Understanding chromosomal mosaicism

What is preimplantation genetic testing for aneuploidy?

Preimplantation genetic testing for aneuploidy (PGT-A) is a screening test that can be used with in vitro fertilization (IVF) to identify embryos that have the correct number of chromosomes (i.e., euploid embryos). By identifying euploid embryos for transfer, PGT-A may improve IVF implantation rates, reduce the time to pregnancy, and increase live birth rates.

PGT-A is performed on cells that have been removed (i.e., biopsied) from the embryo's trophectoderm (TE), which will develop into the placenta. It is not performed on cells from the embryo's inner cell mass (ICM), which will develop into the baby. The cells of the TE and the cells of the ICM typically have the same chromosomal makeup, as both types of cells are derived from the initial cell that forms when an egg and sperm fuse. For this reason, PGT-A is very accurate.

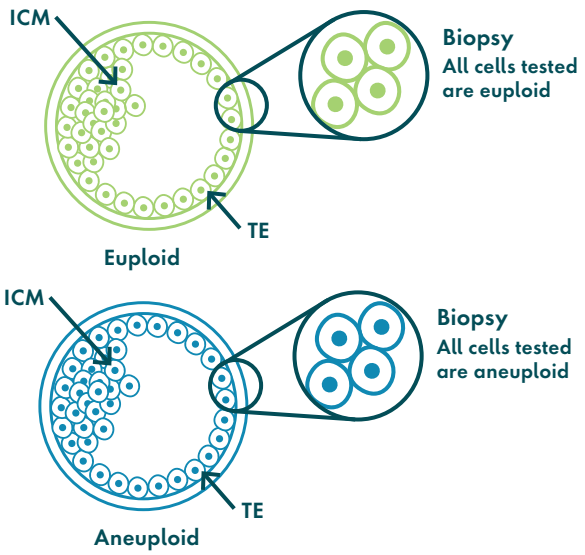
In most cases, PGT-A results show either that all cells tested have the correct number of chromosomes (i.e., are euploid) or that all cells tested have a chromosome abnormality (i.e., are aneuploid) (Figure 1).

What is mosaicism?

In some cases, PGT-A results suggest a combination of euploid and aneuploid cells. This is called mosaicism (Figure 2). Mosaicism is presumed to arise from an error in cell division after fertilization and is likely independent of egg age. The percentage of abnormal cells in an embryo is related to the point at which the initial error occurred; the earlier the error, the larger the percentage of cells impacted.

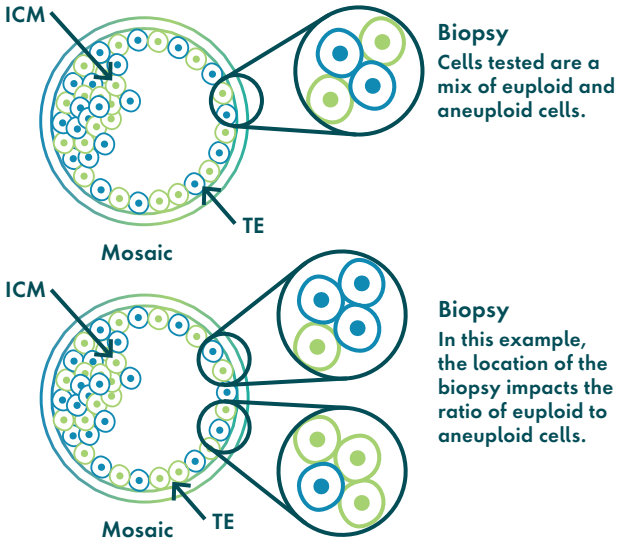
PGT-A can detect mosaicism only if it is present in the few cells that are removed during the biopsy. About 5% to 10% of embryos that undergo PGT-A are mosaic, although this percentage ranges in the published literature from 2% to more than 40%.[1-3]

Figure 1: PGT-A results reflecting the entire embryo's chromosomal makeup



Key: ICM = inner cell mass TE = trophectoderm

Figure 2: PGT-A results suggesting embryonic mosaicism



Key: ICM = inner cell mass TE = trophectoderm

Aneuploid Euploid

What does it mean when an embryo is identified as mosaic?

An embryo is identified as mosaic when PGT-A results suggest a mixture of both euploid and aneuploid cells in the TE biopsy sample. In this scenario, the chromosomal makeup of the entire embryo, a resulting pregnancy, or a baby cannot be accurately predicted.

When mosaicism is detected with PGT-A, it is possible that the ICM is also mosaic. Another possibility is that the mosaicism is isolated to the TE and that the ICM is completely euploid or aneuploid. Of note, mosaicism that is present only in the placenta (i.e., confined placental mosaicism) is well-documented during pregnancy. However, the correlation between TE mosaicism and confined placental mosaicism is not yet understood. Lastly, it is possible for mosaicism to be present in the ICM and not in the TE. These cases are not detected by PGT-A regardless of the technology or where within the TE the biopsy takes place (Figure 3).

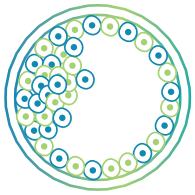
In some cases, the percentage of mosaicism in a biopsy sample can be estimated. There are conflicting data on the correlation between the percentage of mosaicism detected and pregnancy outcomes. However, data suggest that embryos with a lower percentage of mosaicism have a higher likelihood of implantation and ongoing pregnancy than embryos with a higher percentage of mosaicism.[5,6]

Transfer of mosaic embryos

What happens when a mosaic embryo is transferred?

- Our knowledge of the implications of transferring mosaic embryos is continually evolving. However, it is clear that mosaic embryos have a chance of developing into healthy babies. References to help clinicians counsel patients and prioritize mosaic embryos for transfer include the Preimplantation Genetic Diagnosis International Society (PGDIS) Position Statement on the Transfer of Mosaic Embryos 2019,[1] the scoring system proposed by Grati *et al.* 2018,[7] and additional guidance from Besser and Mounts, 2017.[8]

Figure 3: Possible PGT-A results for different categories of mosaicism

Mosaicism categories	Possible PGT-A results
Total mosaic 	Euploid
	Mosaic
	Aneuploid
ICM mosaic 	Euploid
TE mosaic 	Euploid
	Mosaic
	Aneuploid
ICM/TE mosaic type I 	Euploid
ICM/TE mosaic type II 	Aneuploid

ICM = inner cell mass, TE = trophectoderm

Source: Adapted from Vera-Rodriguez and Rubio, 2017[4]

What happens when a mosaic embryo is transferred? *(continued)*

- Possible outcomes after transfer of a mosaic embryo include:
  - failed implantation
  - miscarriage
  - birth of a healthy baby
  - birth of a baby with intellectual and/or physical birth defects
- Factors that may influence the outcome of a mosaic embryo transfer include:
  - the amount of extra or missing chromosomal material
  - the chromosome(s) involved
  - the percentage of euploid versus aneuploid cells
  - the cell types and/or organ systems ultimately impacted by the abnormality
- Outcome information on mosaic embryo transfers is limited. Therefore, precise risk estimates associated with these clinical scenarios are not readily available.

When should a mosaic embryo be considered for transfer?

- Professional groups such as PGDIS and the World Congress on Controversies in Preconception, Preimplantation, and Prenatal Genetic Diagnosis (CoGEN) state that the transfer of mosaic embryos may be considered when there is no alternative (e.g., no euploid embryos are available).[1,9]
- Patients should discuss the benefits and limitations of a mosaic embryo transfer with their reproductive healthcare provider or a genetic counselor to ensure they understand the test results, possible implications, and options.[1,8,10]
- Invitae's experienced genetic counselors are here to help. Counselors may be reached on demand at 800-436-3037 or clinconsult@invitae.com. Patients may also schedule a genetic counseling appointment online at invitae.as.me/schedule.php.

What recommendations should patients consider after they transfer a mosaic embryo?

- When transferred, mosaic embryos appear to be associated with lower implantation rates and higher miscarriage rates than transferred euploid embryos, so it is important to understand the possiblity of an undesirable outcome.[5,11]
- Diagnostic testing during pregnancy is strongly encouraged after a mosaic transfer.[1,10] Results of amniocentesis are the most representative of the baby. Non-invasive prenatal screening (NIPS) and chorionic villus sampling (CVS) test placental cells derived from the TE. They do not test fetal cells.
- Patients should be encouraged to inform both their reproductive health provider and the PGT-A laboratory about the outcome of their pregnancy, including prenatal test results, the results of products of conception testing in the case of a miscarriage, and any genetic or health issues present in the baby or child after birth. Knowledge of outcomes helps improve the care and testing of patients in the future.

Answers to common patient questions

Does a rebiopsy of a mosaic embryo help?

The embryo sample used for rebiopsy is also taken from the TE, so retesting will not provide any information about the ICM. In addition, the results of a rebiopsy do not negate the initial mosaic results. Therefore, rebiopsy of a mosaic embryo is not typically recommended.

I transferred a mosaic embryo and had a miscarriage. Now what?

Unfortunately, miscarriage is common during early pregnancy. Since mosaic embryos have some proportion of aneuploid cells, the mosaic abnormality detected on PGA-T could have led to the miscarriage. It is also possible that the miscarriage was caused by an unrelated chromosome abnormality or that it happened for a reason unrelated to the embryo's genetics.

Testing after a pregnancy loss can determine if there was a chromosomal reason for the miscarriage. If you decide to undergo testing on the pregnancy loss (i.e., products of conception testing), provide the results to both your reproductive health provider and the PGT-A laboratory. This information will help improve the quality of care and testing in the future.

Can I do NIPS during pregnancy to clarify mosaic PGT-A results?

Diagnostic testing is recommended to clarify the results of PGT-A. The cells tested by NIPS (non-invasive prenatal screening, also known as NIPT, or cell-free testing) or by CVS (chorionic villus sampling) are placental cells derived from the TE. While these cells are likely representative of the ICM and the developing baby, only an amniocentesis tests true fetal cells.

I transferred a mosaic embryo and had a normal amniocentesis result. Am I in the clear?

A normal amniocentesis result is very reassuring. However, it cannot rule out the possibility that the abnormal cells detected by PGT-A are present somewhere in the placenta and/or baby and may cause health issues later in development or life. In addition, while "rescue" of aneuploidy has been documented in the literature, this can result in uniparental disomy (i.e., when two copies of a chromosome come from the same parent), which has accompanying risks. Because long-term studies of mosaic embryo transfers are very limited, there is little information about the presence of abnormal cells in children born from mosaic embryo transfers.

References

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8. Besser AG, Mounts EL. Counselling considerations for chromosomal mosaicism detected by preimplantation genetic screening. *Reprod Biomed Online.* 2017;34(4):369–74.
9. CoGEN position statement on chromosomal mosaicism detected in preimplantation blastocyst biopsies. Virtual Academy of Genetics Online Educational Program. Accessed March 5, 2020. https://ivf-worldwide.com/cogen/oep/publications/cogen-position-statement-on-chromosomal-mosaicis2m-detected-in-preimplantation-blastocyst-biopsies.html
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