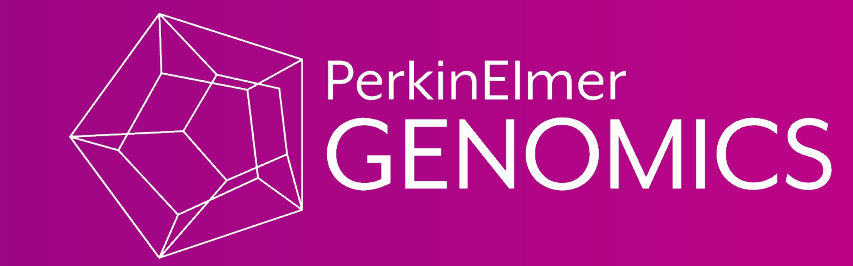
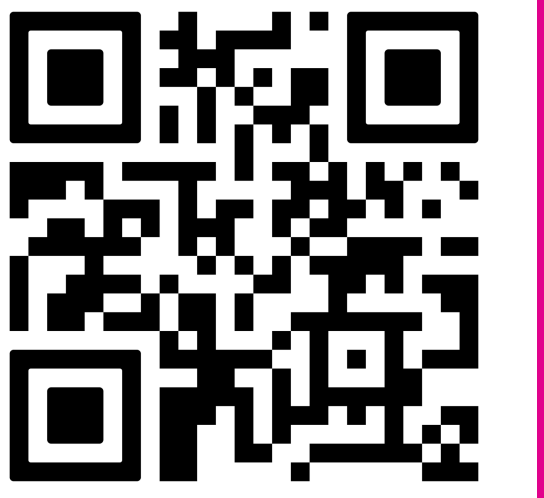


High diagnostic yield from clinical genome sequencing supports genome sequencing as the first-tier genetic test: Evidence-based from 2100 index cases

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BACKGROUND

- Genome sequencing (GS) is one of the most comprehensive tests that interrogate single nucleotide variants (SNV), copy number variants (CNV), mitochondrial variants, repeat expansions, and structural variants in one single assay.
- Despite the clear technical superiority, few studies are available regarding the diagnostic utility of its clinical application.
- In this study, we systematically evaluated 2100 consecutive clinical GS cases performed in our laboratory since 2017 to explore the diagnostic utility of clinical GS.
- Highlights of the genome sequencing performed at PKIG:
 - Mean coverage of 40x throughout the entire Genome;
 - Complete coverage of >99% of the exome, including over 5,400 disease-associated genes;
 - Reliable detection of intragenic deletions and duplications in clinically relevant genes as well as large-scale CNV events and structural rearrangement events;
 - Include the analysis of the mitochondrial genome
 - Include repeat expansion disorder screening of more than 30 genes associated with intellectual disability and movement disorders (since 2020)
 - Include SMN1 copy number screening for Spinal Muscular Atrophy (SMA) (since 2020)

RESULTS

Table 1. Demographics and ordering metrics of patients who underwent clinical genome sequencing

	Total number	Percentage	Prenatal	Pediatric	Percentage	Adult	Percentage
Total cases	2100		8	1487	71%	605	29%
1. Proband Sex							
Female	965	46%	1	645	43%	319	53%
Male	1117	53%	3	836	56%	278	46%
Unknown	18	1%	4	6	0%	8	1%
2. Case category							
Singleton	1080	51%	5	652	44%	423	70%
Dual	101	5%	0	59	4%	42	7%
Trio	861	41%	3	731	49%	127	21%
Quad	58	3%	0	45	3%	13	2%
3. Sample Type							
DBS	233	11%	0	199	13%	34	6%
Saliva	968	46%	0	632	43%	336	56%
whole blood	637	30%	0	461	31%	176	29%
gDNA	252	12%	0	194	13%	58	10%
Prenatal	8	0%	8	0	0%	0	0%
Others (Tissue)	2	0%	0	1	0%	1	0%
4. Secondary Finding Requested							
ACMG-Ped only	52	2%	0	51	3%	1	0.2%
ACMG-ALL	1577	75%	0	1091	73%	486	80%
Other diagnostic finding-Ped only	28	1%	0	27	2%	1	0.2%
Other diagnostic finding-ALL	1259	60%	0	842	57%	417	69%
Carrier	1306	62%	0	884	59%	422	70%
PGx	1298	62%	0	877	59%	421	70%
No SF requested	427	20%	8	312	21%	107	18%

RESULTS

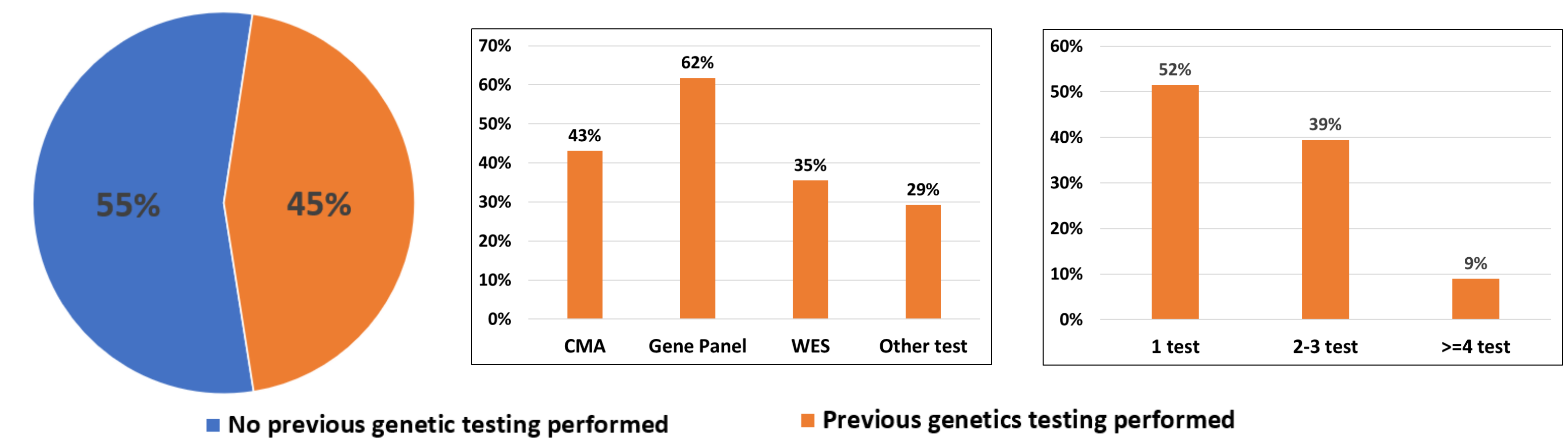


Figure 1 Previous genetic testing performed and its category

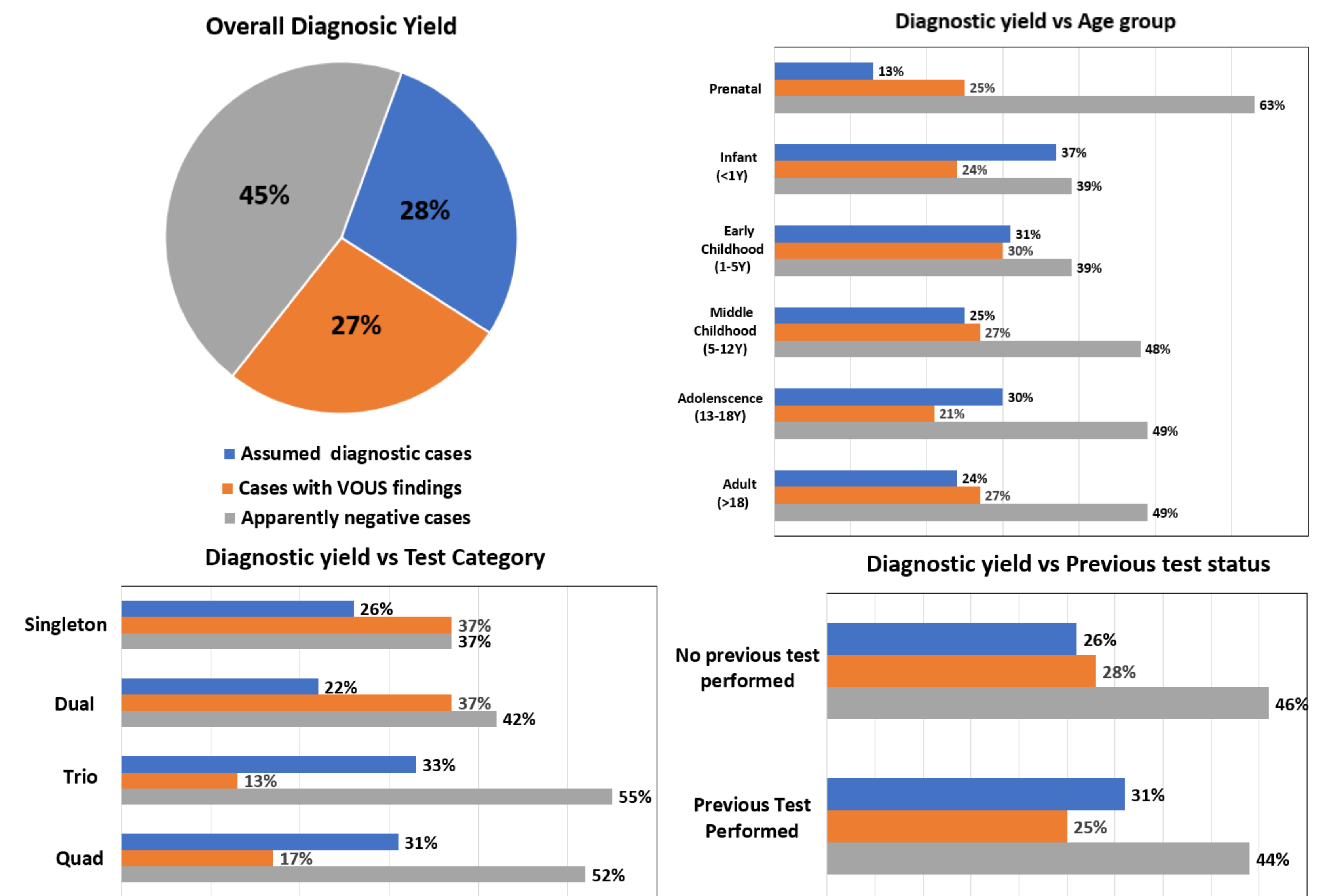


Figure 2 Clinical diagnostic yield and the factors which might affect the diagnostic yield

CONCLUSION

- The diagnostic yield in our cohort is around 28% overall, with 37% in the infant group;
- Around 31% of Cases with previous genetic testing performed yielding diagnosis post-GS further support the clinical utility of using GS as the first-tier genetic test;
- Besides the diagnostic cases, an additional 27% of cases carried the variant(s) of unknown significance which are identified in a previously established disease gene that could explain the patient's phenotype.