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Never Stop Looking: Sequential Diagnoses Due to Updated Gene-Disease Relationships in Exome Patients

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BACKGROUND

- Clinical exome sequencing (ES) interpretation is limited by the understanding of gene-disease relationships (GDRs) at the time of testing.
- Reinterrogation of sequence files over time can uncover new clinically relevant findings, leading to the addition of a second diagnosis over time.

METHODS

- 14 years of clinical ES cases were reviewed to identify cases with initial Positive diagnosis plus an additional Positive diagnosis reported later.
- All cases had an additional (sequential) diagnosis due to an updated GDR or mechanism of disease (MOD). Positive diagnosis is (likely) pathogenic variant.
- Both case and GDR-associated phenotypes were encoded as Human Phenotype Ontology (HPO) terms and compared to determine phenotype overlap.

RESULTS

Which Positive cases tend to receive a sequential additional diagnosis? How long does it take to find?

FIGURE 1: Apparent solve state of cases after diagnosis 1

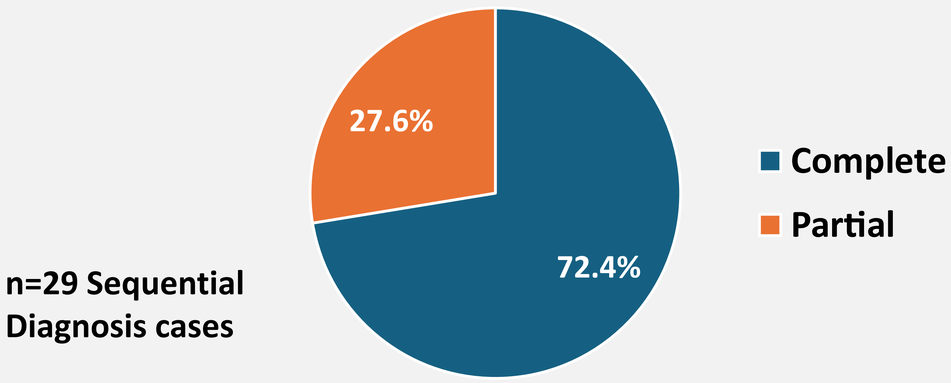
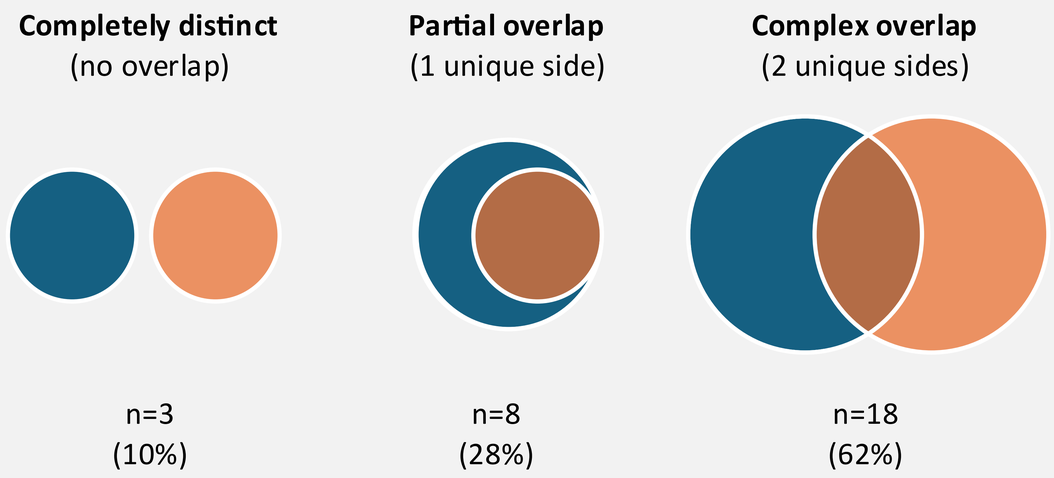


FIGURE 2: Most sequential diagnosis cases have phenotypic overlap between diagnosis 1 and diagnosis 2



Key Finding: 0.5% of initially Positive ES cases received a sequential diagnosis due to updated GDRs

FIGURE 3: Most sequential diagnoses include a neurodevelopmental disorder (NDD) phenotype

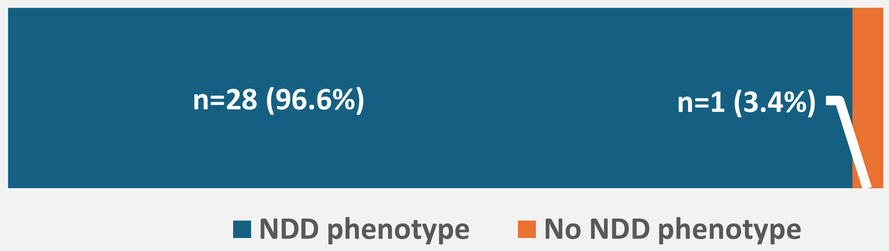
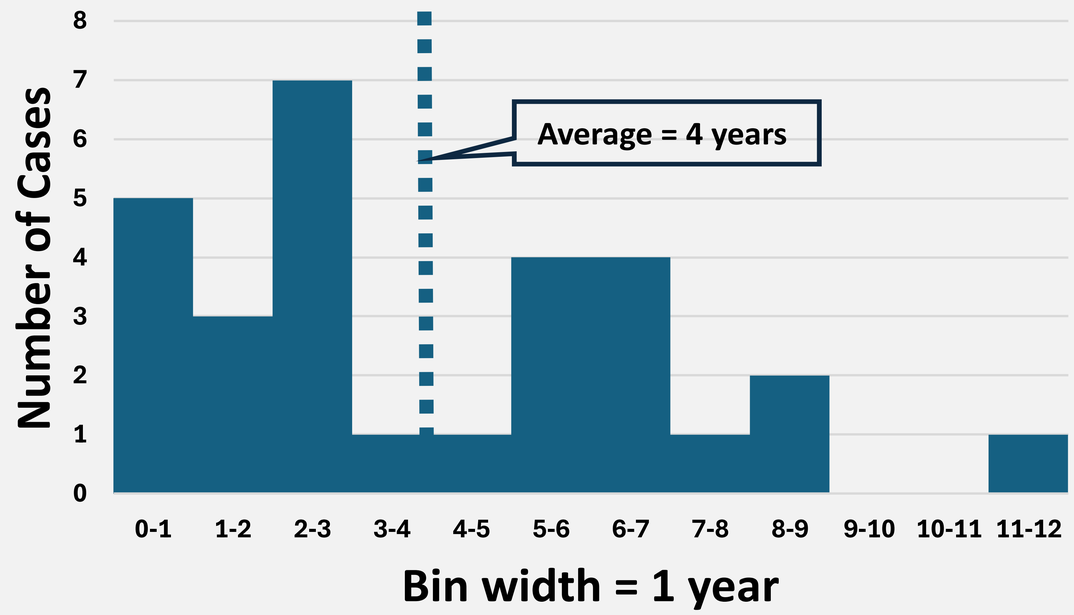


FIGURE 4: Time between diagnosis 1 and diagnosis 2



TAKE HOME POINTS

- Reanalysis of ES cases over time continues to identify new diagnoses, specifically due to updated GDRs and MODs.
- Proactive reanalysis is valuable even in probands with an apparently complete diagnosis. Identification of a sequential diagnosis can more fully explain phenotype.
- Cases with NDD phenotypes may benefit from lab-initiated reanalysis due to potential sequential diagnoses with overlapping features.