WOMEN'S HEALTH

Mosaicism Ratio: Personalized NIPT insights for multifetal gestations

Your patient is pregnant with dichorionic twins. Her NIPT is positive for aneuploidy.

Will one or both fetuses potentially be affected?

Your patient is a carrier of an X-linked recessive disorder and is pregnant with dichorionic twins. Her NIPT has detected Y chromosome material.

Will one or both of her fetuses be at risk for the X-linked condition in the family?

Mosaicism ratio for multifetal gestations may help answer these questions.

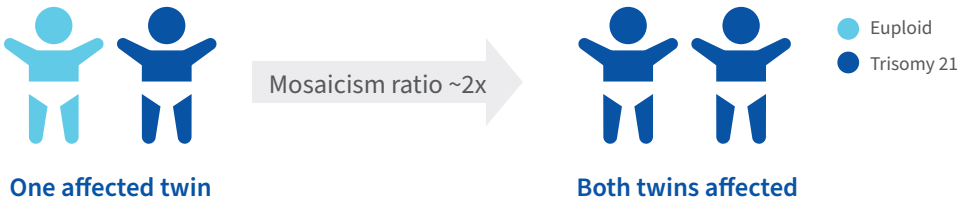
Multifetal mosaicism ratio: Aneuploidy

- Similar to its application in singleton pregnancies, mosaicism ratio can be calculated for multifetal gestations in the event of a positive NIPT result for trisomy 21, 18, or 13.[1,2]
- The mosaicism ratio calculation requires two data points:
  - **Affected fraction** – the percentage of cell-free DNA that is impacted by aneuploidy
  - **Fetal fraction** – the percentage of cell-free DNA contributed by the pregnancy

$$\text{Mosaicism Ratio} = \frac{\text{Affected fraction}}{\text{Fetal fraction}}$$

- **The difference is in the interpretation.** In the context of a singleton gestation, a depressed mosaicism ratio may be indicative of placental mosaicism, co-twin demise, or other biological phenomenon.[2] For a dichorionic twin gestation, the most likely reason for a depressed mosaicism ratio is that only one of the fetuses is affected with aneuploidy.[2]

When only one twin was affected with trisomy 21, the average MR of chromosome 21 was 52% of the MR when both twins were affected.[2]



One affected twin

Both twins affected

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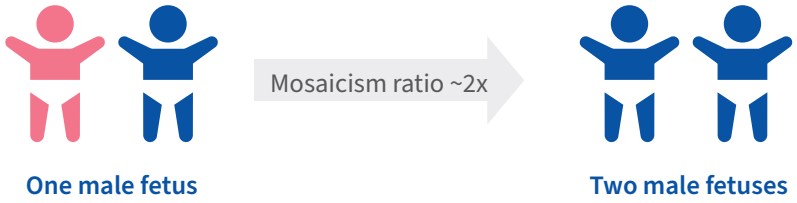
* = Chr21 MR of singleton gestations was used as a biological proxy for two affected twins

Multifetal mosaicism ratio: Y chromosome

- When Y chromosome material is detected by NIPT in a multifetal gestation, at least one of the fetuses is predicted to be male.
- The mosaicism ratio calculation for the Y chromosome compares the amount of Y chromosome material to the overall fetal fraction.

When one twin was male, the average MR of the Y chromosome was 48% of the Y MR of two male fetuses.[2]



One male fetus

Two male fetuses

The importance of chorionicity

Chorionicity is a key factor for risk assessment and the application of multifetal mosaicism ratio to patient counseling. Because cfDNA is assessing DNA from the placenta, the number of placentas will guide interpretation. In general, for a monochorionic twin pregnancy, cfDNA results (for aneuploidy and the Y chromosome) typically reflect both fetuses. In the context of a dichorionic pregnancy, mosaicism ratio may be a useful tool for interpretation of aneuploidy results and for fetal sex determination.[2]

Triplets and higher-order multifetal gestations

The principles of mosaicism ratio are not just applicable to twins, but also have demonstrated utility in triplet and higher-order multifetal pregnancies. Please refer to our new publication in Prenatal Diagnosis, titled "Application of Mosaicism Ratio to Multifetal Gestations", to learn more.[2]

How is multifetal mosaicism ratio reported?

For patients with a positive result for trisomies 21, 18, and 13, a Mosaicism Ratio comment will feature in the Lab Director Comments box on the MaterniT 21 PLUS lab report.

Aneuploidy

Test Result	**Positive** **Trisomy 13**
Lab Director Comments This is a reported twin gestation. This specimen showed an increased representation of chromosome 13, suggestive of trisomy 13. In the context of a twin gestation, data from this sample suggests aneuploidy affecting one fetus, though the possibility of two affected fetuses cannot be ruled out. (Rafalko et al, PLOS ONE, 2021) Results should be interpreted in the context of chorionicity and other clinical information. Genetic counseling and confirmatory diagnostic testing are recommended.	

Y chromosome

Test Result	**Negative**
Lab Director Comments This is a reported twin gestation with Y chromosome material detected. Based on the amount of Y material, the probability of male/female twins is 95.6% and male/male twins is 4.4% (Rafalko et al, PLOS ONE, 2021). Results should be interpreted in the context of chorionicity and other clinical information.	

Summary

- Multifetal mosaicism ratio supports patient counseling by using personalized data specific to *your* patient's specimen
  - In the event of a positive result, multifetal MR may help identify whether one or more fetuses are affected with aneuploidy
  - When Y chromosome material is detected, multifetal MR may help determine whether one or more fetuses are male
- Chorionicity is an important factor in the interpretation of multifetal mosaicism ratio results
- Multifetal mosaicism ratio has applications for twin, triplet, and higher-order multifetal gestations

Test/Panel Name	Test No.	Fetal sex opt-out
MaterniT 21 PLUS Core (Trisomy 21, 18, 13, fetal sex)	**451927**	451951
MaterniT 21 PLUS Core + SCA* (Singletons only)	**451934**	452112
MaterniT 21 PLUS Core + ESS**	**451931**	452136
MaterniT 21 PLUS Core + ESS + SCA* (Singletons only)	**451937**	452122
GENOME-Flex (Add On)	**452104**	n/a
GENOME-Flex (Add On) Redraw	**452114**	n/a
MaterniT GENOME (Singletons only)	**451941**	452106

* Sex chromosome aneuploidies ** Enhanced sequencing series (microdeletions, trisomies 16 & 20)

References

1. Rafalko, J, Caldwell, S, Tynan, J, Almasri, E, Weinblatt, V, & McCullough, R. (2020). Impact of mosaicism ratio on positive predictive value of cfDNA screening. *Prenatal Diagnosis*, 41(1), 28-34. doi: 10.1002/pd.5863
2. Rafalko, J, Caldwell, S, Soster E, Almasri, E, Mclennan G, Liu T, Weinblatt, V, Cacheris P, & McCullough, R. (2021). Application of Mosaicism Ratio to Multifetal Gestations. *PLoS ONE*. Accepted for publication.

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