

Introduction

- As of June 2025, the American Academy of Pediatrics (AAP) now recommends genome sequencing (GS) or exome sequencing (ES) as a first-tier diagnostic test for global developmental delay (GDD) and intellectual disability (ID).¹
- Compared to ES, GS captures a broader spectrum of variant types such as short tandem repeat (STR) expansions, mitochondrial genome variants, and noncoding variants.
- However, the extent to which GS impacts the diagnostic yield in children with GDD/ID is incompletely characterized.

Methods

- We conducted a retrospective analysis of consecutive GS cases performed at our clinical diagnostic laboratory after the AAP guidelines were published.
- Inclusion criteria consisted of (1) the individual was less than 18 years old at time of testing, (2) clinical indication of GDD/ID, and (3) GS results were positive.
- Positive results included pathogenic or likely pathogenic (P/LP) variants associated with the clinical phenotype.
- Cases were reviewed to determine genetic diagnoses that involved the detection of variants with limited to no coverage on ES, including STR expansions, mitochondrial genome variants, noncoding variants, complex structural variants, copy number variants (CNVs) smaller than 10 kb, and uniparental disomy.
- This study was conducted under the approval of the Baylor College of Medicine Institutional Review Board (H-41191).

Comparison of detection capabilities of ES and GS for different variant types.

	Exome Sequencing	Genome Sequencing
Deep Intronic Variants		Capable
Copy Number Variants	Limited	Capable
Short Tandem Repeat Expansions		Capable
Noncoding Variants		Capable
Mitochondrial Genome Variants		Capable
Complex Structural Variants		Limited

Capable Limited

Results

Figure 1. Selection of study cohort.

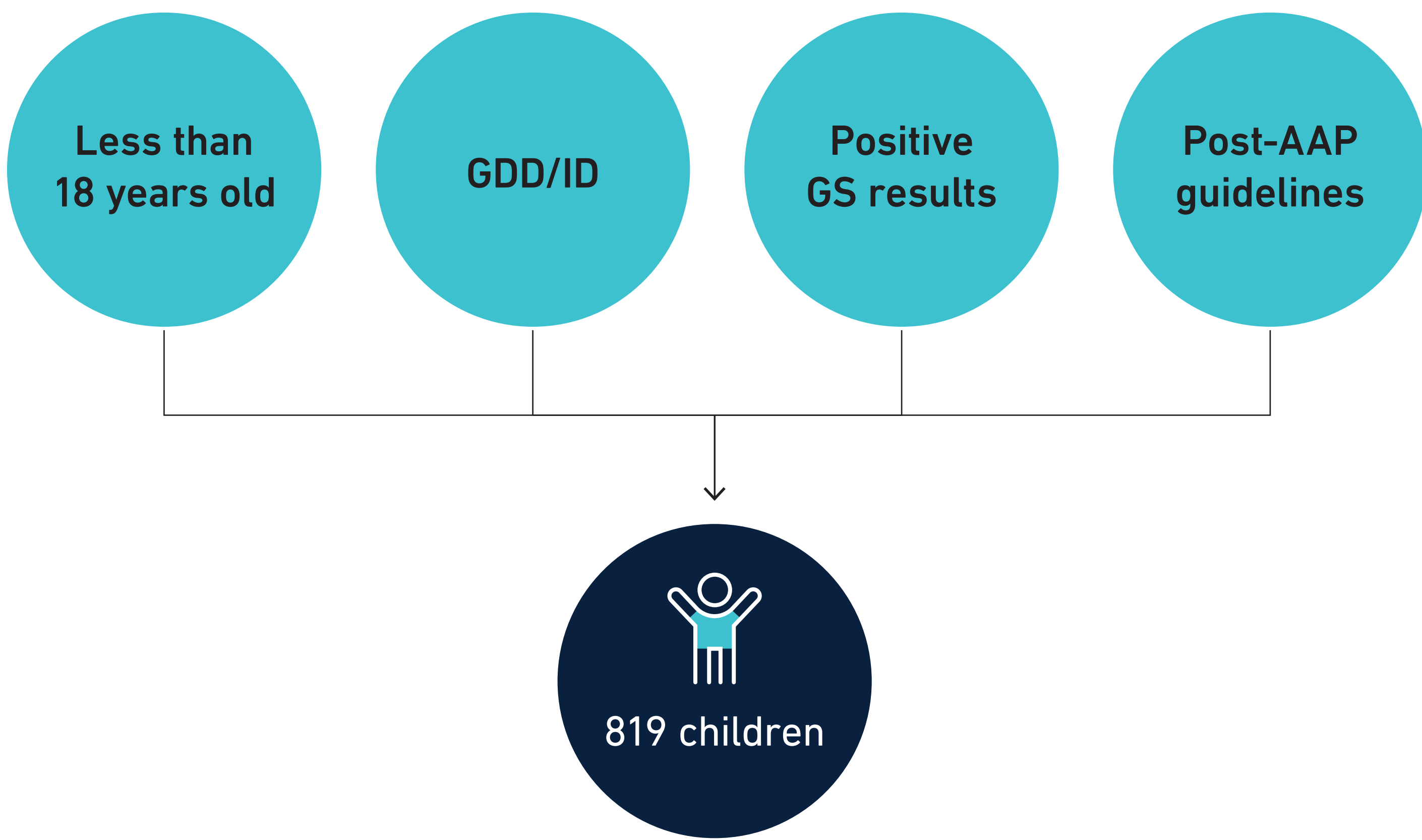


Figure 3. Proportion of positive GS cases that involved a diagnostic variant with limited to no coverage on ES.

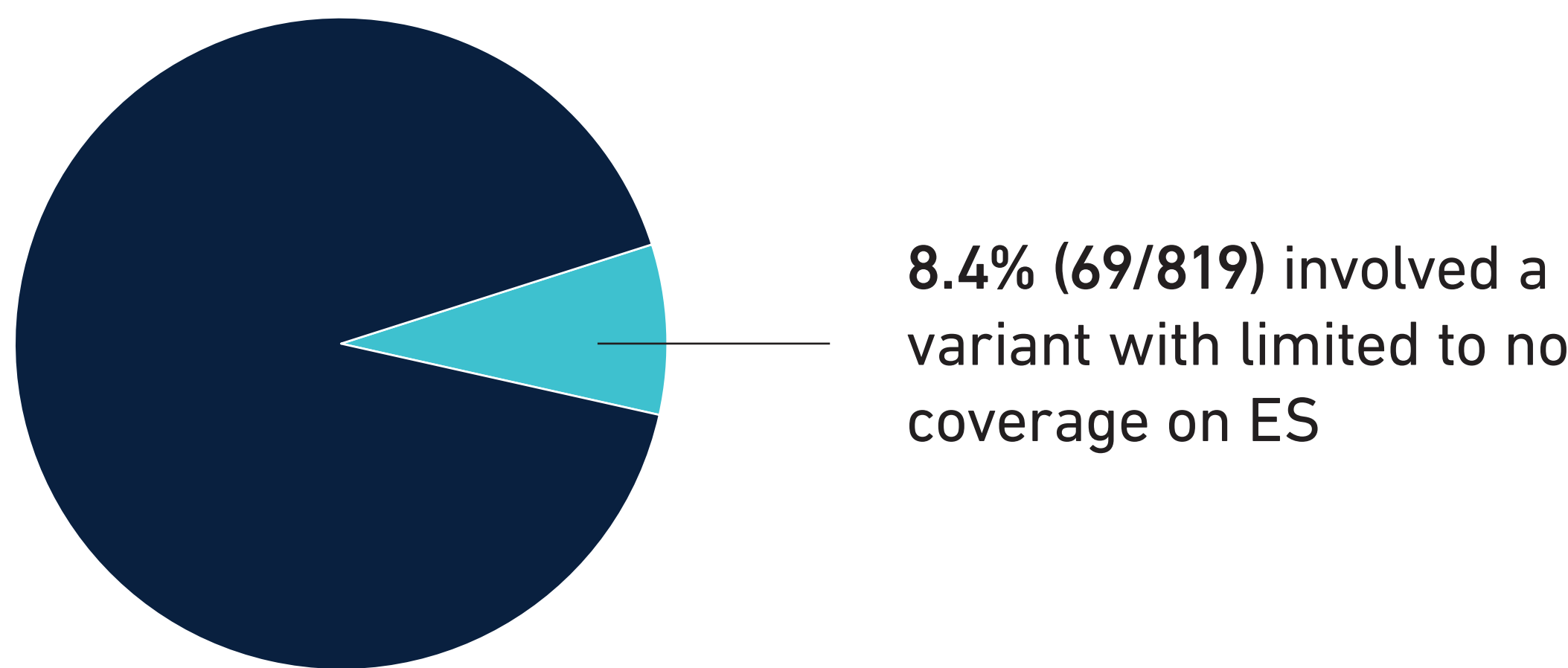


Figure 2. Positive cases stratified by sex, test type, and turnaround type.

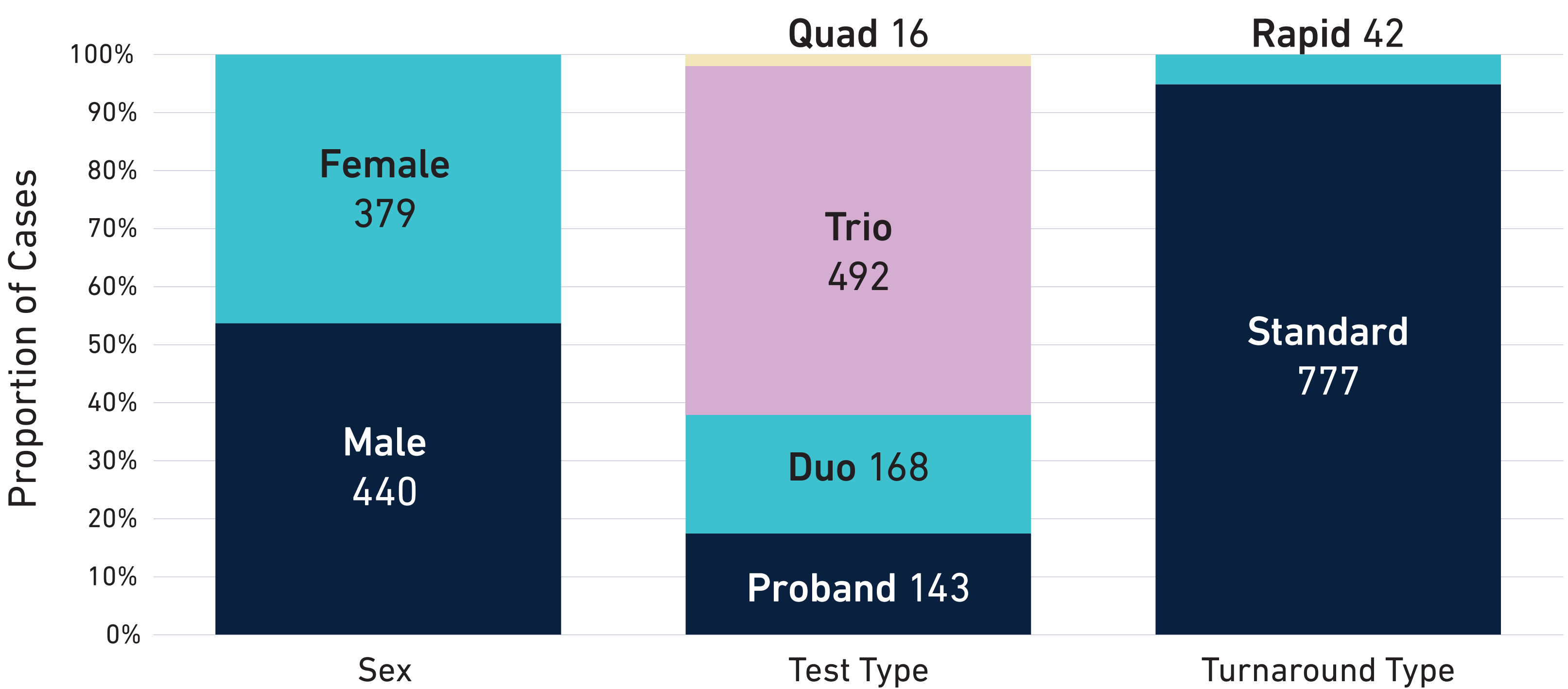


Table 1. Number of cases with different variant types detected through GS.

Variant Type	Number of Cases
Short Tandem Repeat Expansions	17
Mitochondrial Genome Variants	14
Noncoding RNA Gene Variants	13
Complex Structural Variants	10
Copy Number Variants < 10 kb	8
Deep Intronic Variants (> 50 bp from intron-exon boundary)	6
Uniparental Disomy	1

Figure 4. Additional information regarding genetic diagnoses established for each variant type category.

STR Expansions

- Most commonly in *DMPK* (myotonic dystrophy 1) and *FMR1* (fragile X syndrome)

Mitochondrial Genome Variants

- Six homoplasmic variants and eight heteroplasmic variants detected
- P/LP variants were most commonly identified in *MT-TL1*, *MT-ND1*, *MT-ND4*, and *MT-ND6*

Noncoding RNA Gene Variants

- Twelve children were diagnosed with ReNU syndrome due to variants in *RNU4-2*

Complex Structural Variants

- Four cases involved both duplications and triplications

Small CNVs

- Deletions and duplications between 0.28 kb and 7.33 kb
- For those with a small CNV associated with an autosomal recessive condition, another CNV or single nucleotide variant was reported in trans

Deep Intronic Variants

- Three variants had upgraded variant classifications through targeted reflex RNA sequencing

Uniparental Disomy

- Diagnosis of Angelman syndrome due to paternal uniparental isodisomy of chromosome 15

Conclusions

- In total, 8.4% of children received a genetic diagnosis that involved the detection of a variant with limited to no coverage on ES.
- These findings support the utilization of GS as a first-tier diagnostic tool for children with GDD/ID, allowing for greater diagnostic yields and more informed medical management.
- Additional technologies such as long-read sequencing and optical genome mapping could be used to support GS to further increase diagnostic yield and provide clarity on results.