GENT200

The Diagnostic Yield of Exome and Genome Sequencing in a Large and Diverse Cohort of Over 300,000 Patients: Context Matters

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Background

- Exome and genome sequencing (ES/GS) are foundational tools in rare disease diagnostics, with reported molecular diagnostic yields ranging from 23% to 38%.[1,2]
- The wide range in diagnostic yield reflects variability in tested populations, including age, phenotype severity, and clinical indications, which collectively influence the likelihood of an underlying genetic etiology.
- Reported yields also vary depending on whether analyses include clearly causative variants only, or also those considered possibly contributory.
- **We present real-word data on the diagnostic yield of ES/GS from a large and diverse cohort of individuals tested at a clinical diagnostic laboratory.**

Methods & Cohort

- We retrospectively analyzed results from **329,684 patients** that underwent ES/GS between **July 2013 and December 2025** and had appropriate consent for inclusion in de-identified research.
- Diagnostic yield was calculated as the combined proportion of patients with either a **Definitive Molecular Diagnosis (DDx)**✶ or a **Possible Molecular Diagnosis (PDx).**✢
- Patients were grouped by:
  - **Reported clinical features:** multiple congenital anomalies [MCA], neurodevelopmental disorder [NDD], seizures, autism, or concurrent MCA and NDD [MCA/NDD]
  - **Age:** neonatal/infant [0 to <2 years], pre-school child [2–5 years], school-age child and adolescent [6–17 years], adult [≥18 years]
  - **Testing modality:** rapid vs. standard turnaround time [TAT]

Cohort Characteristics

Figure 1. Distribution of Genetic Ancestry in the Study Cohort

Percentages reflect group proportions; counts are shown in the legend.
*Indicates ancestry not calculated.

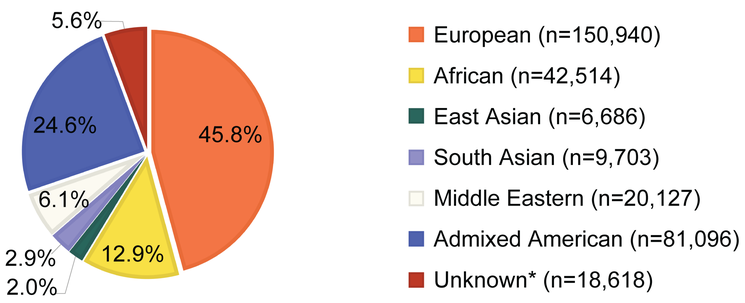


Table 1. Demographics of the study cohort.

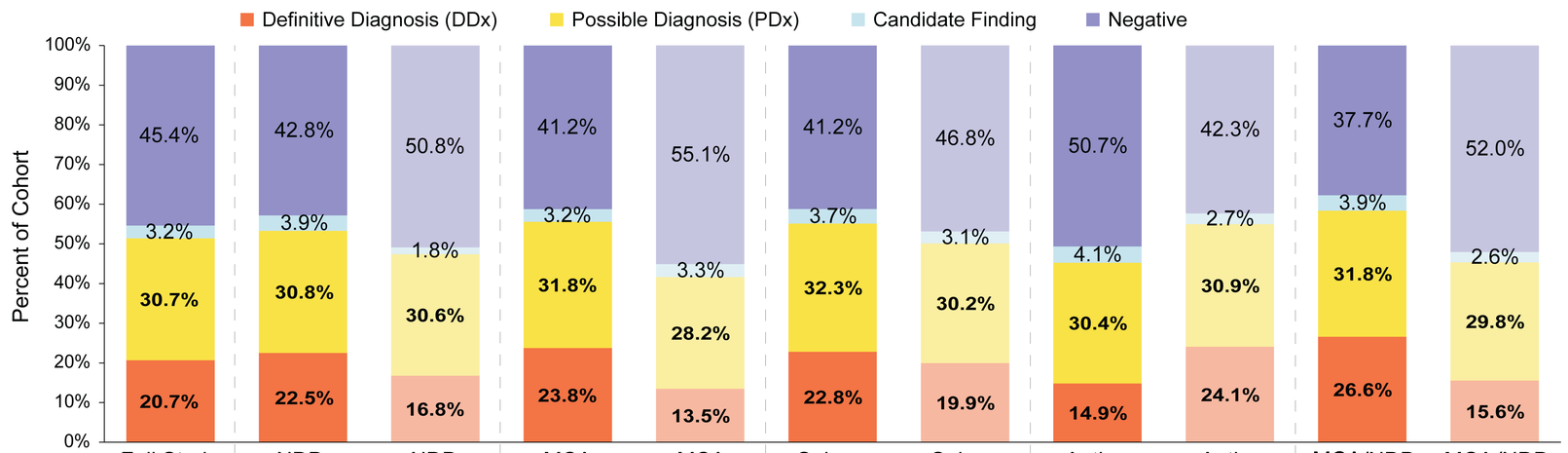
Values are shown as number of individuals and percentage of the total cohort.

Characteristic		n (%)
Sex assigned at birth	Female	137,537 (41.7)
	Male	192,117 (58.3)
	Unknown	30 (0.01)
Age at testing (range 0-89 years)	0 to <2 years	48,795 (14.8)
	2 to 5 years	100,494 (30.5)
	6 to 17 years	125,150 (38.0)
	≥18 years	54,913 (16.7)

Results

Figure 2. Diagnostic Yield by Clinical Indication at the Time of Testing

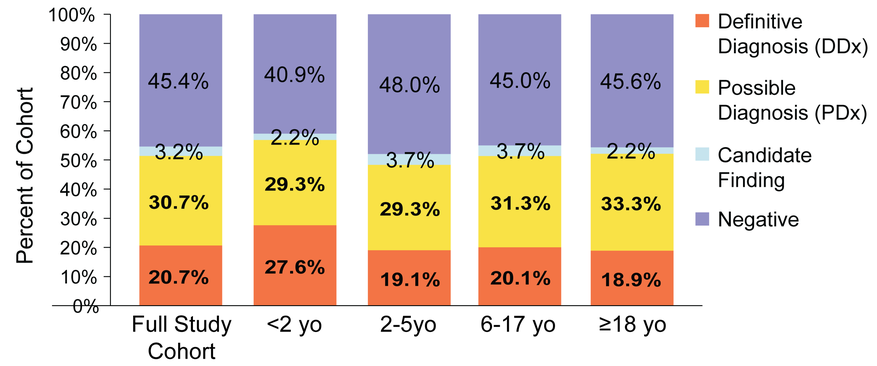
Clinical indication categories are non-exclusive. Bars show diagnostic outcome distributions within each subgroup. Patients may appear in multiple groups. Percentages reflect subgroup distributions, not unique individuals.



	Full Study Cohort	NDD Present	NDD Absent	MCA Present	MCA Absent	Seizure Present	Seizure Absent	Autism Present	Autism Absent	MCA/NDD Present	MCA/NDD Absent
N	329,684	223,813	105,871	230,817	98,867	84,983	244,701	121,005	208,679	153,445	176,239
Diagnostic Yield (DDx + PDx)	51.4%	53.3%	47.4%	55.6%	41.6%	55.1%	50.1%	45.3%	55.0%	58.4%	45.3%

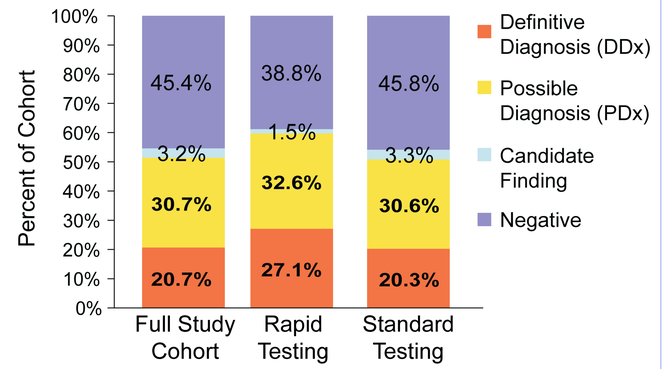
Figure 3. Diagnostic Yield by Age Group

Patients with missing age data (n=322) are included only in the overall cohort.



	Full Study Cohort	<2 yo	2-5yo	6-17 yo	≥18 yo
N	329,684	48,795	100,494	125,150	54,913
Diagnostic Yield (DDx + PDx)	51.4%	56.9%	48.3%	51.4%	52.2%

Figure 4. Diagnostic Yield by Testing Modality



	Full Study Cohort	Rapid Testing	Standard Testing
N	329,684	20,885	308,799
Diagnostic Yield (DDx + PDx)	51.4%	59.7%	50.8%

Figure 5. Multivariable Logistic Regression of Factors Associated with Definitive Diagnosis (DDx)

Odds ratios (ORs) with 95% confidence intervals shown; dashed line indicates OR=1.

The following variables were associated with **higher DDx**:
- MCA (OR=1.54)
- NDD (OR=2.56)
- Trio testing (OR=1.39)
- Rapid testing (OR=1.37)

In contrast, older age at testing was associated with **lower odds** (OR=0.66-0.83).



Conclusions

- ES and GS effectively establish molecular diagnoses across diverse age groups, clinical indications, and genetic ancestries in routine clinical practice.
- This study represents a large and diverse evaluation of diagnostic yield across age, indication, and testing modality. The highest diagnostic yields were observed in:
  - Neonates and infants at 56.9% (27.6% DDx)
  - Rapid sequencing cases at 59.7% (27.1% DDx)
- Stratified analyses demonstrate that diagnostic yield is strongly shaped by testing context, including age, phenotype complexity, and testing modality.
- These findings provide a large-scale clinical benchmark for ES/GS outcomes and support their role in ending prolonged diagnostic odysseys.

Contact info
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References
1. Chung Y, et al. Genetics in Medicine. 2023.
2. Pandey K, et al. Genetics in Medicine. 2025.

Definitions
✶Definitive Dx: P/LP variant(s) in validated disease genes consistent with the reported phenotype.
✢Possible Dx: P/LP/VUS variant(s) in validated disease genes that are possibly associated with the reported phenotype.

Disclosures
Authors were employees of GeneDx at the time the work was completed and may be shareholders GeneDx

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