# Unblurring the ultrasound lines: 45% of infants with prenatal findings receive a reportable result on diagnostic exome sequencing

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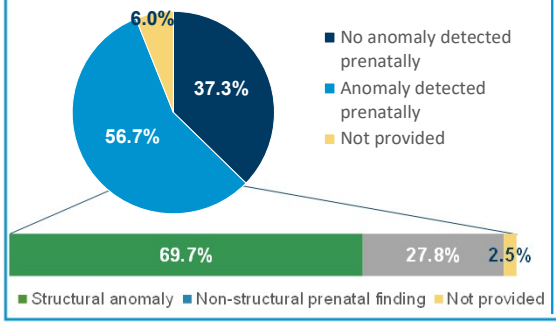
## BACKGROUND

- The utility of diagnostic exome sequencing (DES) in neonates has been well established; however, prenatal DES use remains limited.
- Studies on prenatal DES have reported a wide range of diagnostic rates and are primarily focused on fetal structural anomalies[1-3].
- Here, we retrospectively assessed the prenatal histories of infants who underwent DES at one commercial laboratory.

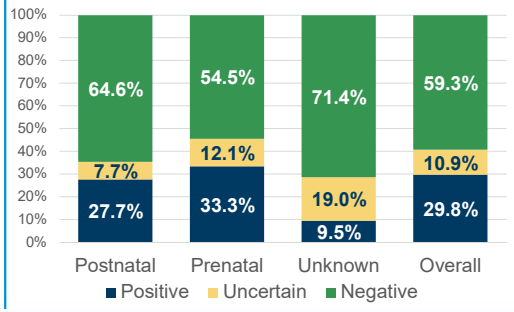
## METHODS

- Clinical and genetic testing histories were reviewed for patients ≤4 months referred for DES.
- Prenatal imaging and previous testing were categorized by type of study, result and time of testing (prenatal or postnatal).
- Prenatal findings were tabulated as
  1) Fetal structural anomalies
  2) Non-structural anomalies (ie. umbilical cord problems, growth or fluid level abnormalities, or placental anomalies)
  3) Fetal edema, which ranged from increased nuchal translucency to hydrops

### Figure 1: Cohort Overview



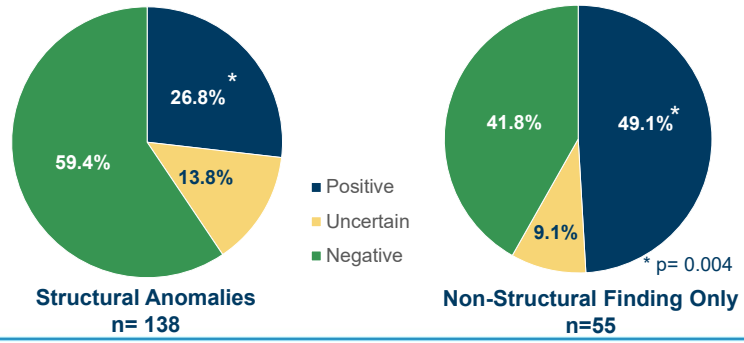

### Figure 2: Diagnostic Rate by Time of Detection



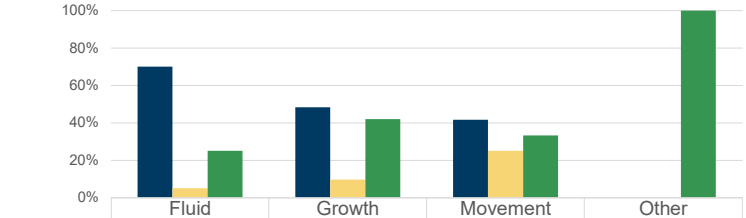

## OVERALL RESULTS

- In total 349 cases were reviewed
  - 198 (56.7%) cases had an anomaly detected prenatally **[Figure 1]**
  - 27.8% of cases (n=55) with a prenatal finding did not have a structural anomaly
- The diagnostic rate for the entire cohort was 29.8% (104/349) **[Figure 2]**
  - 38 additional cases (10.9%) had an uncertain report due to a VUS or uncertain clinical overlap with the reported gene
  - Cases detected prenatally had a higher rate (not sig.) compared to those with normal prenatal imaging
  - Including uncertain findings, 45.4% (90/198) of cases with a prenatally-detected feature had a reportable finding
- Age at testing, positive family history & availability of samples for trio analysis did not significantly impact diagnostic rate
- 25.9% (7/27) of cases with fetal edema had a positive finding
  - Consistent with recent literature reporting 29% diagnostic rate for pregnancies with fetal edema detected[4]
  - In our cohort, severity of fetal edema did not correlate to higher diagnostic rates

### Figure 3: Diagnostic Rates of Structural vs. Non-structural Prenatal Findings




#### Types of Prenatal Findings in Cases without Structural Anomalies




| | Fluid | Growth | Movement | Other |
|---|---|---|---|---|
| Positive | 70.0% | 48.4% | 41.7% | 0.0% |
| Uncertain | 5.0% | 9.7% | 25.0% | 0.0% |
| Negative | 25.0% | 41.9% | 33.3% | 100.0% |

## NON-STRUCTURAL FINDINGS

- 55 cases (15.7%) had at least one prenatal finding in the absence of any fetal structural anomalies
  - 25 with abnormal fluid levels
  - 31 with fetal growth abnormalities
  - 11 with decreased/abnormal fetal movements
  - 5 with other pregnancy-related anomalies (ie. umbilical cord, placental anomalies)
- The diagnostic rate in this group was 49.1% (27/55)
  - Significantly higher than the 26.8% (37/138) rate for cases with at least one structural anomaly reported (p=0.004) **[Figure 3]**

## TAKE-HOME POINTS

- Overall, 45.4% of infants with any abnormal prenatal ultrasound finding had a reportable result on DES, which is more than infants who came to medical attention after birth (35.4%).
- Infants with abnormal ultrasound findings other than structural fetal anomalies had a diagnostic rate of 49.1%, significantly higher than the rate for cases with a structural anomaly reported (26.8%; p=0.004).
- Prenatal DES, even in the absence of structural fetal anomalies, is a valuable diagnostic tool. Specifically, pregnancies with fetal edema, abnormal fluid levels, growth anomalies and abnormal fetal movements may benefit from DES.

## REFERENCES

1) Petrovski S, et al. (2019) *Lancet* 393:758 - 67.
2) Lord J, et al. (2019) *Lancet* 393:747-57.
3) Vora NL, et al. (2017) *Genet Med*19:1207–1216.
4) Sparks TN, et al. (2020) *N Engl J Med*. 10.1056/NEJMoa2023643. [published online ahead of print, 2020 Oct 7].

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