Diagnostic Utility of Whole Exome and Genome Sequencing Among Adult Patients

Robert Rigobello, MS, CGC[1], Xiaonan Zhao, PhD[1,2], Leah Campbell, MS, CGC[1], Eileen Barr, MS, CGC[1], Lisa Salz, MS, CGC[1], Sydney A. Lau, MS, CGC[1], Jason Chibuk, MS, CGC[1], Linyan Meng, PhD, FACMG[1,2], Fan Xia, PhD, FACMG[1,2], Christine M. Eng, MD[1,2]

1. Baylor Genetics, Houston, TX, USA
2. Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, TX, USA

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Background

- Medical professional organizations such as the American College of Medical Genetics and Genomics (ACMG) and American Academy of Pediatrics (AAP) have endorsed genome sequencing (GS) and exome sequencing (ES) as first-tier genetic tests for pediatric patients with congenital anomalies, developmental delays (DD), and intellectual disability (ID).[1,2]
- While there is ample literature on the diagnostic utility of GS/ES for pediatric patients, literature on adult cohorts is more limited.
- Adult cohorts are often of limited size, within a single healthcare system, and/or focused on specific indications.
- We present analysis of diagnostic yields and other trends within an adult cohort tested by GS/ES at our clinical diagnostics laboratory.

Methods

Study Design: Retrospective review of consecutive GS/ES cases

Inclusion Criteria:

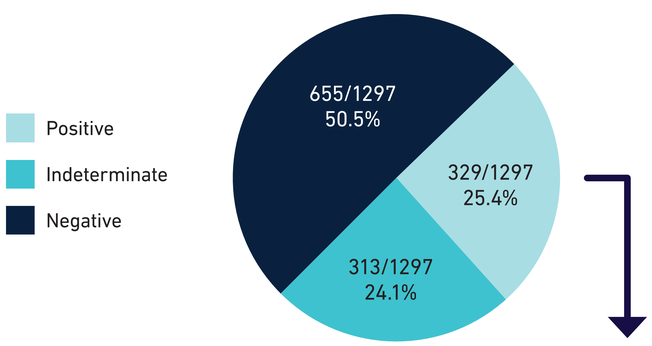
- GS/ES completed at one clinical laboratory
- Patient was 18 years of age or older at the time of testing

Analysis:

- We reviewed the clinical and genetic data to determine the frequency of positive results (defined as pathogenic and likely pathogenic variants associated with the clinical indication) detected by GS/ES.
- Patients were grouped by age (18-24, 25-34, 35-44, 45-54, 55-64, and 65+) and clinical indication for testing for further analysis.

Results

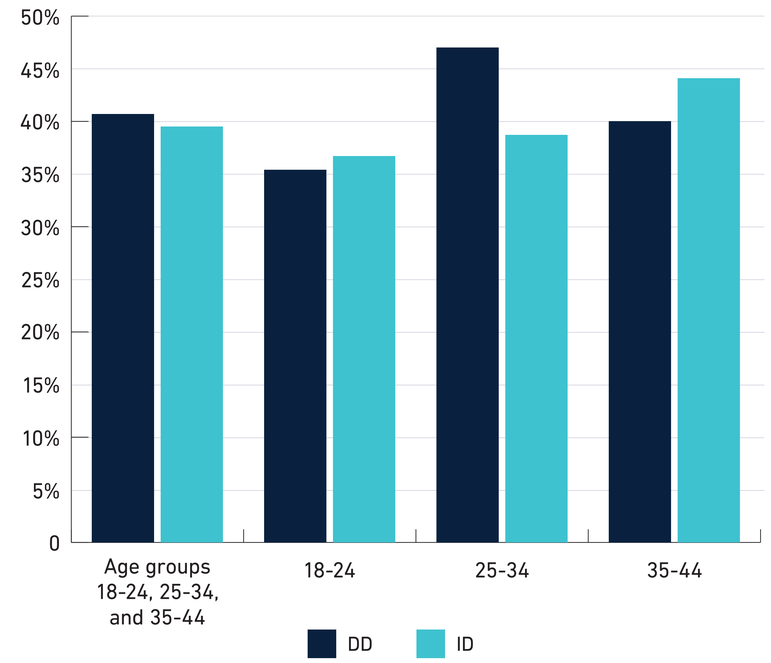
Overall Diagnostic Yield



Quick Facts About Positive Results

- The **18-24 and 65+** groups had the highest diagnostic yields (91/333, **27.3%** and 82/307, **26.7%**, respectively), while the 55-64 group had the lowest yield (26/122, 21.5%).
- **GS yield** was higher than ES yield (249/968, **25.7%** vs 80/329, 24.3%).
- Diagnostic yield was 24.1% (200/830) for proband-only testing compared to 27.8% (131/472) for patients with familial comparators.
- Variant types included single nucleotide variants, copy number variants, short tandem repeat (STR) expansions, and mitochondrial variants.

Diagnostic Yield for DD/ID Across Age Groups



The overall diagnostic yield for DD and ID was 40.3% (64/159) and 38.7% (75/194).* Diagnostic yield was highest for patients age 25-34 with DD (20/43; 46.5%) and patients age 35-44 with ID (15/34, 44.1%).

*Age groups 45-54, 55-64, and 65+ were excluded as each group had 10 or fewer patients with DD and/or ID.

Among GS cases, 75 patients had pathogenic STR expansions, with over two-thirds having expansions within spinocerebellar ataxia (SCA)-associated genes. 94% (45/48) of patients with SCA27B were over 65 years old.

GENE (ASSOCIATED DISORDER)	# OF PATIENTS
FGF14 (SCA27B)	48
ATXN8OS (SCA8)	3
ATXN2 (SCA2)	2
FXN (Friedreich ataxia)	6
TCF4 (Fuchs endothelial corneal dystrophy 3)	3
ATN1 (dentatorubral-pallidoluysian atrophy)	1
HTT (Huntington disease)	3
CNBP (congenital myotonic dystrophy 2)	2
DMPK (congenital myotonic dystrophy 1)	4
FMR1 (Fragile X syndrome)	2
CSTB (progressive myoclonic epilepsy 1A)	1

Conclusions

- **This cohort's diagnostic yield was approximately 25% across all ages reviewed, with ~40% yields among patients with ID and DD. These yields are similar to those for pediatric patients that benefit from ACMG and AAP guidelines.**
- **Most of this cohort were adults prior to these guidelines existing, many having decades-long diagnostic odysseys.**
- **These findings support broadening testing guidelines to include adult patients, particularly for those with DD and ID.**
- **GS has additional utility given its enhanced yield for findings including SCA expansions in older patients and other variants that ES might not capture.**

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References:

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2. Rodan, L.H., Stoler, J., Chen, E., Geleske, T., & the Council on Genetics. (2025). Genetic Evaluation of the Child With Intellectual Disability or Global Developmental Delay: Clinical Report. *Pediatrics*, e2025072219. https://doi.org/10.1542/peds.2025-072219