Utilization of Whole Genome Sequencing to Improve Diagnostic Yield in Patients with a Suspected Genetic Disorder(s)

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Background

With an estimated 15% of disease-causing variants suspected to be outside coding regions of the genome, whole genome sequencing (WGS) has long been expected to increase the diagnostic yield over that of whole exome sequencing (WES) or targeted panels through the analysis of these regions. Additionally, some of the technical advantages of WGS, including more uniform coverage of coding regions, have also shown promise in increasing the diagnostic yield for patients, suggesting that WGS is a promising alternative as a first-line diagnostic test for patients. Here we present data from the first 284 cases referred for clinical WGS, with the cohort consisting of 208 pediatric patients and 76 adult patients.

Methods

Comprehensive clinical grade WGS has been validated in our laboratory for detection of single nucleotide and copy number variation at a depth of 40X and mitochondrial genome at a depth of 1000X, using a PCR-free library preparation protocol followed by sequencing on the Illumina NovaSeq. Primary data processing was performed using the Edico Dragen system and bioinformatic analysis using our in-house proprietary program ODIN (Ordered Data Interpretation Network). Data was categorized into the following subsets: genes causing disease (GCD: 5300 genes), genes of unknown significance (GOUS), ACMG59, known common and founder pathogenic changes, and intragenic and intergenic variants with tagged variants which have been established to be disease causing.

Results

- Overall diagnostic yield of 42% across the mixed cohort of adult and pediatric cases. Of note, another 9% of patients were diagnosed with conditions unrelated to the clinical phenotype and reason for testing.
- This broke down to a diagnostic yield of 44% in pediatric cohort (n = 208) and a 38% diagnostic yield in the adult cohort (n=76).

Figure 1: Diagnostic yield in mixed cohort

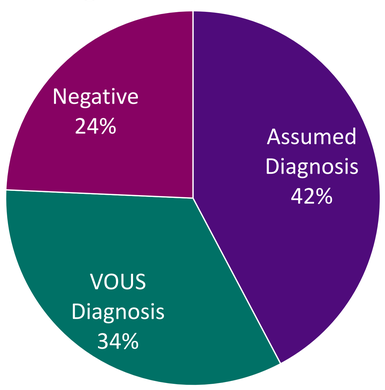


Figure 2: Diagnostic yield in pediatric cohort

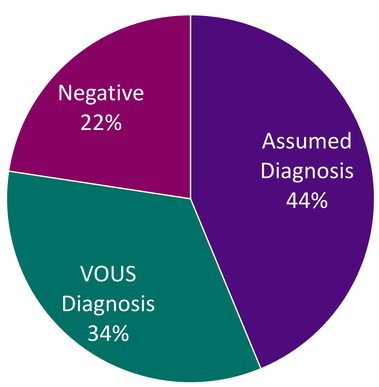
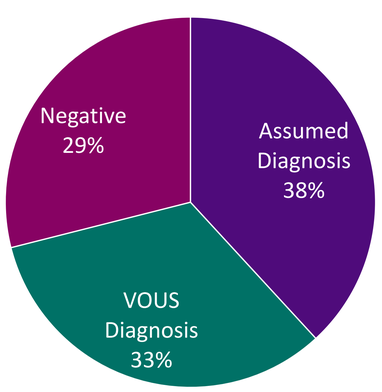


Figure 3: Diagnostic yield in adult cohort



Singleton vs. TRIO Diagnostic Yield

- In a pediatric population of 208 patients, we found a diagnostic yield of 41% in singleton cases where as we found a diagnostic yield of 47% in TRIO cases

Figure 4: Diagnostic yield in singleton cases

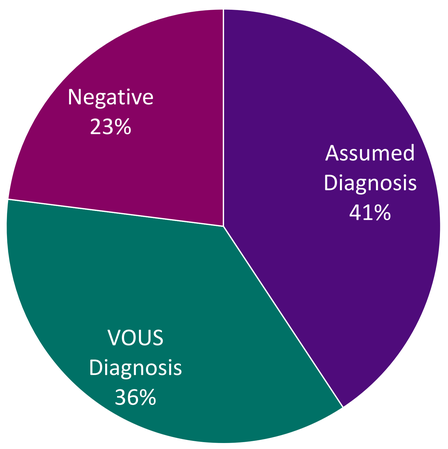
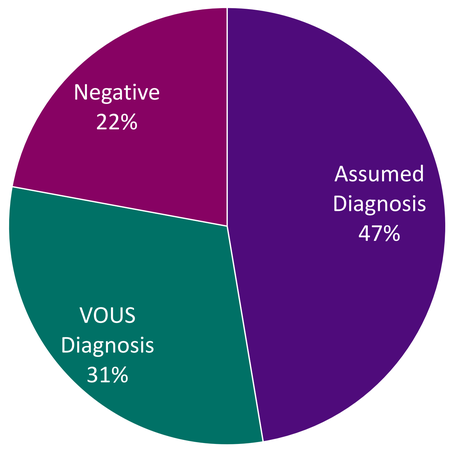


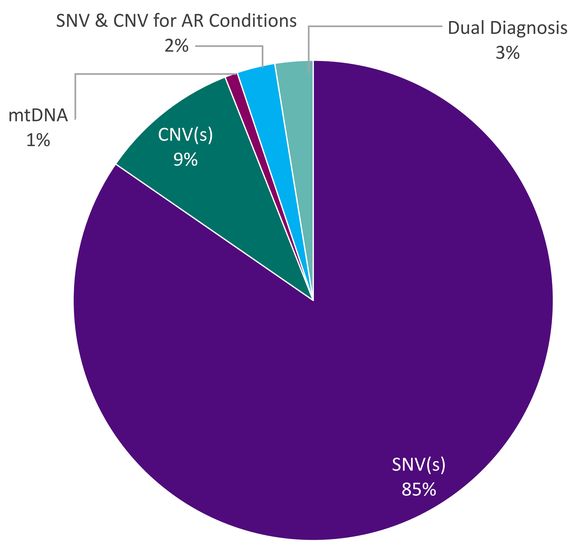
Figure 5: Diagnostic yield in TRIO cases



Types of Variants Reported

Figure 6: Breakdown of causative variants identified

- 85% of cases had SNV(s)
- 9% of cases had CNV(s)
- 3% of cases had “dual” diagnoses
- 2% of cases had AR conditions caused by a SNV and CNV
- 1% of cases had a mtDNA variant



Discussion

- The patient cohort presented here demonstrates an improved diagnostic yield for WGS (42%) compared to traditional types of testing including panel-based testing and WES. Furthermore, this diagnostic yield was found to be as high as 47% for TRIO-based testing in a pediatric population, with lower yields found in singleton and/or adult cohorts.
- This cohort demonstrates the power of WGS to identify a large range of variants in patients ranging from SNVs to both small and large CNVs.
- Interestingly, we found that approximately 3% of patients were found to have 2 or more pathogenic findings (dual diagnoses). In several cases included in this cohort, WGS was able to identify a second previously unidentified finding that was able to explain additional clinical symptoms in patients.
- The demonstrated improved diagnostic rate of WGS coupled with decreasing costs and turn-around-times suggest that WGS should be considered as a first-tier test for pediatric patients.