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

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BACKGROUND

- Diagnostic exome sequencing (ES) relies on phenotyping to report relevant variants
- In the prenatal setting, phenotyping is obtained through maternal imaging during pregnancy
  - Concerns that resolution & scope may lead to miscategorized phenotyping & missed diagnoses

Study Aim

Evaluate use of prenatal ES in identifying genetic disorders in fetuses & products of conception (POC)

METHODS

Retrospective review of ES cases for ongoing pregnancies and POCs at clinical laboratory between 1/2013 – 7/2023. n = 157

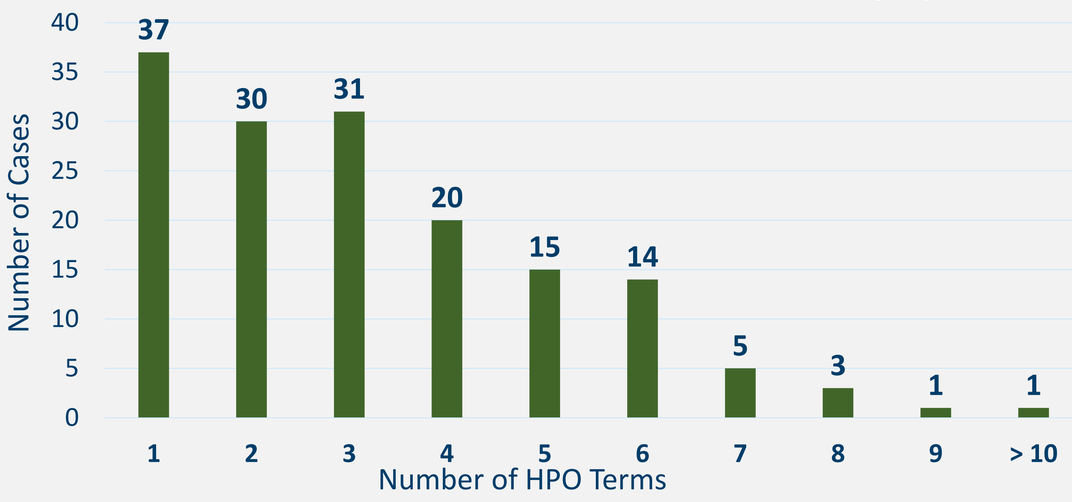
Genetic counselors reviewed clinic notes to summarize prior genetic testing & prenatal imaging results & to assign a clinical indication

Human Phenotype Ontology (HPO) terms used to group cases by "HPO term category" as defined by impacted organ systems, growth, amniotic fluid level, or cord/placental anomalies

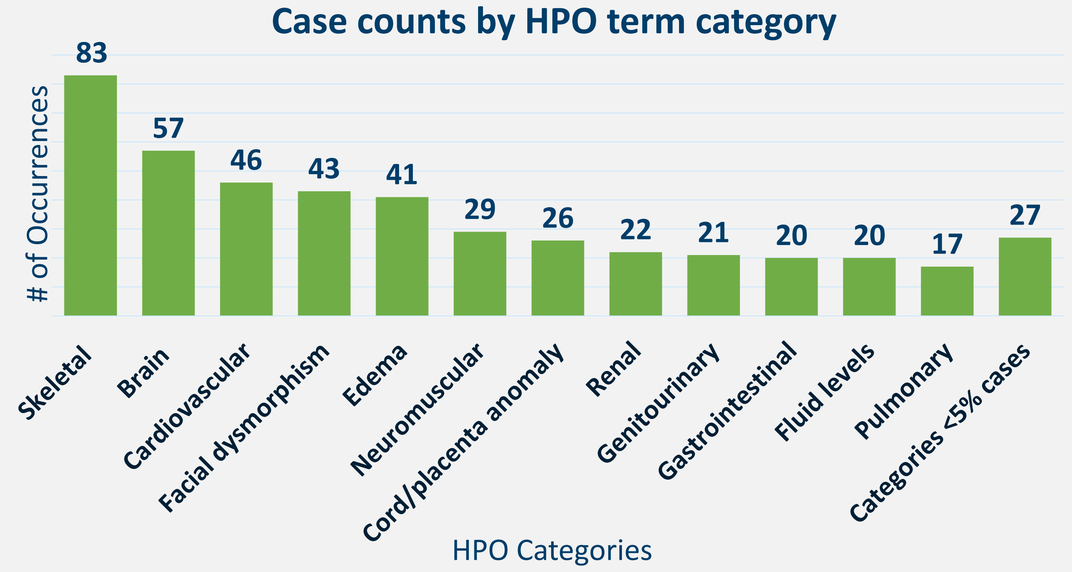
Testing outcomes, including genes with reported variants, were analyzed.

HPO Term Category Analysis

76% of cases had HPO terms in more than one category



Case counts by HPO term category

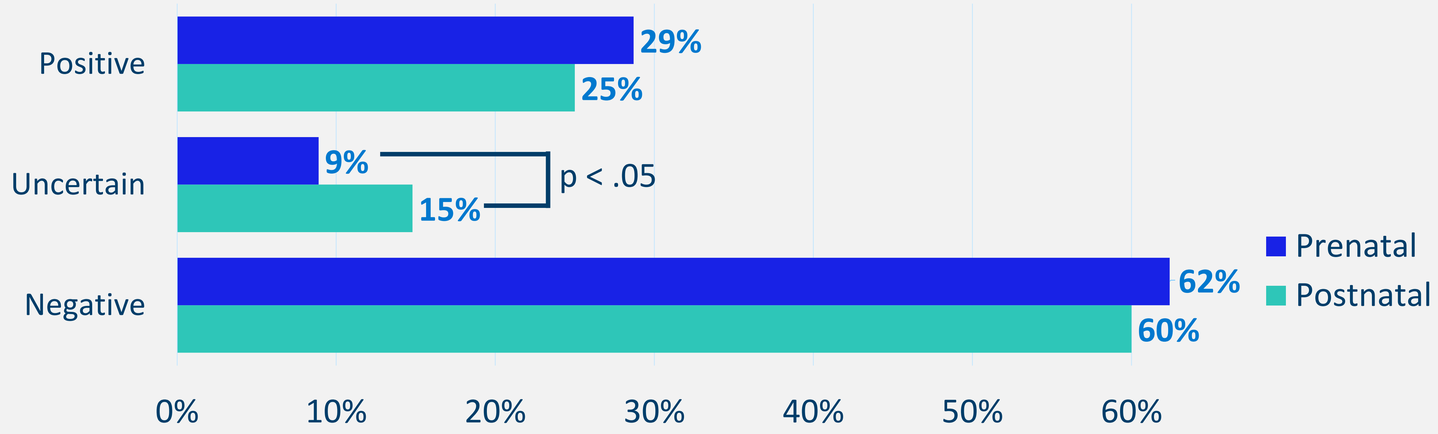


Categories with <5%; ears/nose/throat, immune, endocrine, metabolic, overgrowth

TAKE HOME POINTS

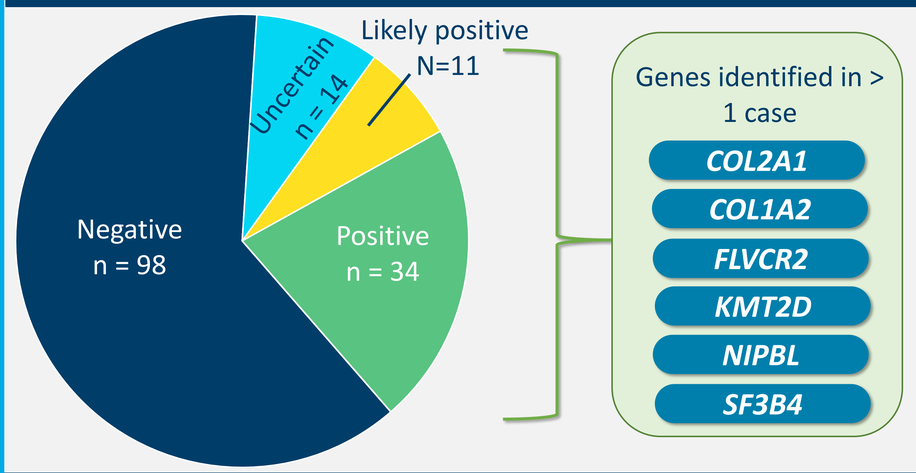
1. Prenatal ES is a clinically useful tool for diagnosing genetic disorders in fetuses and products of conception.
   - **29% overall diagnostic rate is consistent with postnatal cases, despite prenatal phenotyping limitations**
2. Prenatal ES remains a secondary test to karyotype and CMA
   - Providers should consider ES given the time considerations of prenatal testing

Testing Outcomes of Prenatal ES vs Postnatal ES



The positive diagnostic rate in prenatal ES cases was found to be as high as the positive diagnostic rate of postnatal cases (n=10816) with a statistically significantly lower rate of uncertain results

Results of Positive Cases



Results of positive and likely positive cases were unique, suggesting a high degree of genetic heterogeneity

Of the 45 cases with diagnostic findings, only 6 genes had positive findings identified in >1 case

98% of Cases had Previous Genetic Testing

75% of cases had two genetic tests done & 20% of cases had three genetic tests done