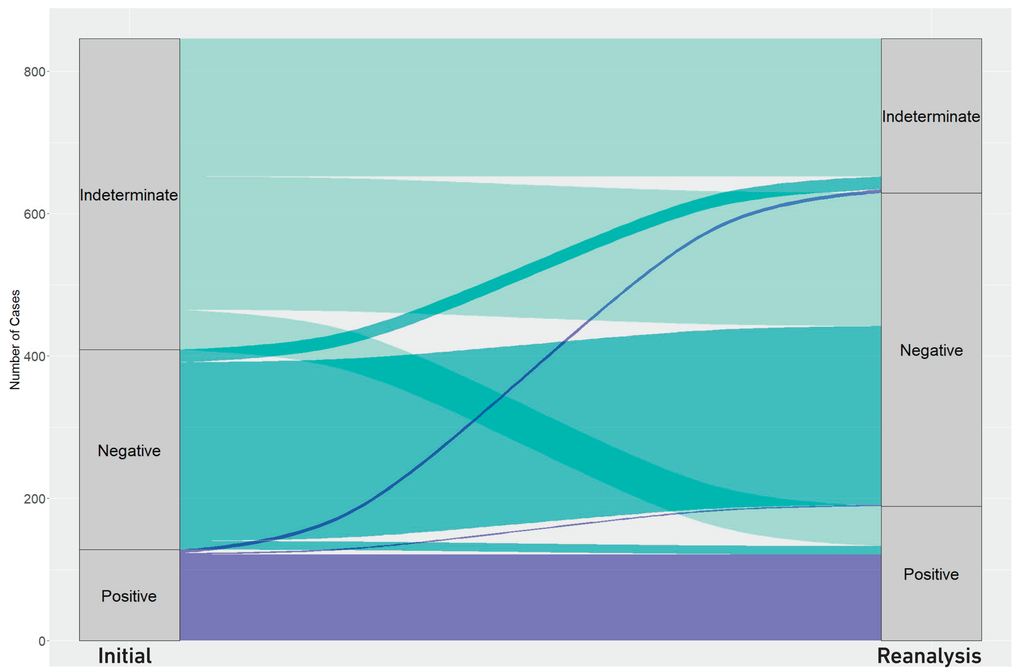
Background

- Genome sequencing (GS) and exome sequencing (ES) have been increasingly used as clinical diagnostic tools for individuals with a suspected underlying genetic disorder.
- Depending on the clinical indication and other factors, GS/ES have a diagnostic yield of ~25-40%.[1,2,3,4]
- However, there are many individuals who remain undiagnosed following GS/ES.
- As gene-disease associations are established, variant classifications are updated, and bioinformatic analytic workflows improve over time, reanalysis of GS/ES data can increase diagnostic yield and reduce uncertainty of previous genetic findings.

Results

- 846 cases reanalyzed (681 ES, 165 GS)
  - ES reanalysis yielded new genetic diagnoses in 9.3% (63/681) of cases
  - GS reanalysis yielded new genetic diagnoses in 7.3% (12/165) of cases
- 75 (8.9%) had at least one new genetic diagnosis identified
  - 4 of the 75 had two new genetic diagnoses identified

Figure 2. Changes in Overall GS/ES Result from Original Analysis to Reanalysis



56 individuals had a positive reanalysis report following an original indeterminate report

12 individuals had a positive reanalysis report following an original negative report

7 individuals had a previously positive report with a new genetic diagnosis on reanalysis

6 individuals had a downgraded genetic diagnosis following reanalysis

Methods

- Study Design: Retrospective analysis of consecutive provider-initiated GS/ES reanalysis cases at our clinical diagnostic laboratory was conducted.
- Inclusion Criteria: For families with multiple affected individuals who underwent reanalysis, only one individual was included in this analysis. Cases with initial prenatal testing were excluded.
- Analysis: Previous GS/ES reports were reviewed to determine changes in the overall call of the report, genetic diagnoses, variant classifications, and year of previous analysis.

Figure 1. Method of New Diagnosis Made From Reanalysis

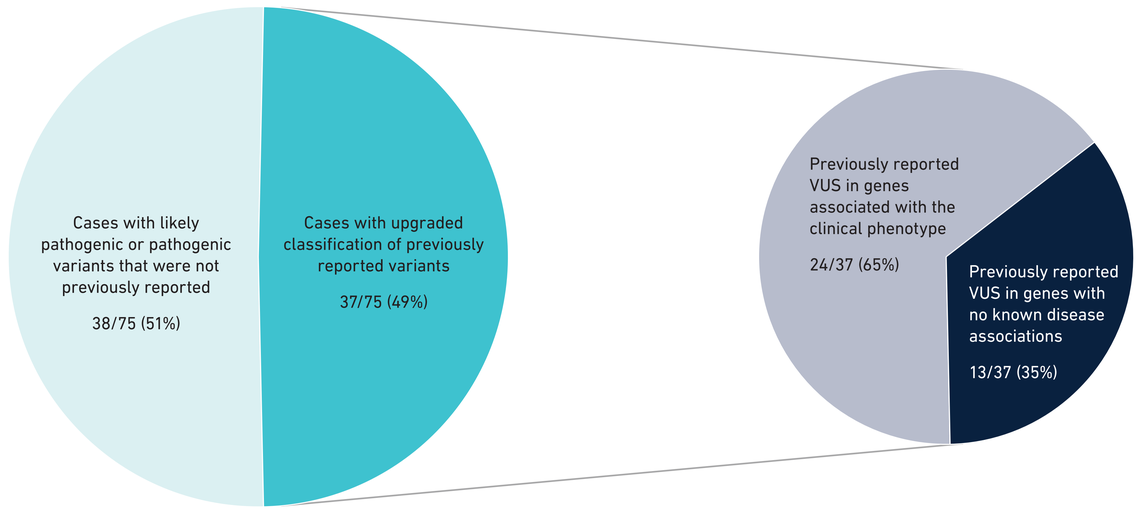


Table 1. Case Examples of New Diagnoses from Reanalysis

	Case 1	Case 2
Case	Original trio WES in 08/2017 Reanalysis in 08/2024	Original trio WES in 11/2018 Reanalysis in 09/2024
Original Finding(s)	8 VUS findings in 8 genes, including *H3-3B* gene. 1 VUS in a gene with no known disease association.	Heterozygous paternally inherited likely pathogenic variant in *RAPSN* gene. Heterozygous VUS finding in 4 genes.
Reanalysis Outcome	*H3-3B* VUS upgraded to likely pathogenic, consistent with a diagnosis of Bryant-Li-Bhoj neurodevelopmental syndrome 2.	Maternally inherited pathogenic deletion of exons 7-8 of *RAPSN* detected due to copy number detection enhancements. Biallelic P/LP variants in *RAPSN* are consistent with a diagnosis of congenital myasthenic syndrome 11.

Conclusions

- GS/ES reanalysis identified new genetic diagnoses in almost 9% of cases. This was due to new gene-disease associations that were established since the initial analysis, new phenotypes included with the reanalysis, and improved analytic pipelines to address prior technical limitations.
- Reporting variants in genes with no known disease association identified through initial GS/ES can be informative for clinicians in order to prompt subsequent clinical re-evaluation and reanalysis.
- The incorporation of multi-omic approaches such as RNA sequencing and metabolomics into reanalysis may further improve the diagnostic potential of GS/ES.

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