TITLE: The Other Half of the Story: High Rates of Unique Parental Secondary Findings

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INTRODUCTION

Secondary findings (SF) are available for patients and their families as an optional component when receiving Exome and/or Genome testing. The purpose of reporting secondary finding is to give individuals the choice to receive actionable findings not related to the primary reason for genomic testing.

METHODS: We did a retrospective review of probands and their families who underwent exome testing at a single clinical laboratory between 2016 and 2024.

We investigated trends in secondary finding orders and results among patients and their families who underwent exome testing at a single clinical laboratory between 2016 and 2024.

RESULTS: Of the 15,492 probands that received exome sequencing, most probands (86.6%, n =13,423) opted to receive secondary findings, with an average positive rate of 2.9% (n = 388/12,441). Between 2016 and 2024, there was not a significant change in opt-in rates or positive SF rates. Probands ages 1-5 had an opt-in rate of 86.2% (n= 4,963/5,758). The prenatal group had the lowest opt-in rate of 74.3% (n= 124/167) and the 51+ group had the highest opt-in rate of 91.3% (n= 387/424). These percentages reflect an upward trend in opt-in rates with increasing age among probands.

In this cohort, SF analysis included independent analysis and reporting for up to three family members. This enables analysis of variants reported in parent reports regardless of whether the variant was detected in proband. For both parents and probands, variants in BRCA2 were the most commonly reported, with LDLR and BRCA1 following. Cancer predisposition was the leading genetic condition reported in secondary findings. For mothers, the average opt-in rate was 86.8% (n = 10,518/12,117) and the average rate of positive findings was 2.2% (n =229/10,518). For fathers, the average opt-in rate was 85.2% (8,797/10,327) and the average rate of positive findings was 2.4% (n = 215/8797). In parent-proband trios, 13.2% (n = 32/243) of positive secondary findings were confirmed to be de novo. 1.00% (n =100/10,049) of mothers had an SF finding that was not present in the proband. Similarly, fathers had a rate of 1.2% (n = 97/8,406)of having a different variant than their child who opted in.

Among all secondary finding orders, 66.7% (n = 8,960/13,423) were from parent-proband trios, while 3.4% (n = 459/13,423) were from non-parental trios.

CONCLUSIONS: Although the ACMG list of secondary finding genes has evolved, diagnostic rates and commonly reported conditions have remained stable. Nearly half of reported secondary findings (43.7% of mothers; n = 100/229 and 45.2% of fathers; n = 97/215) were not present in the proband. This underscores the importance of laboratories offering independent secondary finding testing for each individual. If reporting relied solely on the proband's results, almost half of parents would have missed critical information leading to life-saving interventions. Independent testing provides an opportunity for early detection and disease prevention, making comprehensive reporting essential.