

# Discordant noninvasive prenatal testing (NIPT) results and placental health: A blessing in disguise

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## INTRODUCTION

Since the introduction of NIPT 4 years ago, discordant invasive and noninvasive testing results have challenged providers and patients alike. Commonly dismissed as technical error or artifact, 'false positive' NIPT results often go unexplained and unexplored. The inherent 'biological limitation' of NIPT reflecting early placenta trophoblast is generally poorly understood by providers, in part due to the unclear impact of a genetically abnormal placenta on pregnancy health. Conversely, we propose this 'limitation' of sorts can be exploited as a reflection of placental health risk and predictor of potential pregnancy complications. Herein we describe a retrospective review of a subset of discordant NIPT results and the associated placental findings and outcomes.

## BACKGROUND

Trisomy 16 (T16) and Trisomy 22 (T22) are unique for being relatively common abnormalities found in abortus tissue, and yet rarely confirmed via amniocentesis. Grati et al, 2014, found confined placental mosaicism (CPM) to be the rule with T16 and T22 rather than the exception, with placenta dysfunction a common byproduct. Maternal meiotic error is considered the usual culprit, with trisomy rescue common. Confounding the issue is the likelihood that chromosome 16 is imprinted, and thus every rescue event risks the possibility for uniparental disomy (UPD). Of significant relevance, the combination of CPM and UPD for chromosome 16 is thought to confer the greatest risk for placental dysfunction.

## RESULTS

Over one hundred cases of Trisomy 16 and Trisomy 22 have been reported in the last two and a half years. A disproportionately high number of positive serum screens and/or ultrasound findings (>50%) prompt testing in the T16 positive cohort, compared to our general high risk population. T22 indications were more similar to the general high risk population cohort, with a notable increase in complex, multiple indications cases. Eighty six percent of T16 and 71% of T22 'false positive' cases report some degree of placental dysfunction or pregnancy complication, including abnormal serum values, intrauterine growth retardation (IUGR), placental abruption, preeclampsia, preterm delivery, or co-twin demise. Residual risk for UPD16 went largely untested among the discordant cohort, and likely contributed to placental dysfunction and ultrasound findings.

## CONCLUSIONS

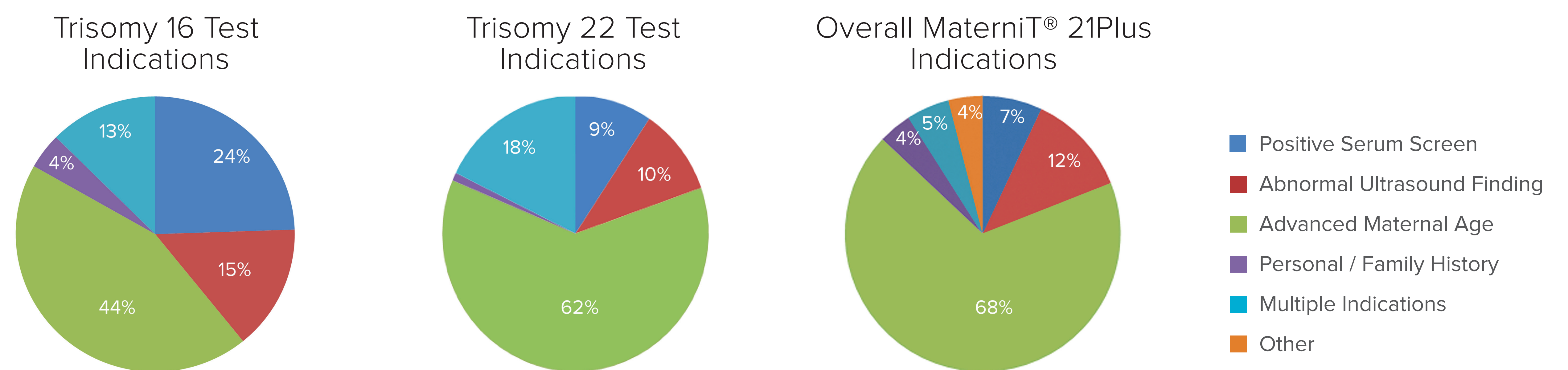
Noninvasive prenatal testing for esoteric trisomies such as T16 and T22 represents a new and expanding paradigm shift in NIPT testing. While fetal constitutional studies remain necessary for confirming any positive finding, careful consideration of the possible implications for discordant results is likewise recommended and can offer invaluable insight and benefit to pregnancy care. Cautionary surveillance of placenta health should ideally extend through term, as pregnancy and delivery complications are commonly reported.

Intrauterine growth retardation, historically a complication of CPM, was consistently reported in our T16 and T22 cohort and often only presents late in pregnancy. Likewise, commonly reported preterm delivery (+/- preeclampsia) poses a late pregnancy complication that clearly would benefit from increased surveillance and preparation.

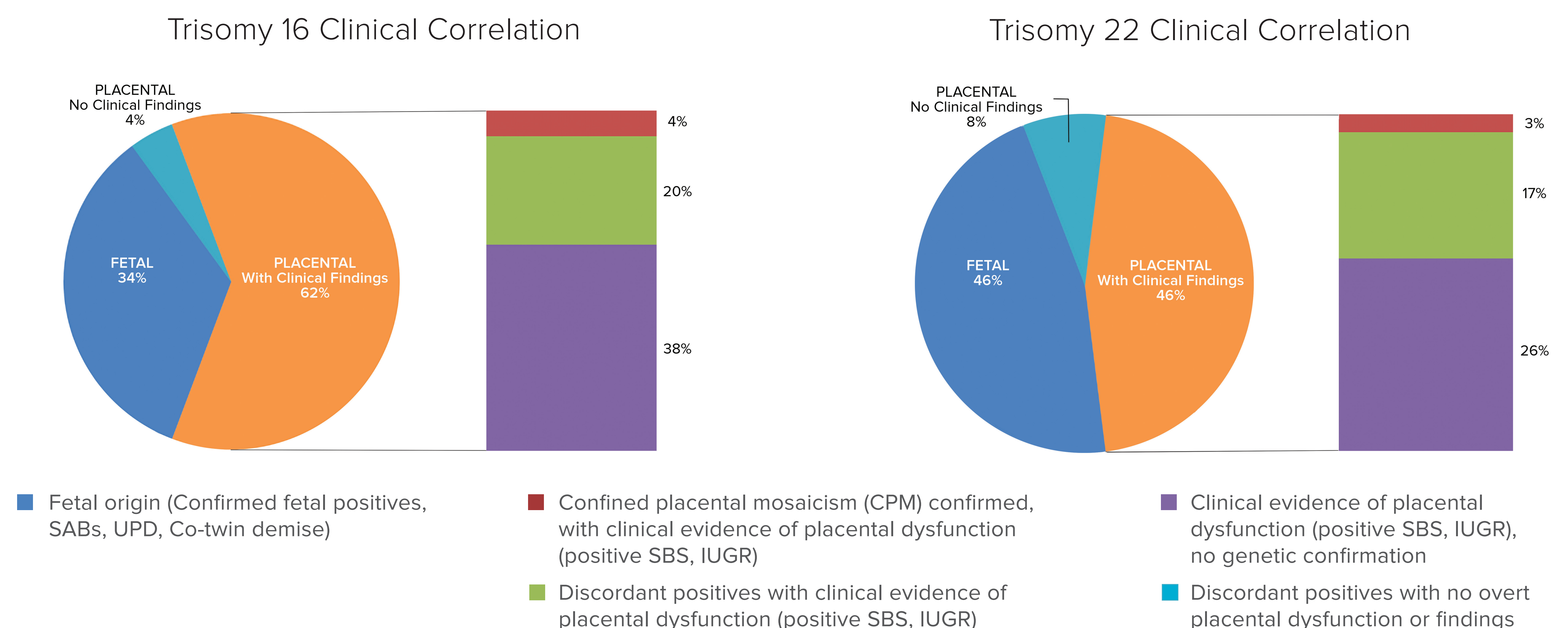
Additional consideration and testing for UPD risk, when applicable, is likewise indicated and often overlooked. For imprinted trisomies detected through NIPT, the addition of targeted UPD studies or SNP array analysis via amniocentesis offers an ideal, comprehensive evaluation of global genetic risk. The presence of UPD in a fetus may lead to phenotypic abnormality as well as increased dysfunction of the placenta in utero.

As NIPT technology and understanding evolves, the utility and focus of this screening tool will likely expand beyond fetal status prediction to include broader pregnancy health concerns and risks. Understanding and appreciating the potential implications of concordant and discordant NIPT results alike can greatly assist providers in the global management of their pregnant patients.

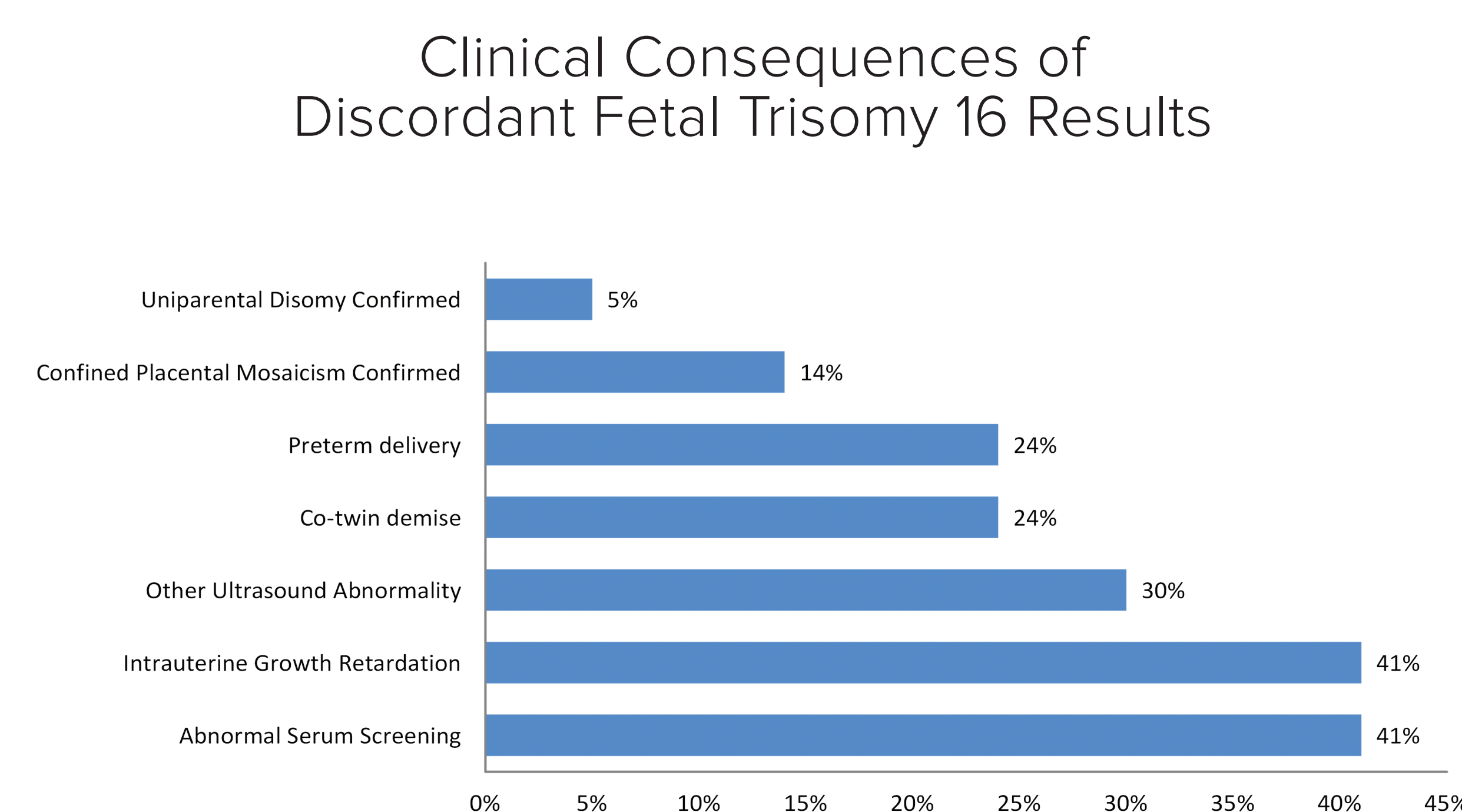
## RESULTS



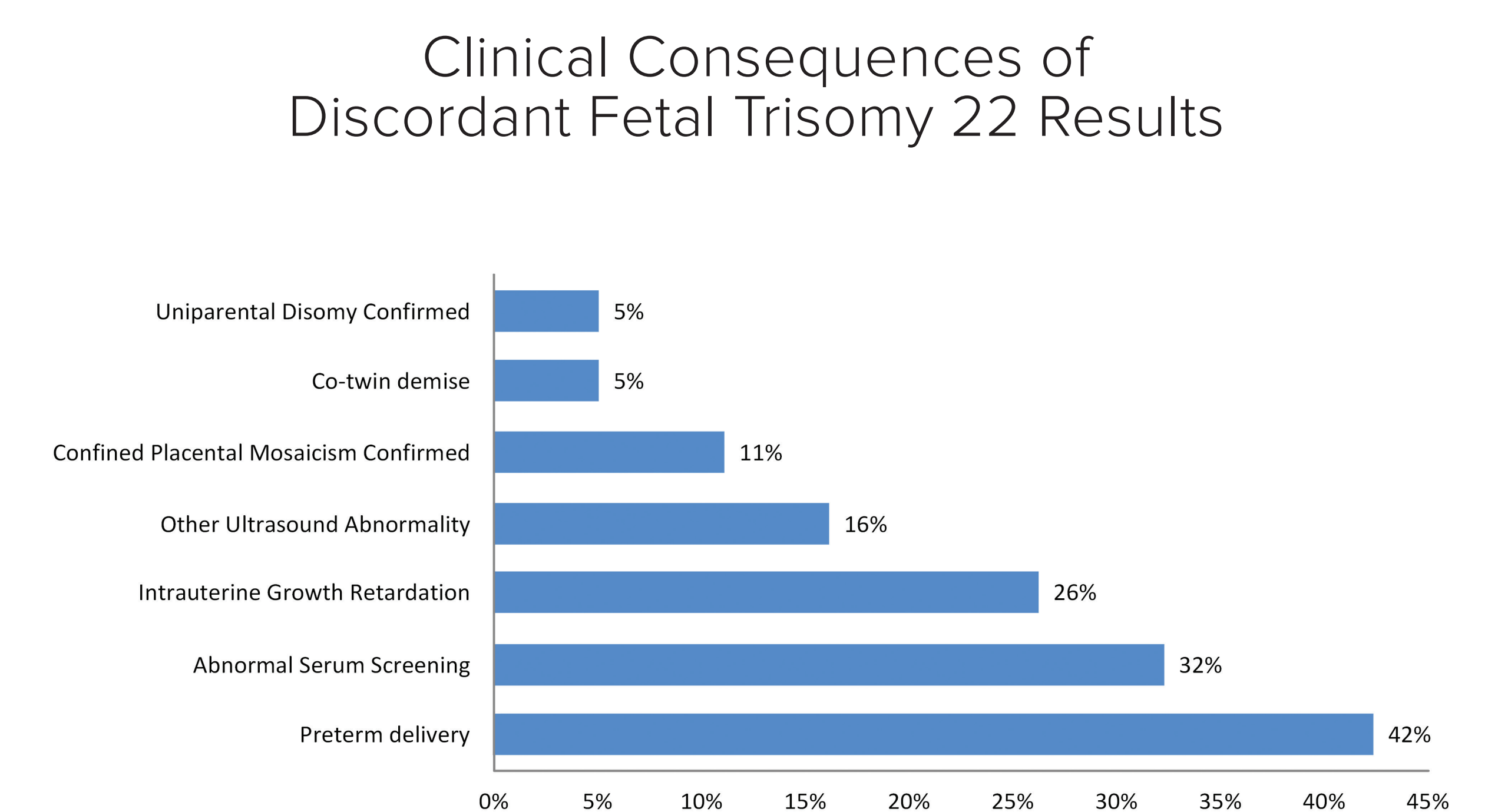
**Figures 1-3:** Trisomy 16 and 22 high risk indications as indicated on test order requisitions compared to overall MaterniT® 21Plus indications as reference. T16 shows a marked increase in positive serum screening and abnormal ultrasound finding indications, prompting testing in over 50% of T16 positive results (inclusive of multiple indications). T22 is more similar to the overall MaterniT® 21Plus breakdown, with a notable increase in complex, multiple indications cases.



**Figures 4, 5:** Trisomy 16 and 22 clinical correlation, inclusive of all confirmed outcomes, grouped by embryologic origin. Specific subsets of placental involvement are delineated.



**Figure 6:** 86% of confirmed discordant T16 positives exhibit clinically relevant pregnancy complications. IUGR and abnormal serum screening were commonly reported among the discordant cohort (41%).



**Figure 7:** 71% of confirmed discordant T22 positives exhibit clinically relevant pregnancy complications. Note marked increase of preterm delivery (42%) among this discordant cohort.

## REFERENCES

- Grati, F.R. Chromosomal mosaicism in human fetoplacental development: Implications of prenatal diagnosis. (2014) J Clin Med. 24;3(3): 809-37. doi: 10.3390/jcm3030809.

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