Clinical Utility of Prenatal Exome Sequencing: Insights From a 10-year Cohort

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Introduction: Diagnostic exome sequencing (ES) relies on precise phenotyping to accurately report clinically relevant variants. For prenatal ES, phenotyping is primarily obtained through maternal imaging studies during pregnancy, potentially limiting the features that can be identified. While maternal imaging provides valuable insights, there is concern that its resolution and scope may lead to miscategorized phenotyping and missed diagnoses. This study aimed to assess the clinical utility of prenatal ES by describing the clinical presentations and genes with reported findings in a cohort of fetuses and products of conception (POC) with suspected genetic disorders.

Methods: We performed a retrospective review of ES cases for ongoing pregnancies and POCs conducted at one clinical laboratory between January 2013 and July 2023. Laboratory genetic counselors reviewed clinic notes submitted at the time of testing to summarize prior genetic testing and prenatal imaging results and to assign a primary clinical indication. Clinical data were further categorized using Human Phenotype Ontology (HPO) terms and grouped by impacted organ systems or specified as growth abnormalities, amniotic fluid level abnormalities, or cord/placental anomalies. Testing outcomes, including genes with reported variants, were analyzed.

Results: A total of 157 prenatal ES cases were assessed, yielding an overall diagnostic rate of 29% (n=45). Variants of uncertain significance (VUS) were reported in an additional 9% (n=14) due to positive phenotypic overlap. Diverse clinical indications were observed across the cohort. In cases with positive or likely positive results, the highest diagnostic rates were observed in cases with an ocular indication (100%, n=1), skeletal indication (44%, n=23), or multiple congenital anomalies (30%, n=94). Notably, 76% of cases had HPO features in >1 clinical category (range 1-12; mean 3). Skeletal (53%) and brain anomalies (36%) were the most frequent, followed by dysmorphic facial features (27%), edema (26%), and undergrowth (26%). Nearly all cases (98%) had undergone previous genetic testing, with both karyotype and chromosomal microarray (CMA) reported in 26% (n=41). Results identified in the positive and likely positive cases were largely unique, suggesting a high degree of genetic heterogeneity in prenatal genetic disorders, even with similar clinical presentations. Of the 45 cases with diagnostic findings, positive or likely positive findings in only six genes were identified in >1 case: *SF3B4, FLVCR2, COL1A2, NIPBL, COL2A1,* and *KMT2D*. Reanalysis of eight cases postnatally did not result in reclassification despite the additional clinical information obtained after delivery or fetopsy.

Conclusions: Prenatal ES is a valuable diagnostic tool for a variety of prenatal presentations, with an overall positive rate comparable to postnatal cases and a lower rate of reported uncertain results. Prenatal ES remains a secondary test to fetal karyotype and CMA, which are standard prenatal practices. This study illustrates the potential of ES to unveil rare, diverse genetic diagnoses even in the setting of limited prenatal phenotyping ability. Technological advancements will likely enhance the capabilities of prenatal ES as a first-tier genetic test.