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# Clinical outcomes of genome-wide cfDNA for cases screening positive for trisomies 3, 7, 15, 16, and 22

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## I. Objectives

Cell-free DNA (cfDNA) testing for common aneuploidies has been integrated into prenatal care for both high-risk and average-risk pregnancies. Expansion of cfDNA technology includes select microdeletions, large copy number variants, and esoteric aneuploidies. Initial data regarding outcomes from a commercial genome-wide cfDNA test has been previously described.[1,2,3] When positive results for esoteric aneuploidies are reported, residual risk for fetal mosaicism/aneuploidy, confined placental mosaicism, uniparental disomy, and adverse pregnancy outcome may exist. The outcomes of the five most common esoteric aneuploidies seen with a commercial genome-wide cfDNA test are described here and are consistent with recent literature[4,5] from other groups.

## II. Methods

A retrospective analysis was performed on over 28,000 maternal blood samples submitted for genome-wide cfDNA analysis. Samples were subjected to DNA extraction, library preparation, and genome-wide massively parallel sequencing.[6] Sequencing data were analyzed using a novel algorithm to detect trisomies and subchromosomal, genome-wide copy number variant (CNVs) 7Mb and larger.[1] The results that screened positive for an esoteric aneuploidy (excluding 21, 18, 13, X and Y) were reviewed. Clinical outcomes were requested from ordering providers as part of routine follow-up of all positive samples. Adverse pregnancy outcomes were defined as growth restriction, preterm labor, miscarriage/fetal demise, or structural ultrasound anomalies based on clinical information available from providers.

## III. Results

Approximately 1400 of over 28,000 samples (~5%) returned a positive result for any aneuploidy, CNV, or microdeletion included on the test. Among these, approximately 200 cases (~14%) were positive for an esoteric aneuploidy. In order of frequency, the most common positive result for an esoteric aneuploidy involved chromosomes 7, 16, 22, 3, and 15. Cases that screened positive for trisomy 15, 16, or 22, were more likely to have an adverse outcome (>70%) while trisomy 7 was less likely to have an adverse outcome (<30%). Cases with reported trisomy 3 risk appear to fall in between the two groups

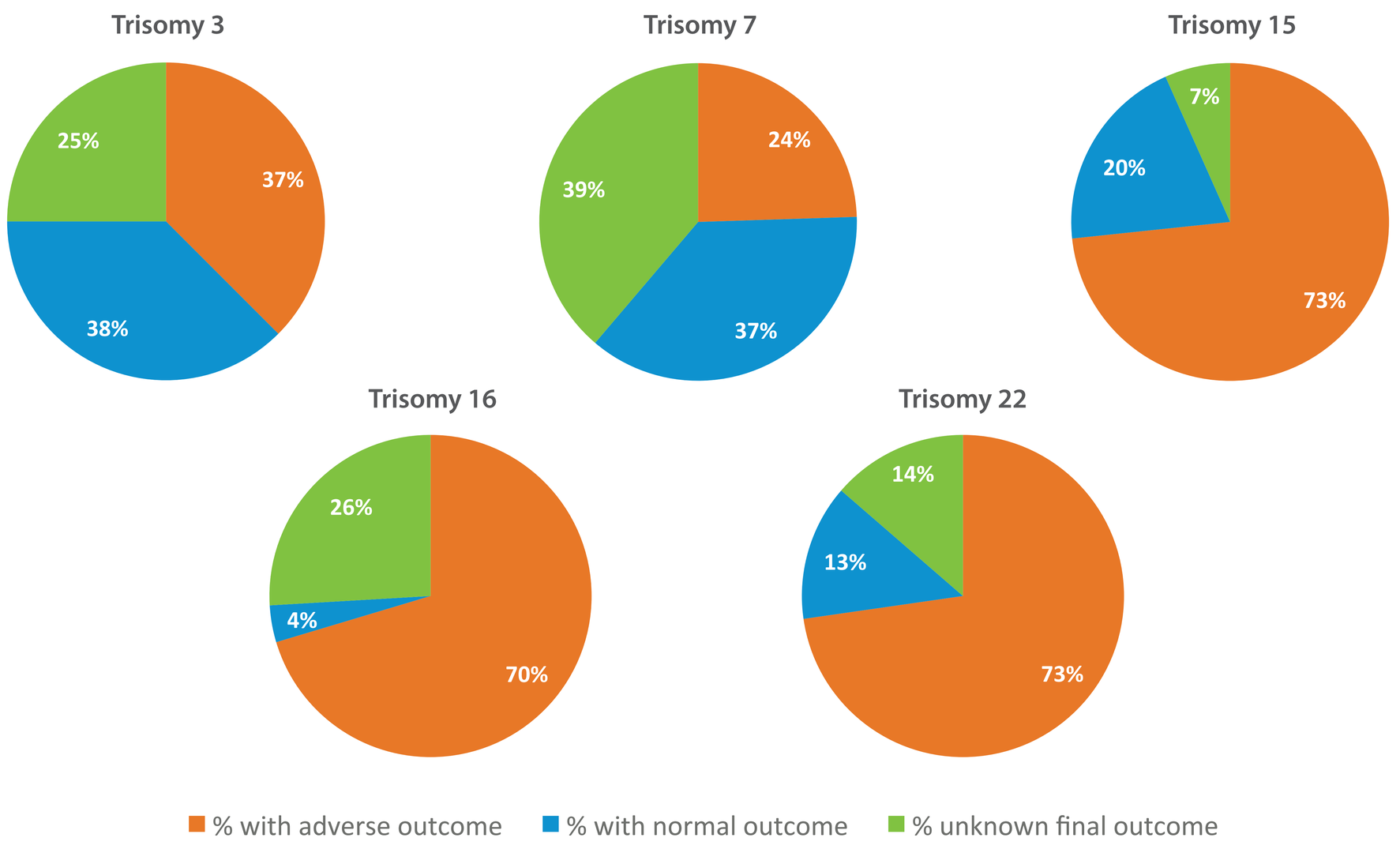
### Table 1. Distribution of outcomes by chromosome

**Confirmed fetal events include cases of fetal mosaicism or uniparental disomy in addition to cases of full trisomy.**
**Cases that were suspected true positives had significant ultrasound findings suggestive of some degree of fetal or placental involvement.**

| Trisomy | # of cases | Confirmed fetal event | Confirmed placental event | SAB/FD – no testing | Suspected true positive – no testing | Discordant – twin demise | Discordant | Normal outcome – no testing | Unknown |
|---|---|---|---|---|---|---|---|---|---|
| 3 | 16 | 0 | 0 | 1 | 0 | 1 | 7 | 1 | 6 |
| 7 | 49 | 1 | 0 | 0 | 2 | 1 | 22 | 6 | 17 |
| 15 | 15 | 3 | 0 | 6 | 0 | 2 | 3 | 0 | 1 |
| 16 | 27 | 3 | 1 | 5 | 3 | 2 | 4 | 0 | 9 |
| 22 | 22 | 4 | 1 | 7 | 0 | 1 | 5 | 0 | 4 |

### Figure 1. Distribution of pregnancy outcomes by chromosome

**Adverse pregnancy outcomes were defined as growth restriction, preterm labor, miscarriage/fetal demise, or structural ultrasound anomalies based on provider feedback.**




## IV. Conclusions

A cfDNA result that is positive for trisomy 15, 16, or 22 carries a significant risk for adverse outcome in the pregnancy, even when amniocentesis does not confirm the result. Although the risk is lower for results that are positive for trisomy 3 or 7, a risk of 24-37% for an adverse outcome is not insignificant. If a patient wishes to defer confirmation until after birth or has a normal amniocentesis result, the provider may consider additional surveillance of the pregnancy given the risk for adverse outcomes.

The differences between outcomes can likely be attributed to the origin of the trisomic event. Literature on placental mosaicism describes meiotic events (as is often seen with trisomies 15, 16 and 22) to be at increased risk for fetal trisomy, uniparental disomy, or pregnancy complications.[7,8] Conversely, mitotic events (as is often seen with trisomies 3 and 7) are more likely to be benign. Although sample sizes are limited, preliminary conclusions about the increased risk for adverse outcome can be drawn from this cohort. Missing or incomplete follow-up for clinical cases is a limitation of this cohort, but the available data provides a valuable tool for clinical counseling.

**Key points:**

- The most common esoteric aneuploidies suggested by genome-wide cfDNA are trisomies of 7, 16, 22, 3, and 15.
- A positive cfDNA result for trisomy 15, 16, and 22 carry a >70% risk for an adverse pregnancy outcome.
- A positive cfDNA result for trisomy 3 or 7 carries a risk for an adverse pregnancy outcome, but this risk appears to be less than that of certain other chromosomes.
- Underlying biological mechanisms may explain the difference in adverse outcome rates.

## V. References

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