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Whole genome sequencing is a powerful “one-stop shop” screening assay for uncovering undiagnosed conditions in apparently healthy pediatric cohort

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Whole genome sequencing (WGS) is a powerful genomic diagnostics tool. It provides higher clinical sensitivity than exome testing, in part due to a uniform coverage across the genome facilitating copy number variant (CNV) calls, and inclusion of deep intronic variant and mitochondrial DNA (mtDNA) analysis. With decreased sequencing costs, WGS is becoming a feasible option for screening healthy people. Benefits of WGS-based healthy screening include uncovering genetic risks beyond those found in standard carrier and/or newborn screening, informing timely medical management efforts and identifying variants of pharmacogenomic (PGx) significance.

Here we present data from WGS-based healthy screening test for a pediatric population which covers 22000 genes and analyzes 2500 genes relevant for pediatric onset diseases. Only diagnostic findings (Dx) and PGx variants are reported. Carrier status or diagnoses in adult-onset disorders are not included in pediatric reports.

Since 2018, we performed WGS on 532 reportedly asymptomatic pediatric subjects (51% females and 49% males). The median age at testing was 33 days of age, with consent for newborns obtained at pre-delivery counseling. Dried blood spots constituted 95% (503/532) of the specimens. Overall, 8.1% (43/532) children received potential Dx, and 90% (479/532) received at least one PGx variant. Sequence variants (SV) constituted 70% (30/43) of the Dx (with 1 heteroplasmic mtDNA SV), while 30% (13/43) Dx were CNV analysis assisted calls (4 microdeletions [1q21.2, 16p13.11, 20q13.33 and Xp22.33], a partial *ASH1L* deletion , 4 microduplications [7q11.23, 16p11.2, 17p12, 22q11.2], mosaic 12p triplication, likely der(4)t(4;9)(p16.1;p24.3), mosaic trisomy 8 and uniparental disomy 16). Pathogenic SVs in medically actionable (ACMG) genes constituted 14% (6/43) of Dx (2x*LDLR*, 2x*BTD*, *MYBPC3*, *HNF1A*). Reduced penetrance (RP) variants comprised 30% (13/43) of Dx, including SVs in *TNFRSF13B, IFNGR1, G6PD, SGCE, COL4A3, PROKR2, HNF1A,* and recurrent CNV syndromes (1q21.1 and 16p13.11 deletion, and 16p11.2 duplication syndromes). In one individual 2 RP variants were found (*G6PD* and *COL4A3*). Other Dx SVs involved genes associated with range of conditions, including collagenopathies, cancers, eye, heart, or blood defects, as well as skeletal and neurodevelopmental disorders.

Our results indicate that WGS screening can serve as a “one-stop shop” for uncovering a wide range of looming genetic conditions in apparently healthy children, this way enabling the family and treating clinicians to take timely appropriate actions to maximize their healthcare outcomes and inform future reproductive decisions.