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

F. Guo, R. Liu, A. Mathur, C. Da Silva, B. Nallamilli, C. Collins, L. Bean, N. Guruju, X. Chen-Deutsch, R. Yousaf, Z. Ma, J. Balciuniene, M. Hegde

Scan to Download

## 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

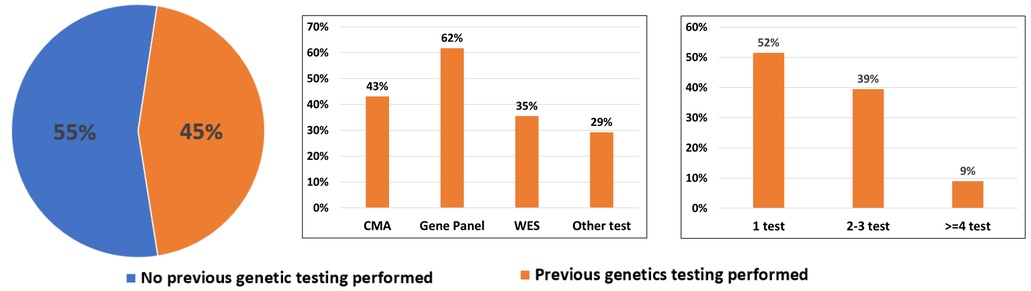


**Figure 1** Previous genetic testing performed and its category

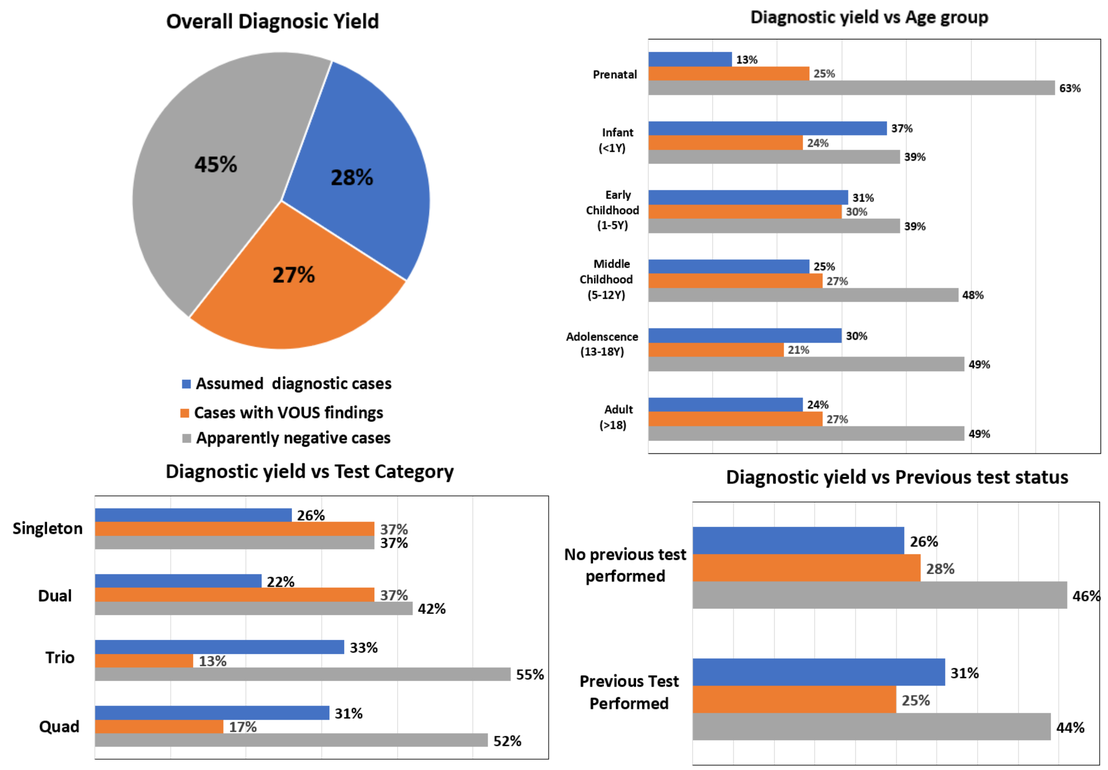


**Figure 2** Clinical diagnostic yield and the factors which might affect the diagnostic yield

## 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.