

Evaluating Secondary Findings in Prenatal Exome Sequencing: A Study of Uptake and Yield for ACMG and Childhood Onset Disorder Results

Authors: Kayleigh Avello, Brooklynn Gross, Erica Smith, Christina Alamillo, Steven Harrison, Kelly Hagman, Kelly Radtke, Wendy Alcaraz

Introduction:

In 2020, the American College of Medical Genetics and Genomics (ACMG) published a points to consider document on prenatal exome and genome testing¹. Recommendations included offering a new category of secondary findings (SFs) for prenatal cases: Childhood Onset Disorders (COD). While no specific gene list was provided, ACMG recommended that laboratories prioritize conditions that have high penetrance, are moderate to severe in clinical presentation and are pediatric in onset. Although several years have passed, limited data has been published on prenatal SFs. This study evaluates the uptake and incidence at a large clinical laboratory using both the standard ACMG list as well as an internally curated list of COD genes.

Methods:

This study was a retrospective review of prenatal exomes reported at Ambry from 2018-2026. In total, 226 prenatal cases were analyzed to determine whether ACMG and/or COD secondary findings were requested, and if any secondary findings were reported. Additionally, primary diagnostic results were reviewed to determine the prevalence of diagnostic variants within genes included on the COD list. Lastly, all pediatric and adult exome cases in this time period were also reviewed to determine if the primary result encompassed a COD gene variant(s) as the molecular diagnosis to compare incidence of these rare diseases across the lifespan.

Results:

In this study, 60% of prenatal cases (N= 135/226) opted into SFs (ACMG only: 114, Both: 21). Four cases (3%, N= 4/135) received positive SF results in genes specific to the ACMG medically actionable list; however, none of those cases yielded a primary finding that explained the clinical indication for ordering the exome. Further, no case in the total cohort received a positive SF report in a COD gene. In comparison, a primary diagnostic result within a gene on the current internal COD list was found in 8% (N= 18/226) of prenatal cases. Four additional prenatal cases had uncertain primary reports due to either a variant(s) of uncertain significance or a single pathogenic/likely pathogenic variant in a recessive gene. Across all pediatric and adult patients tested via exome at Ambry, 3.1% (N= 940/30,000) had a relevant variant(s) reported within a gene on the COD list.

Conclusions:

Most patients opted in for prenatal SFs, and the overall positive rate was in line with the reported range of 2-5%² for ACMG SFs. While many families selected to receive COD SFs, no positives were reported in this small cohort. Instead, most findings in genes on the COD list were reported as primary findings. This suggests that a large number of the current curated

COD SF conditions have an early prenatal onset, where the phenotype can be utilized for finding a diagnostic result, or the phenotype develops after birth and the molecular cause is determined after the prenatal period. Additionally, the number of positive SF results may increase over time as the respective gene lists evolve, more uncertain variants are upgraded, and SFs are increasingly requested in the prenatal setting overall.

References:

Monaghan KG, Leach NT, Pekarek D, Prasad P, Rose NC; ACMG Professional Practice and Guidelines Committee. The use of fetal exome sequencing in prenatal diagnosis: a points to consider document of the American College of Medical Genetics and Genomics (ACMG). *Genet Med*. 2020;22(4):675-680. doi:10.1038/s41436-019-0731-7

Haverfield EV, Esplin ED, Aguilar SJ, et al. Physician-directed genetic screening to evaluate personal risk for medically actionable disorders: a large multi-center cohort study. *BMC Med*. 2021;19(1):199. Published 2021 Aug 18. doi:10.1186/s12916-021-01999-2