528

Mosaicism Ratio in cfDNA Testing: A Potential Tool to Identify Discordant Results

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I. Objective

In prenatal cfDNA testing one of the main underlying causes for discordant results is a difference between the genetic makeup of the placenta and the fetus. Chromosomal abnormalities limited to the placenta are often mosaic and may be confined to the placenta. In these cases not all cell free DNA in maternal plasma is affected. This observation can be used to calculate a mosaicism ratio (MR) of affected cfDNA and total cfDNA. This retrospective study aims to determine if this ratio can be used to prospectively identify patients with a higher chance for discordant positive results due to confined placental mosaicism (CPM).

II. Study Design

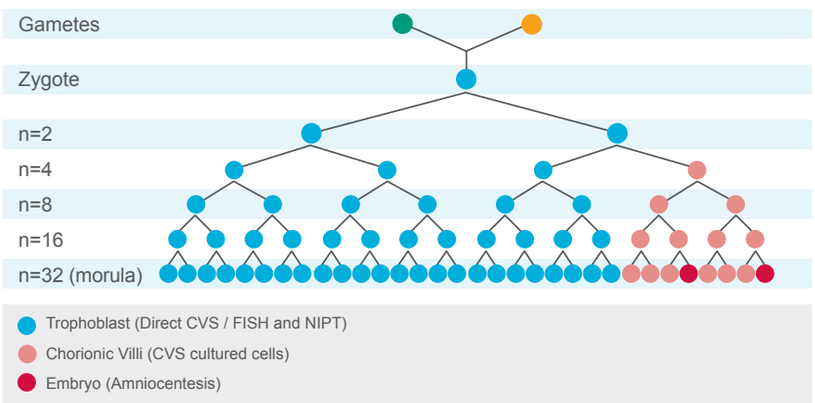
A cohort of 3,373 samples that screened positive for trisomy 21/18/13 with Sequenom Laboratories® NIPT was analyzed using all available *ad hoc* clinical feedback on discordant results. A MR was generated by dividing the fetal fraction estimated for only the aneuploid chromosome over the fetal fraction estimated for all chromosomes. These ratios were then compared to discordant clinical feedback and analyzed.

III. Results

Analysis of MR across all reported positives for trisomies 13, 18, and 21 shows a difference in frequency of potential mosaic results with trisomy 13 showing the greatest likelihood of being mosaic and trisomy 21 the lowest. In all chromosomes, the MR is inversely related to discordant results. In this tested cohort, the PPV decreased from > 99% at an MR ≥ 0.7 to a low of 73% at an MR of 0.1.

Figure 1. Early cell lineage post conception

- The majority of cells develop into placental trophoblast / chorionic ectoderm (Direct CVS preparation & NIPT)
- A small minority of cells develop into chorionic villi / mesoderm (CVS cultured cells)
- Only two cells go on to form the embryo and amniotic tissues (Amniocentesis)



Thomas, D et al. (1994, July 10) *Trisomy 22, placenta*. Retrieved from https://www.sonoworld.com/Fetus/page.aspx?id=182.

Figure 2. Impact of mosaicism ratio on positive predictive value

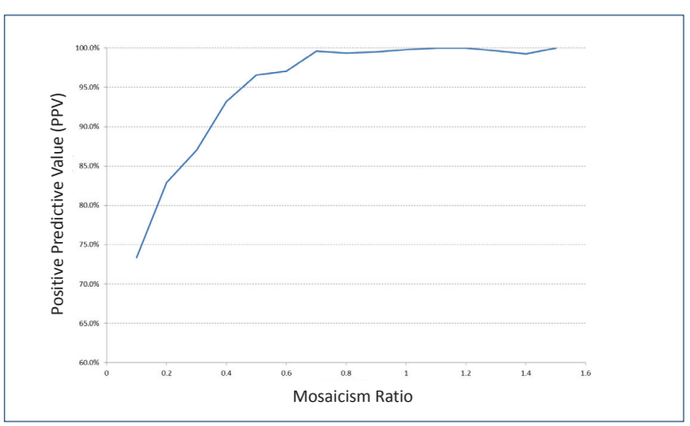


Figure 3. Discrepant results as a function of mosaicism ratio

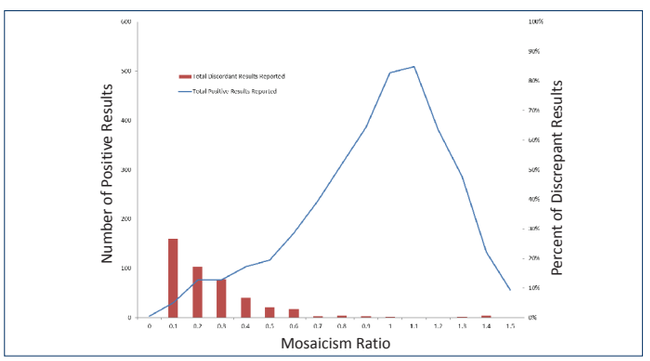


Figure 4. Case examples at varying mosaicism ratios

	Case 1	Case 2	Case 3
Trisomy	18	9	13
Mosaicism Ratio	0.20	0.77	1.07
High Risk Indication	AMA	USF (IUGR and VSD)	AMA
Diagnostic testing	CVS	20% Mosaic T9 on Amnio	Amnio
Outcome	Normal CVS, normal US	Cord blood normal	TOP

IV. Conclusion

Prenatal management is a 40-week continuum of care for the patient, rather than a discrete event. Therefore each data point gathered throughout the gestation should provide as much clinically relevant information to clinicians to allow them to contextualize all the information available. Ideally clinical data, including CVS analysis and/or postnatal placental studies on all discordant results, would help to solidify the biological connection between MR and CPM, however, it is clear from this study that a value like mosaicism ratio could be used by health care providers to better interpret positive cfDNA screening results.

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