P578: Lessons Learned From Incidental or Secondary Findings Consented in Clinical Genome Sequencing for Pediatric Patients

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1 Introduction

- Whole genome sequencing (WGS) is increasingly recognized as a first-line diagnostic tool for children with suspected genetic disorders, congenital anomalies, developmental delays, or intellectual disabilities.
- Its high diagnostic yield and ability to deliver rapid, comprehensive results make it a superior alternative to traditional stepwise genetic testing.
- WGS can detect a broad spectrum of genetic variants, including those missed by targeted methods, and has shown clinical utility in managing acutely ill infants.
- Beyond primary diagnostic results, WGS also generates incidental or secondary findings (ISFs), genetic variants unrelated to the patient's current condition but potentially significant for future health.
    - Secondary findings: pathogenic variants identified in genes recommended by ACMG
    - Incidental findings: pathogenic variants identified in genes unrelated to the test indications or reported phenotypes but consistent with a clinical diagnosis
- Our previous retrospective study found that WGS revealed potential pediatric-onset diagnoses in 8.2% of apparently healthy infants through proactive genome screening, with nearly half of these associated with high-penetrance conditions (PMID: 37523181).

2 Methods

In this study, we retrospectively examined diagnostic ISFs unrelated to the test indication in a cohort of pediatric patients who underwent clinical WGS (PMID: 37838930).

3 Results

Table 1: Demographics and consent status of patients in this study

Number of patients					
Age	Total	<1 year old	<2 years old	2-10 years old	>10 years old
Biological sex					
Male	1163	237	89	599	238
Female	869	200	73	406	190
Grand Total	2032	437	162	1005	428
Consent - Opt in					
Male	980	175	76	521	208
Female	688	130	61	337	160
Total	1668	305	137	858	368
Consent - Opt out					
Male	183	62	13	78	30
Female	181	70	12	69	30
Total	364	132	25	147	60
Pediatric findings only					
Male	36	17	2	15	2
Female	43	13	3	20	7
Total	79	30	5	35	9
Pediatric and adult findings					
Male	944	158	74	506	206
Female	645	117	58	317	153
Total	1589	275	132	823	359

- Our cohort includes 2032 pediatric patients, 869 females and 1163 males.
- Of the 2,032 patients, 1,668 (82.0%) opted to receive ISFs, while 364 (17.9%) declined.
- Among those who consented, 79 patients (5%) requested pediatric-onset findings only, whereas the majority (1,589 patients, 95.3%) chose to receive information on both pediatric and adult-onset conditions.

Fig 1

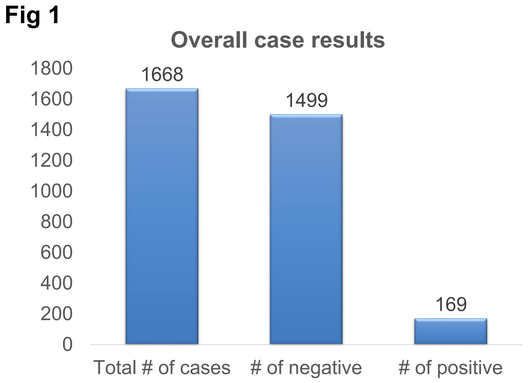


Fig 2

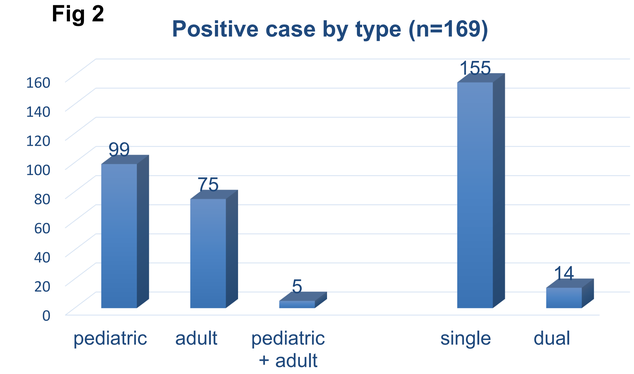
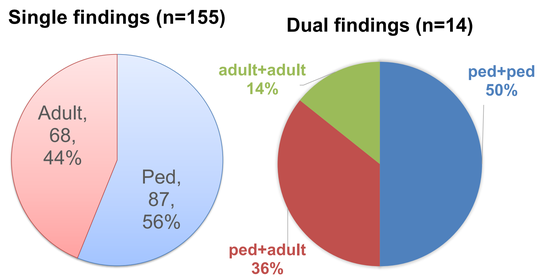


Fig 3



- Among the 1,668 patients opted in ISFs, 169 cases (10.1%) harbored variants consistent with a potential diagnosis (Fig 1).
- 99 patients (5.9% of the total cohort) had variants in genes linked to early-onset diseases, and 75 patients (4.5% of total) had variants associated with adult-onset conditions. Five patients had variants in both categories (Fig 2).
- 155 patients (91.7% of positive cases) had variants associated with a single condition including 87 with early-onset and 68 with adult-onset diseases. Fourteen patients (8.3% of positive cases) had dual diagnoses, including seven with two early-onset conditions, five with both early and adult-onset findings, and two with dual adult-onset conditions (Fig 2 and 3).

Fig 4

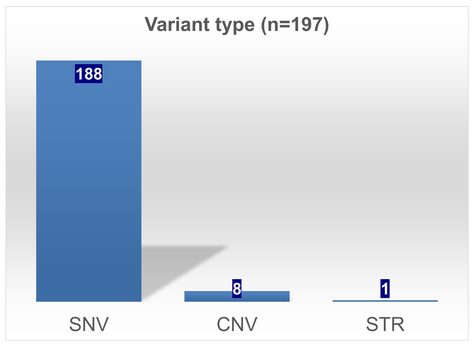


Fig 5

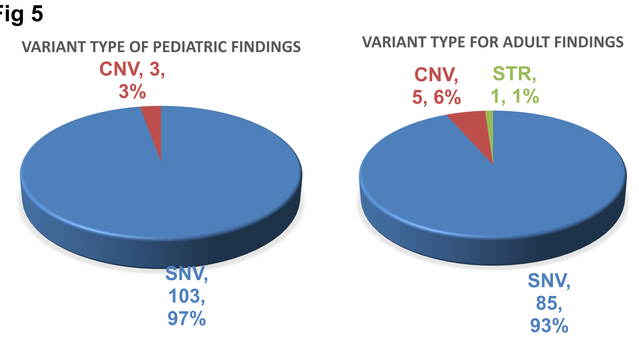
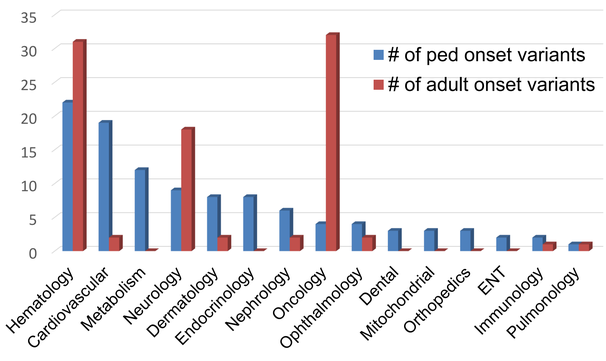


Fig 6



- A total of 197 variants including 188 SNV, 8 CNV and 1 short tandem repeat (STR) were identified (Fig 4).
- The 106 variants associated with early-onset diseases include 103 SNVs in 47 nuclear genes and three mitochondrial genes, and 3 CNVs. For adult-onset conditions, 91 variants were found in 26 genes, including 5 intragenic CNVs and 1 STR (Fig 5).
- Pediatric onset variants spanned 15 diverse clinical categories, with hematologic, cardiovascular, and metabolic systems being the most frequently affected (Fig 6).
- Adult onset findings were concentrated on oncology (32 variants), hematology (31 variants), and neurology (18 variants) (Fig 6).

4 Summary

- Our data suggests that parents are highly interested in receiving diagnostic ISF, with most expressing a desire to learn about both childhood and adult-onset risks. This underscores the importance of comprehensive pre-test and post-test genetic counseling to address concerns such as the psychological burden of learning about untreatable or uncertain conditions, the potential loss of a child's autonomy in future decision-making regarding their genetic information, and the appropriate timing and method of disclosing such information to the child.
- Compared to our previous retrospective analysis of genomic newborn screening, the diagnostic yield for early-onset diseases in this cohort was lower, possibly due to differences in patient population. This study focused on symptomatic pediatric patients across a broader age range seeking a clinical diagnosis, rather than healthy infants undergoing screening. Some variants may have been reported based on their relevance to clinical phenotype rather than as ISFs.
- While diagnostic ISFs are relatively uncommon, they may hold clinical significance. These findings reinforce the value of WGS in pediatric diagnostics and underscore the ethical and counseling considerations essential for its responsible implementation.