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Diagnostic Exome Sequencing in Adults with Neurological Disorders

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BACKGROUND

- Diagnostic exome sequencing (DES) is increasingly utilized in identifying genetic etiologies and informing medical management decisions for neurological disorders in pediatric patients.
- There is a lag in adoption of DES in the adult neurology population due to limited guidelines and the perception that testing is primarily experimental.
- Existing test utilization studies in adult populations represent small cohorts within one specialty clinic (Bardakjian *et al.*, 2018).
- Herein, we report characteristics and diagnostic rates in a large cohort of adult patients with neurological disorders undergoing DES.

METHODS

- Clinical and genetic testing histories were reviewed for an unselected cohort of 2,127 adults (age ≥ 18 years) with neurological findings referred for DES at one commercial laboratory between January 2012 and July 2019.
- Patients with only one unprovoked seizure or whose neurological features were secondary to another health condition (e.g. cardiovascular involvement such as stroke) were excluded from analysis.
- A primary neurological indication was assigned to each patient based on available clinical histories (Table 1).
- Overall result categories (Negative, Uncertain, Likely Positive, and Positive) were determined according to predefined diagnostic variant assessment criteria and assessment of clinical overlap (Farwell *et al.*, 2015).
- Statistical analyses were performed using Fisher's exact test.

Table 1. Primary Neurological Indication Categories

CATEGORY	DEFINITION
ASD	Autism Spectrum Disorder
DD/ID	Developmental Delay/Intellectual Disability
MNP	Mixed Neurological Phenotype
MD	Movement Disorder
MMP	Multi-Organ Mixed Phenotype
NC	Neurocognitive Disorder
NDD	Neurodevelopmental Disorder (seizures with ASD and/or DD/ID)
NMD	Neuromuscular Disorder
EP	Isolated Epilepsy

RESULTS

- 916/2,127 probands (43.1%) met the criteria for one of the clinical indication categories.
  - 474 (51.7%) were male and 442 (48.3%) were female.
  - Average age at testing was 30.7 years (range 18 – 88).
  - 869 (94.9%) patients had additional clinical findings beyond their primary neurological indication (Figure 1).
- A positive/likely positive report was issued to 181 (19.8%) individuals for a phenotypically-relevant alteration in 147 characterized genes, while 163 (17.8%) patients had an uncertain overall result for inconclusive findings in 156 characterized gene. Novel candidate gene findings were identified in 8/457 (1.8%) patients who underwent uncharacterized gene analysis, most of whom were patients with MNP (4/76, 5.3%). Negative results were reported in 564 (61.6%) patients.
- Patients with DD/ID, NDD, and MMP* had the highest diagnostic yields compared to other indications, while MD*, NMD*, and EP* were significantly less likely to have a P/LP result (*p<0.05) (Figure 2).
- In patients with previous genetic testing (714; 77.9%), the diagnostic yield was 21.1% (151/714), which is significantly higher than the diagnostic yield of patients with no reported previous testing (30/202; 16.6%) (p=0.05) (Figure 3).
  - Of the previous multigene panel testing (MGPT) performed, 187 (84.2%) were for neurological indications
- Diagnostic rates were highest for probands with informative family members available for trio analysis (Figure 4).

Figure 1. Additional Clinical Findings

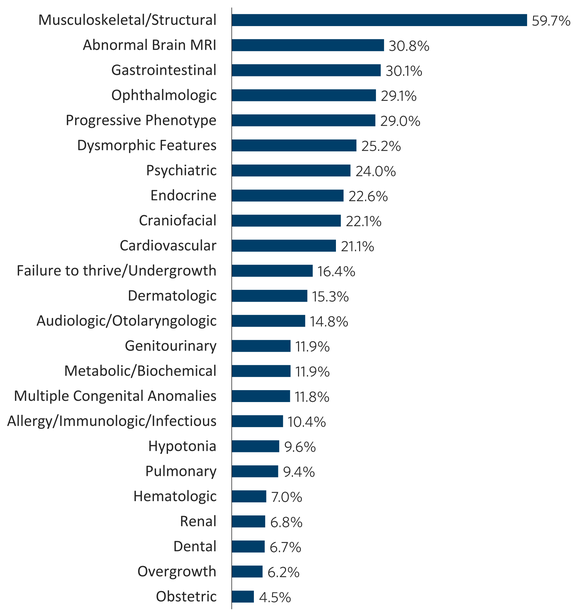

Figure 2. Overall Detection Rates by Primary Neurological Indication

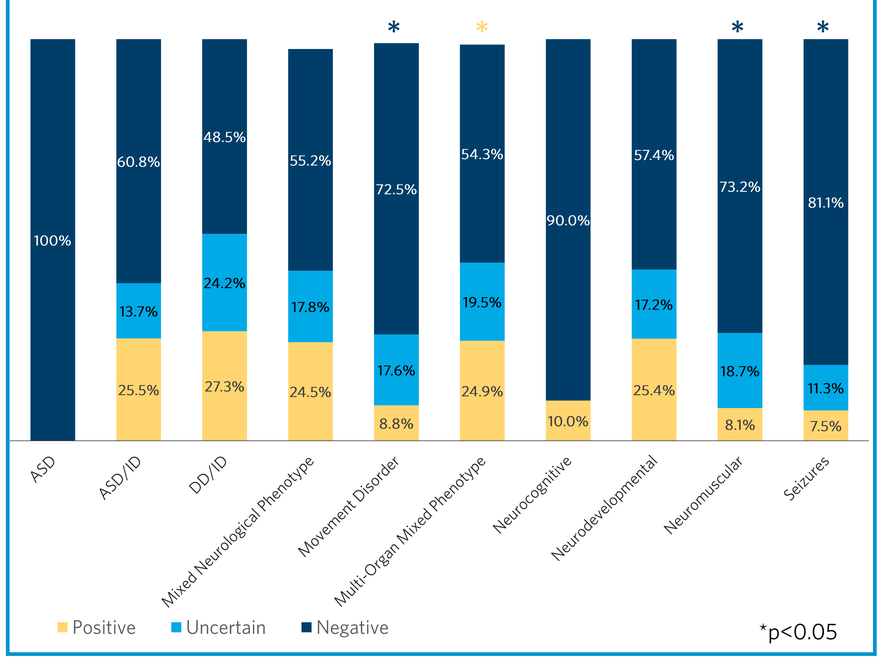

Figure 3. Previous Genetic Testing

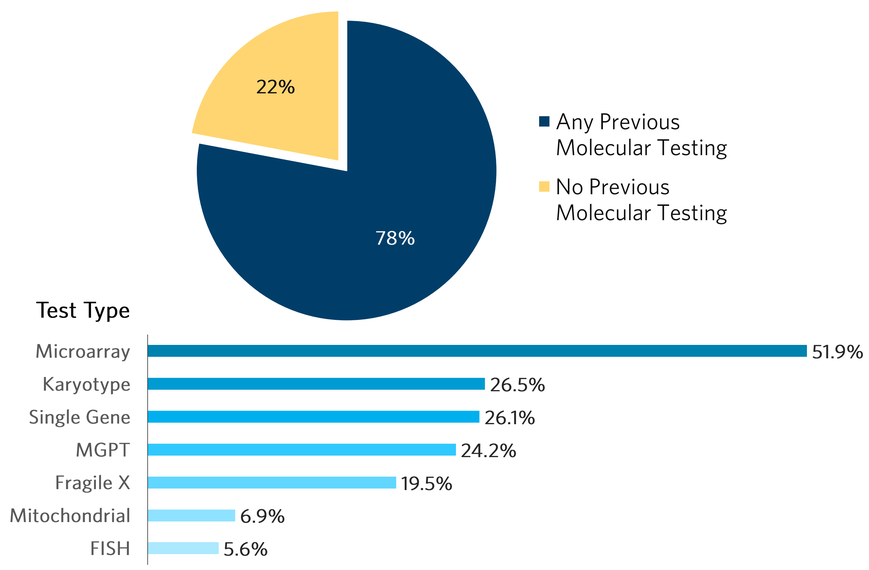

Figure 4. Overall Detection Rates for Proband-Only, Duo, and Trio Analysis

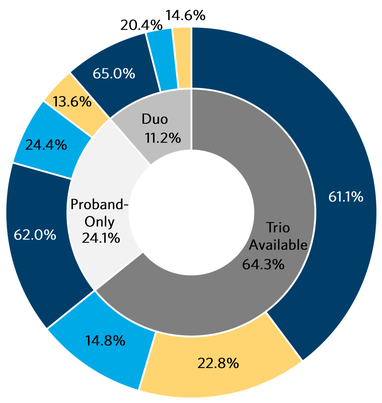

Figure 4a. Adult neurology DES cohort

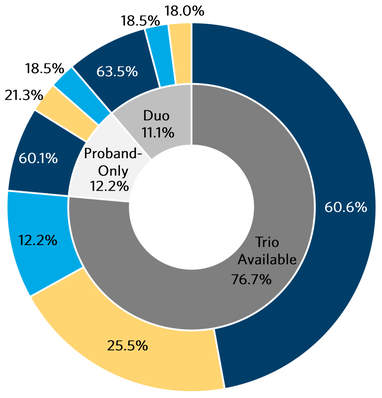

Figure 4b. Overall DES cohort

Positive
Uncertain
Negative

TAKE-HOME POINTS

- DES is a valuable tool for diagnosing adults with neurological disorders, particularly for patients with DD/ID and complex phenotypes (NDD and MMP).
- The diagnostic yield for patients who had negative previous genetic testing was higher than patients who had no testing prior to DES, and in some cases the reported alteration was in an uncharacterized or newly characterized gene which was not included on the MGPT.
- While parental samples may be more difficult to obtain for adult patients, trio analyses with informative family members' samples were associated with higher diagnostic rates and helped to confirm *de novo* occurrence of a result in more than a third of results.

REFERENCES

1. Bardakjian TM, et al. (2018). Genetic test utilization and diagnostic yield in adult patients with neurological disorders. *Neurogenetics* 19:105-110. DOI:10.1007/s10048-018-0544-x.
2. Farwell KD, et al. (2015). Enhanced Utility of Family-Centered Diagnostic Exome Sequencing With Inheritance Model-Based Analysis: Results From 500 Unselected Families With Undiagnosed Genetic Conditions. *Genetics in Medicine* 17(7):578-86.