

Introduction

- Genome sequencing (GS) and exome sequencing (ES) have become key clinical diagnostic tools for individuals with congenital anomalies, and the American College of Medical Genetics and Genomics has recommended GS/ES as a first-tier test for children with congenital anomalies since 2021.¹
- Although the utility of GS/ES have been demonstrated across clinical settings, most of the existing literature involves pediatric cohorts with congenital anomalies that also have some degree of neurodevelopmental phenotype or infants with congenital anomalies in which neurodevelopmental phenotypes may not have been observed at the time of testing.²
- Therefore, data regarding the utility of GS for individuals with congenital anomalies in the absence of neurodevelopmental indications is limited.

Results

Figure 1. Demographic and test characteristics for the study cohort.

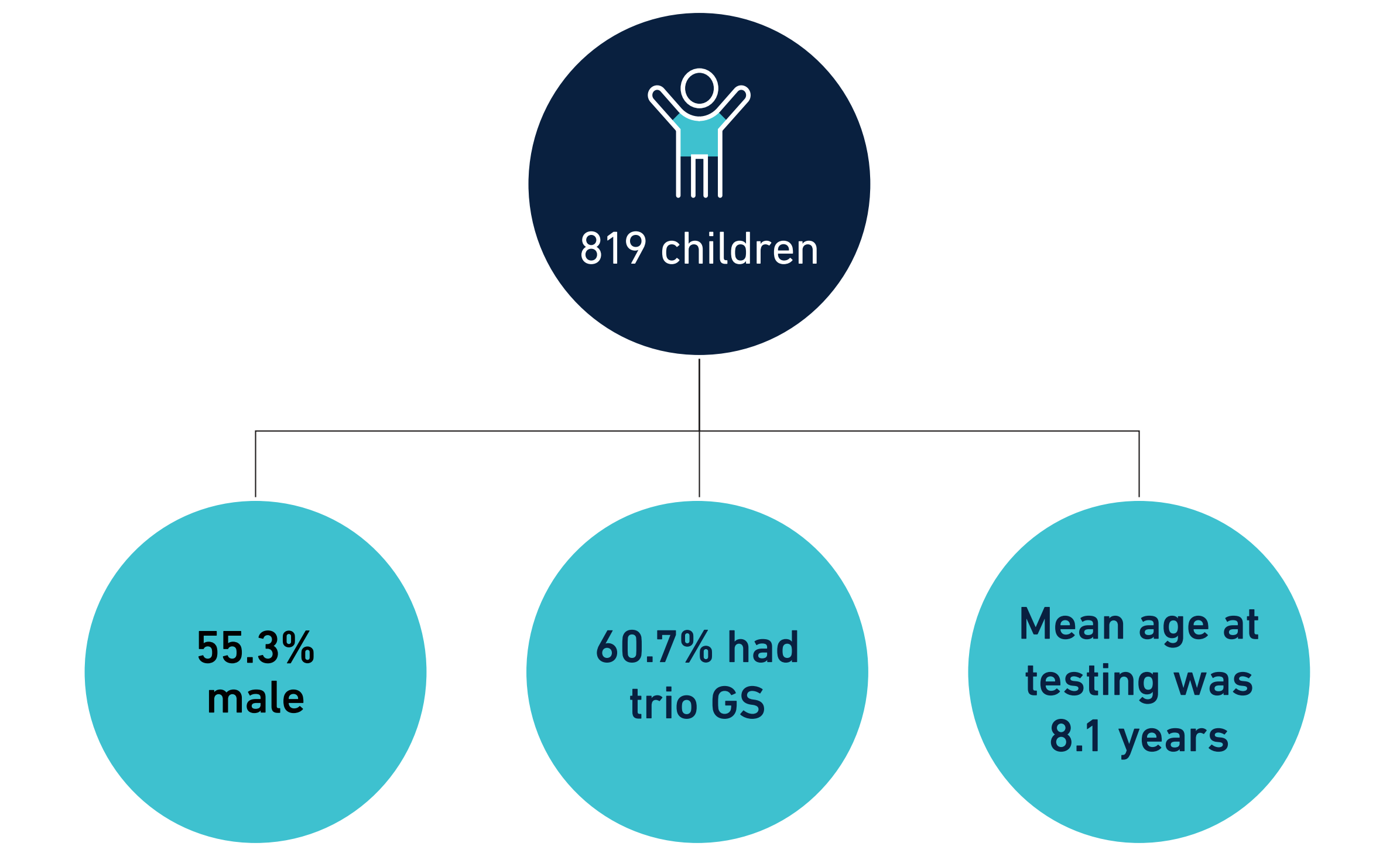


Figure 2. Number of cases with increasing counts of congenital anomalies included in the clinical indication for GS.

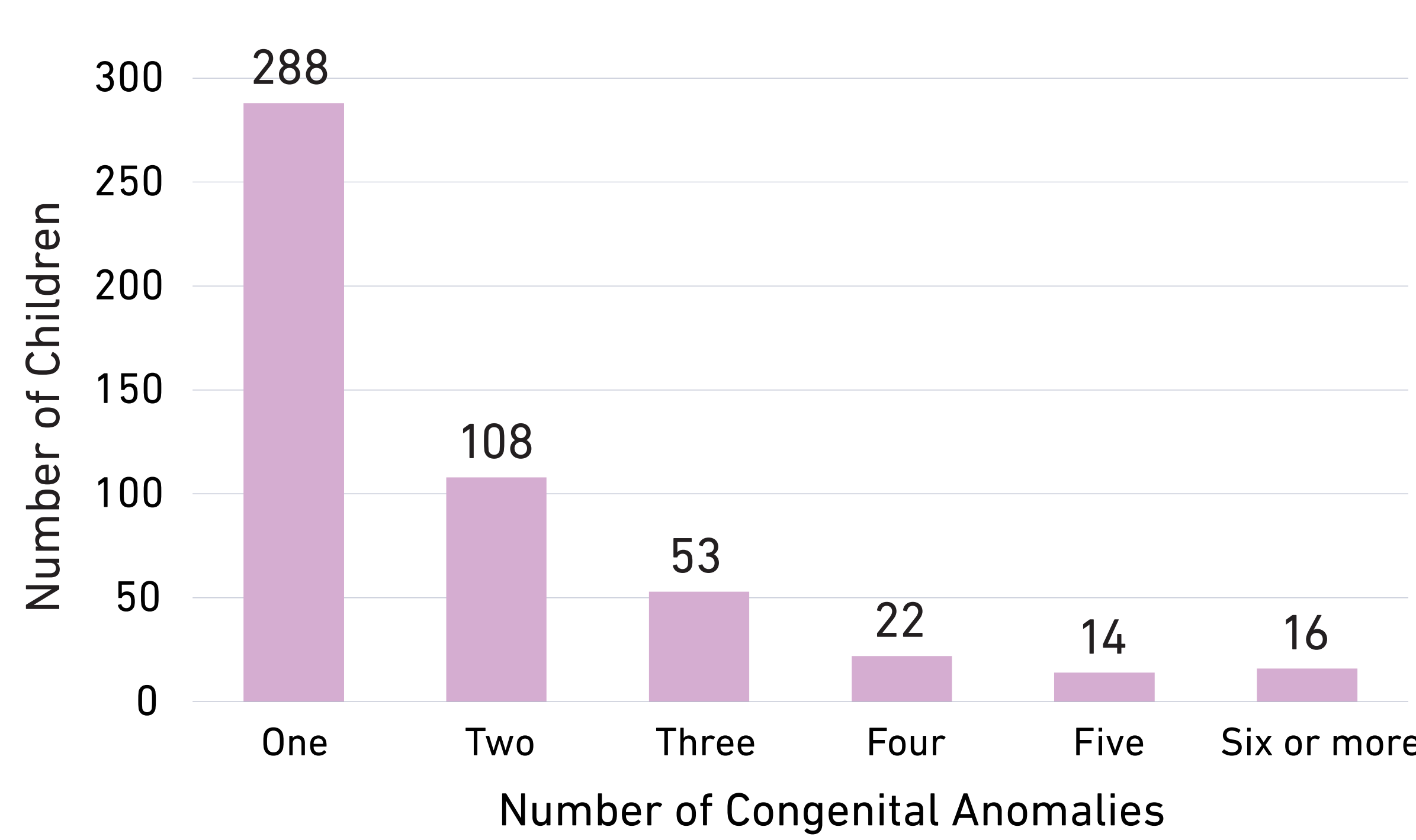


Figure 3. Overall GS results for children with congenital anomalies in the absence of neurodevelopmental indications.

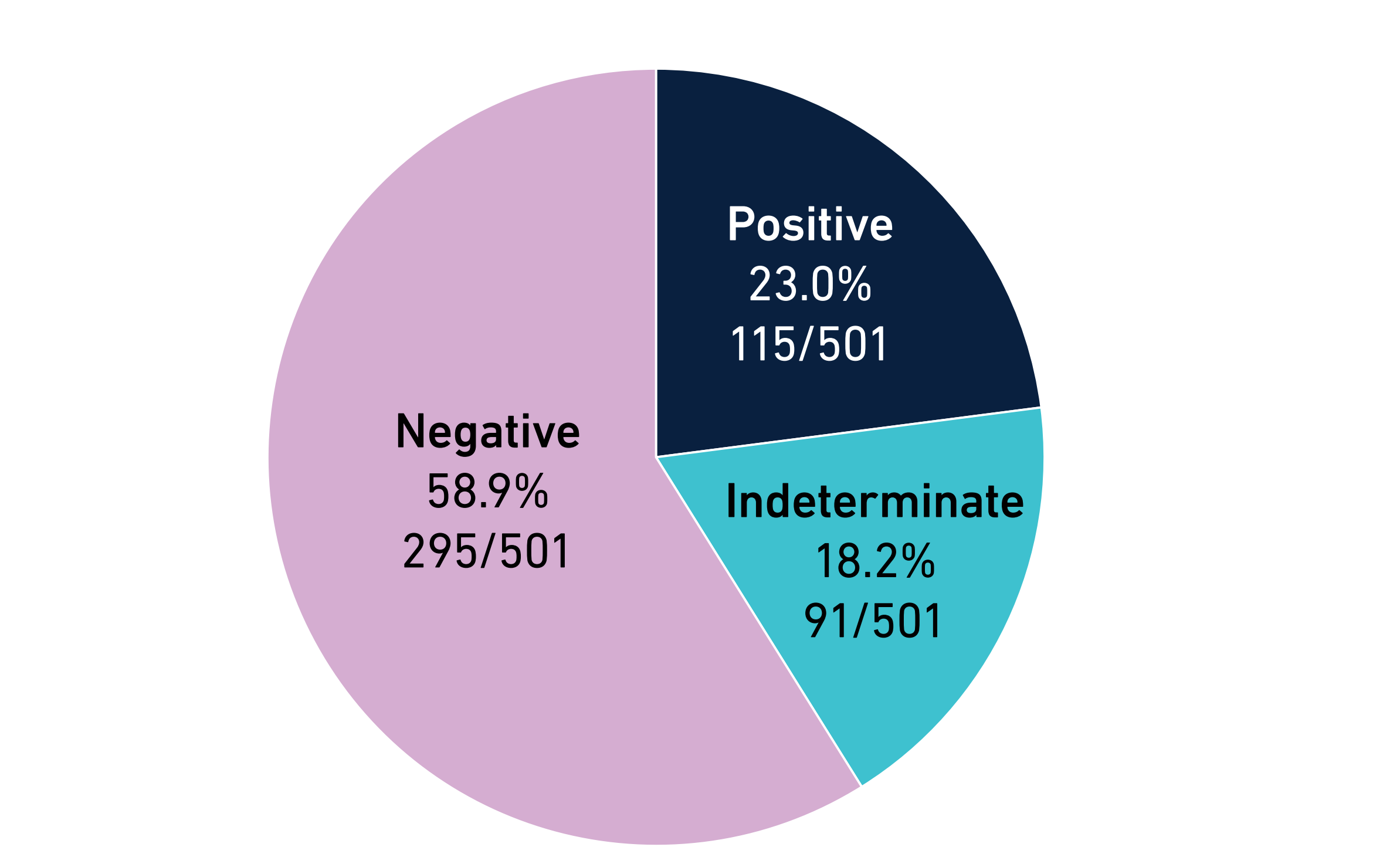
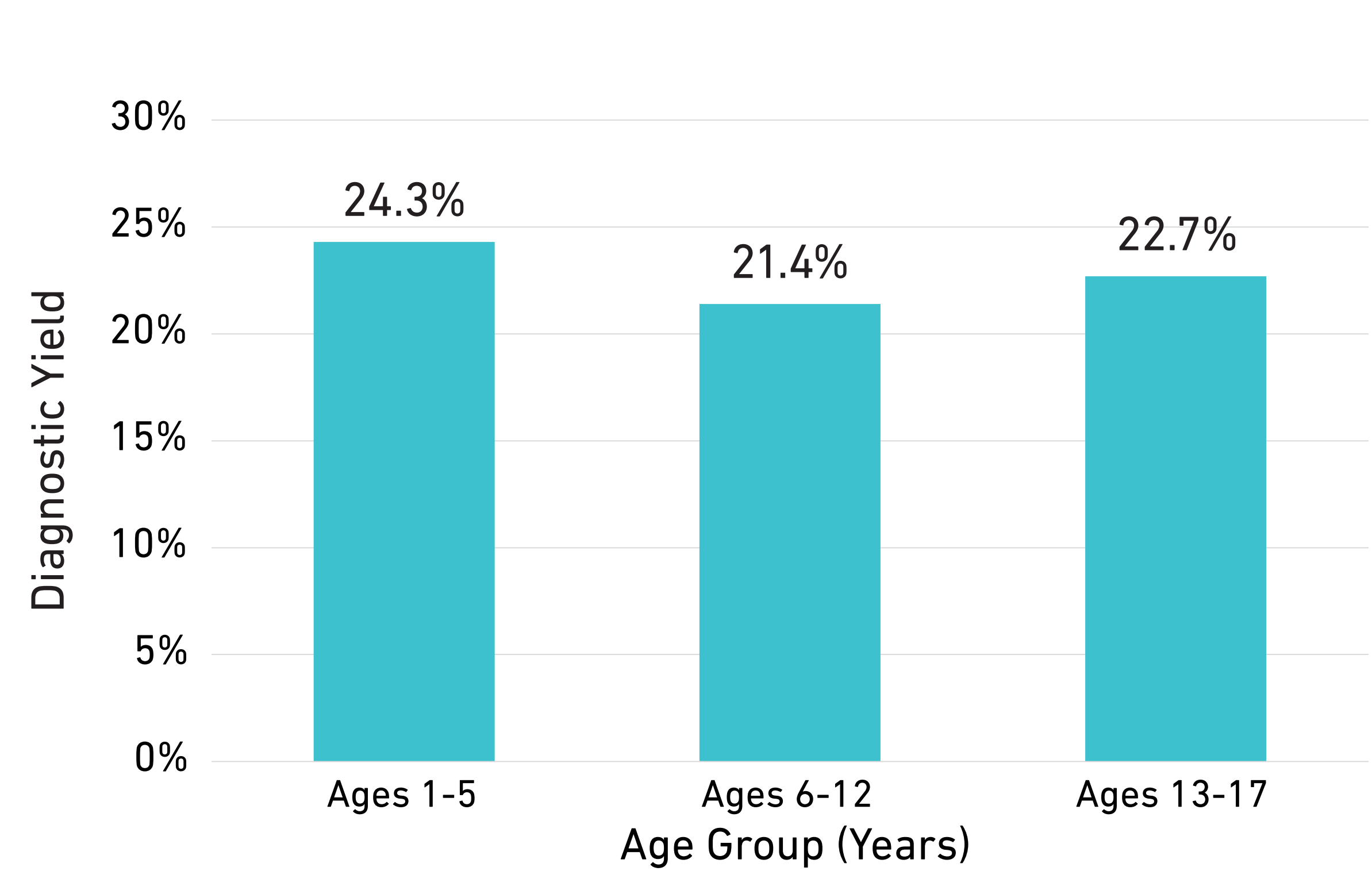


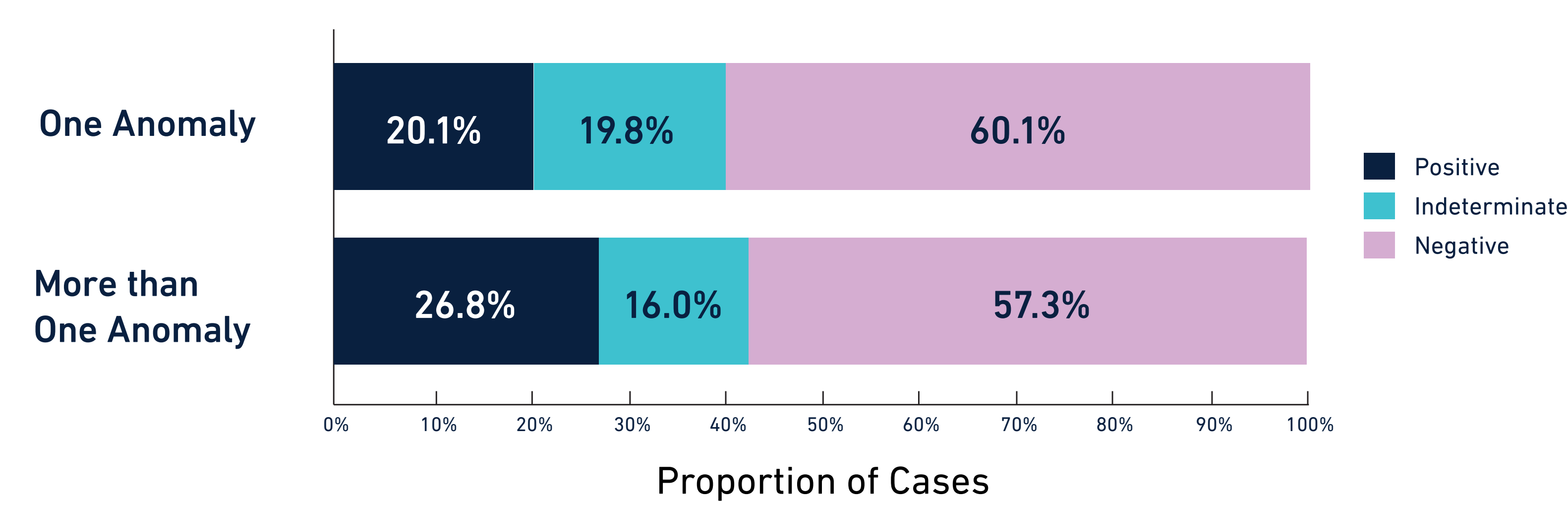
Figure 4. Diagnostic yield of GS across age groups.



Methods

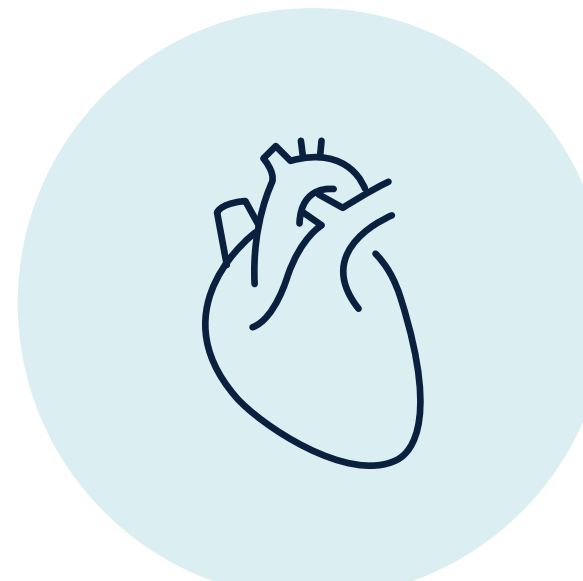
- A retrospective review of consecutive non-rapid GS cases from our clinical diagnostic laboratory was conducted.
- Cases were included if (1) the individual was at least one year old and less than 18 years old at the time of testing and (2) the individual had a clinical indication of at least one congenital anomaly. Minor facial dysmorphism was not considered.
- Cases were excluded if there was a clinical indication associated with a neurodevelopmental phenotype, such as intellectual disability, developmental delay, or autism spectrum disorder.
- Positive results included pathogenic and likely pathogenic variants associated with the clinical indication, while indeterminate results included variants with uncertain clinical significance.
- Diagnostic yield of GS was assessed across demographic and clinical characteristics.
- This study was conducted under the approval of the Baylor College of Medicine Institutional Review Board (H-41191).

Figure 5. GS results for children with only one congenital anomaly compared to those with more than one.



Key Takeaway:
Almost a quarter of children with congenital anomalies but no reported neurodevelopmental indication had positive GS results.

Figure 6. Diagnostic yield of GS across different phenotype categories of congenital anomalies.

					
System	Musculoskeletal (e.g., skeletal dysplasia, micrognathia, polydactyly)	Cardiovascular (e.g., dextrocardia, atrial septal defect, hypoplastic left heart)	Genitourinary (e.g., renal hypoplasia, horseshoe kidney, ambiguous genitalia)	Ear (e.g., microtia, inner ear malformation, ear anomaly)	Gastrointestinal (e.g., congenital diaphragmatic hernia, omphalocele, tracheoesophageal fistula)
Diagnostic Yield	26.2% (45/172)	23.3% (35/150)	28.1% (16/57)	27.7% (13/47)	26.2% (45/172)

Conclusions

- Regardless of age or phenotype category related to the presenting congenital anomaly, the diagnostic yield of GS was relatively consistent, highlighting broad utility of GS for children with congenital anomalies even in the absence of neurodevelopmental phenotypes.
- Given the presence of congenital anomalies early in life, these findings support the use of early GS as a first-tier test for children with congenital anomalies, enabling more informed clinical care throughout childhood.
- Reanalysis of GS data and supplemental technologies such as RNA sequencing and optical genome mapping may be beneficial for resolving indeterminate results and further increasing the diagnostic yield of GS.