Consider the Net You Cast: Multigene Panel Testing Misses 15% of Diagnostic Results Compared to Exome Sequencing

Catherine Schultz, Dana Stolar, Melissa Holman, Carrie Horton, Meghan Towne

Ambry Genetics, Aliso Viejo, CA

Abstract #203

cschultz@ambrygen.com

SCAN ME

BACKGROUND

- Evidence supports exome sequencing (ES) as a first-tier test for intellectual disability (ID), neurodevelopmental disorder (NDD), autism spectrum disorder (ASD), and epilepsy [1,2,3]
- However, MGPT is still widely used for these indications

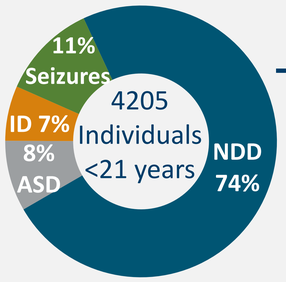
Exome sequencing (ES)
- Lower VUS rate and higher diagnostic yield compared to MGPT[4]
  - Especially in the setting of ES run as trios

Multigene panel testing (MGPT)
- Targeted list of genes associated with the phenotype
- VUS rates on MGPT increase with panel size[4]

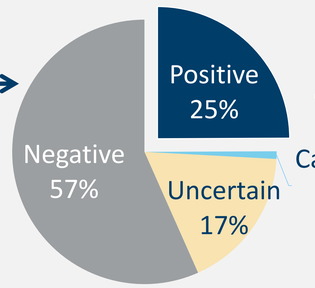
PROJECT AIM: Assess the probability that pathogenic/likely pathogenic (P/LP) variants reported on ES would have been detected on MGPT

METHODS

1 ES run for neuro indications 2016-2021



2 Stratify by report outcomes



Genes with P/LP variants

3 Assess overlap with current MGPT offerings

RESULTS

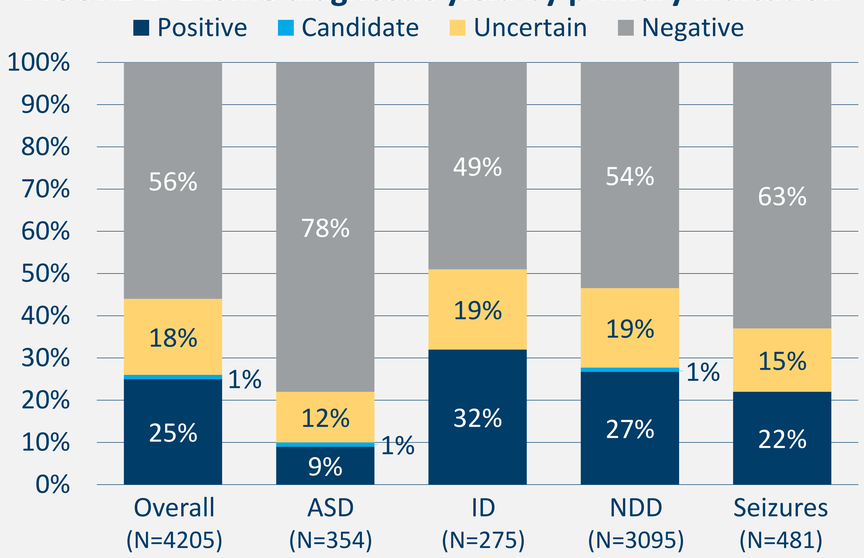
1046 positive ES cases

423 unique genes

29 cases with dual diagnoses

- ES diagnostic yield was 25% (1046/4205) and varied by indication **(Figure 1)**
- 77% of ES were trios which showed 30% increase in diagnostic yield and 40% decrease in uncertain results compared to non-trio ES **(Figure 2)**
- 15% of positive cases (161/1046) would have had ≥1 P/LP variants missed if only MGPT was ordered **(Figure 3)**
  - 2/3 of missed genes were reported in single patients, representing more rare genetic etiologies

FIGURE 1. Exome diagnostic yield by primary indication



TAKE HOME POINTS

Multigene panel testing missed 15% of diagnostic results compared to exome sequencing

Over half of patients with multiple diagnosis would not have been detected with MGPT

Trios provide variant segregation data which reduces VUS rates and increases diagnostic rates

FIGURE 2. Impact of trio-based ES testing on overall result

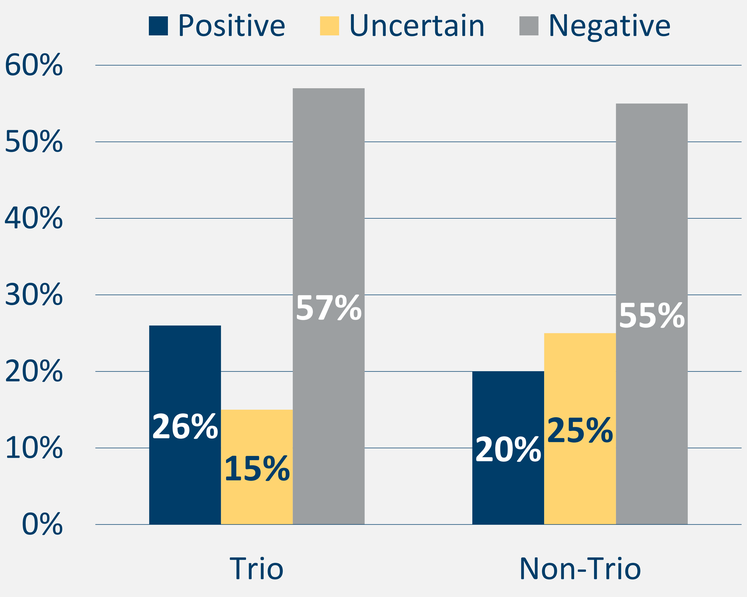
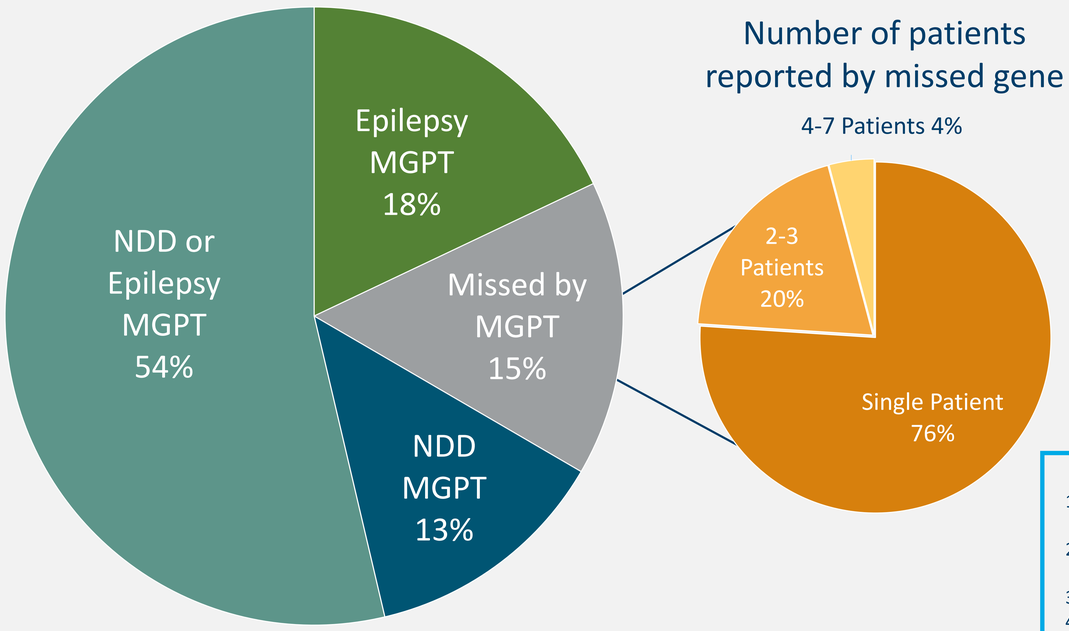
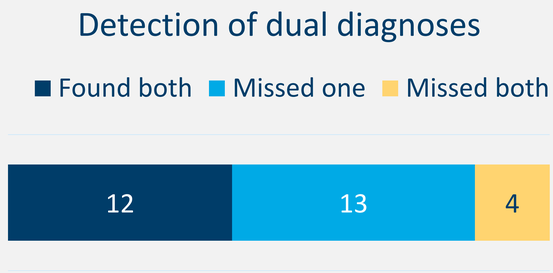


FIGURE 3. Detection of Genes with P/LP variants by MGPT Type





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