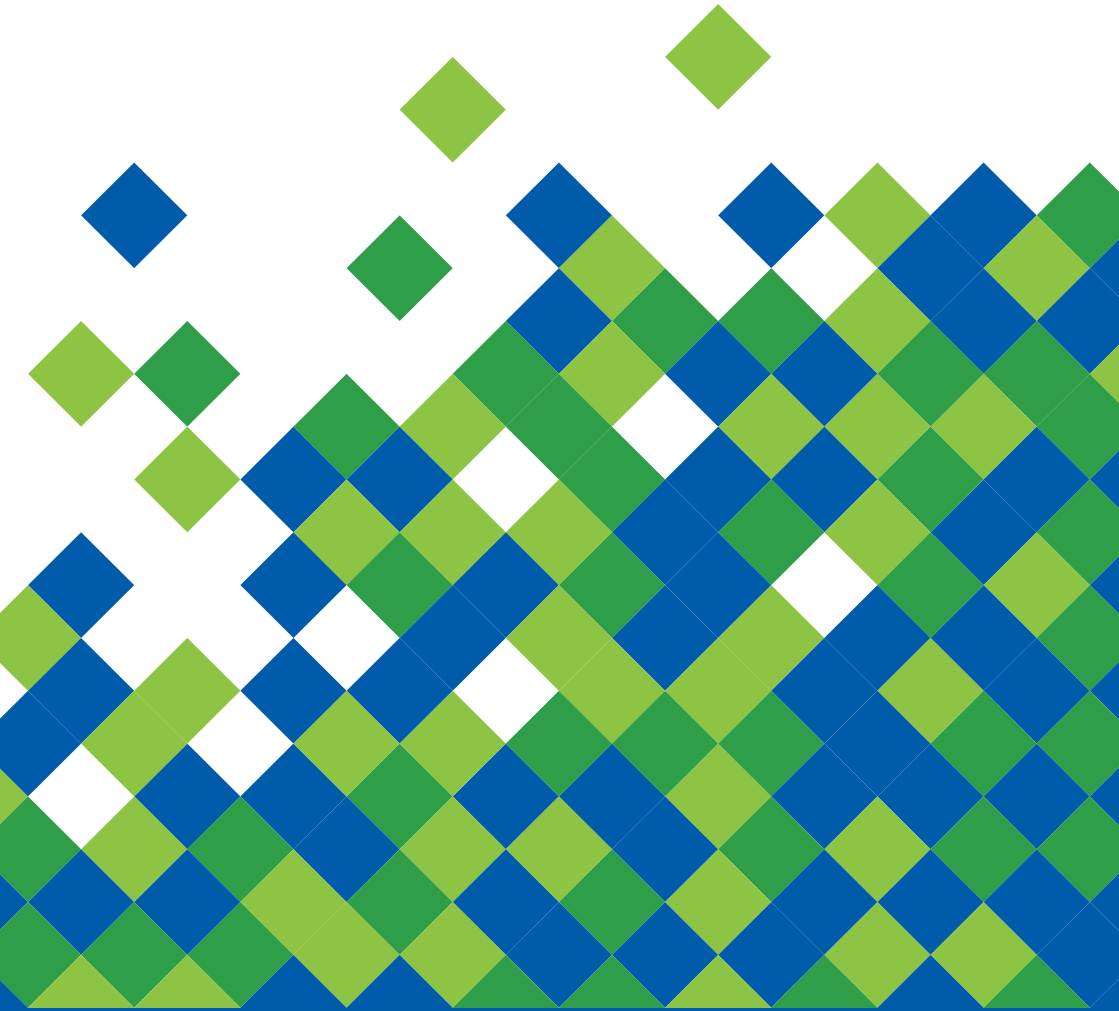


# Clinicians' Guide to Mosaicism

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## Introduction

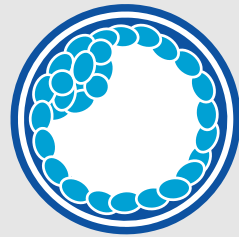
In the last several years, a new technology called Next Generation Sequencing (NGS) has emerged for preimplantation genetic testing for aneuploidies (PGT-A, previously known as PGS), which has enabled the reliable detection of [mosaic](#) in PGT-A samples.<sup>1</sup> As a result of this advancement, mosaic is now recognized as a third category of potential PGT-A results, alongside euploid and aneuploid.



Euploid



Mosaic



Aneuploid



While we continue to examine and learn about this new class of results, this guide explains what we have learned so far and provides a summary of current guidelines and research. It is important to note that mosaic follow-up data is limited, and the research performed to date is preliminary and based on small sample sizes.

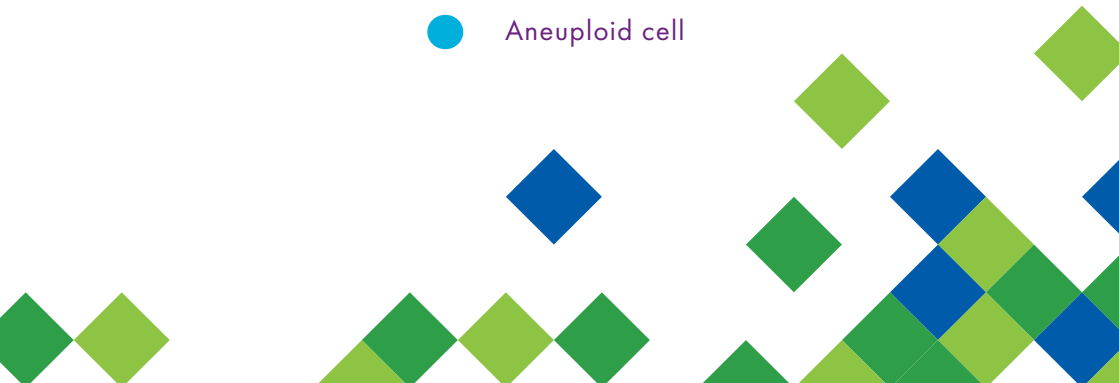
Further studies are needed, and CooperSurgical Fertility and Genomic Solutions is proud to be at the forefront of this discussion, performing key research to advance our understanding of the clinical impact of mosaic and ultimately improve patient outcomes.

## What is mosaicism?

Mosaicism is the presence of two or more cell lines, each with a different genotype, within a single embryo, tissue, or individual. Mosaic embryos contain two or more populations of cells with differing chromosome content (e.g. some cells are euploid and others aneuploid).

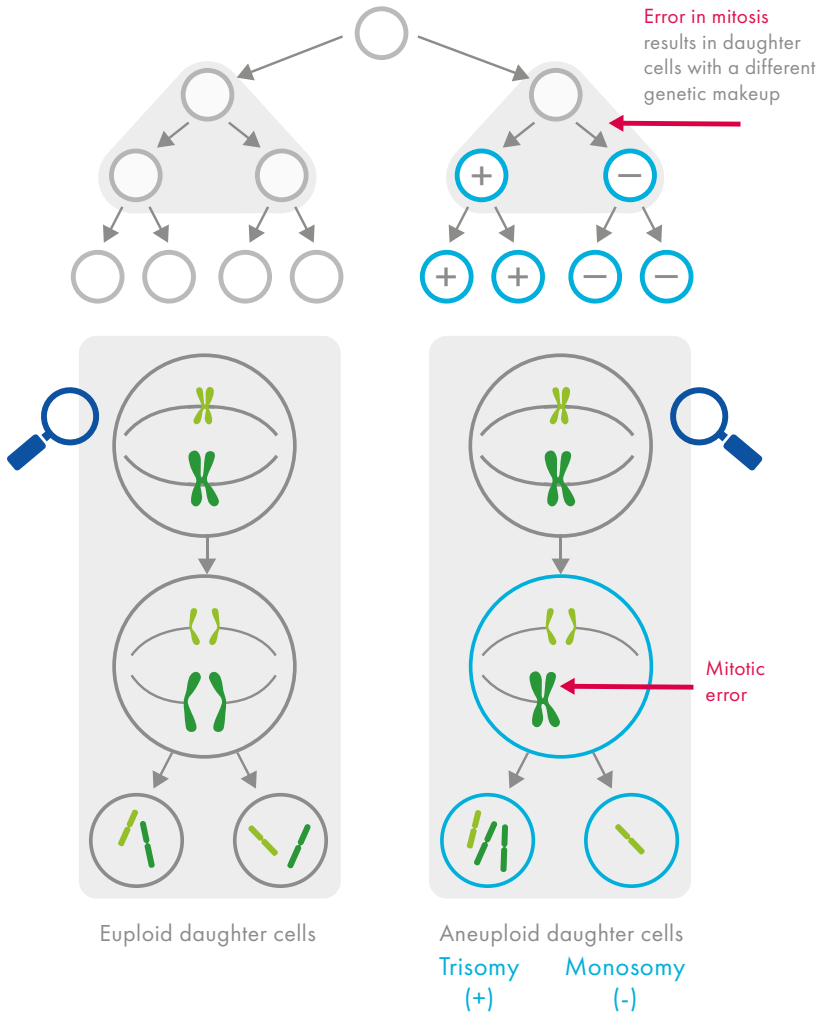


-  Euploid cell
-  Aneuploid cell



# How does mosaicism arise?

Complete aneuploidy is a result of errors in **meiosis** that occur during gamete maturation; thus, aneuploidy rates increase with maternal age. Conversely, mosaicism is thought to result from errors in **mitosis**, not meiosis, that occur during embryo development. Thus, mosaicism rates appear to be **independent of maternal age**.<sup>1</sup>

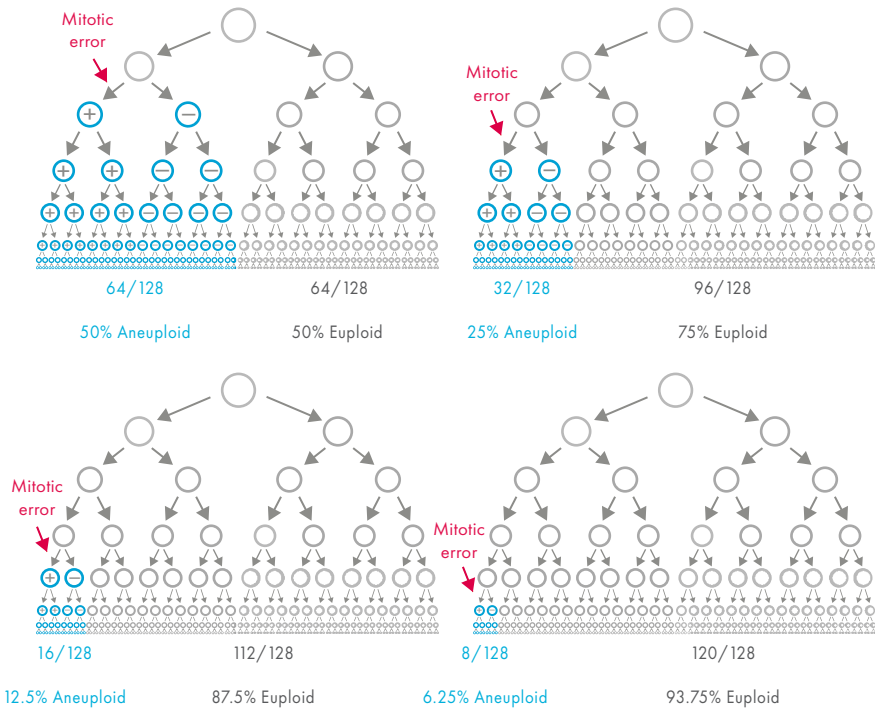


Due to the nature of mitotic cell division (as shown above), the presence of mosaic monosomy does not preclude the presence of mosaic trisomy in the same embryo.

# The impact of timing

The proliferation of embryonic mosaicism is related to the timing of the mitotic error. If the error happens in an early round of cell division, there will be more cells impacted than if it happens in a later round.

## Mosaicism models based on the timing of mitotic error



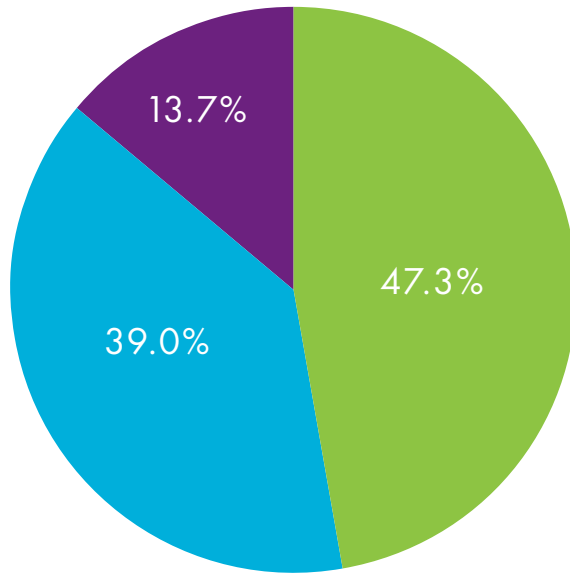
PGT-A is typically performed on day 5 (blastocyst stage) biopsies when the cell has approximately 100–200 cells. The models shown represent embryos with 128 cells.



## Mosaicism incidence

Our data suggest that the **clinical incidence of mosaicism is around 14%**. Many current studies, though, quote the rates of mosaicism in blastocyst biopsies to be higher at 20–30%.<sup>1-5</sup> Approximately, 4.7% of the aneuploid samples found to be mosaic in one or more chromosomes and aneuploid in one or more chromosomes. Because these samples contain a meiotic aneuploidy, they would be clinically classified as ‘aneuploid,’ not ‘mosaic.’

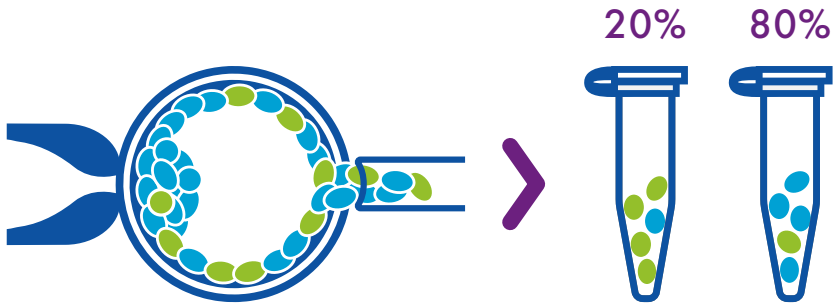
## PGT-A result distribution



| PGT-A finding | Clinical result |
|---------------|-----------------|
| Euploid       | Euploid         |
| Mosaic        | Mosaic          |
| Aneuploid     | Aneuploid       |

# Detecting mosaicism

Routine day 5 biopsies typically contain between 5–10 cells. In a mosaic biopsy of only 5 cells, the lowest possible percent aneuploidy is 20% (1 of 5 cells), and the highest is 80% (4 of 5 cells). Thus, professional society guidelines have recommended that PGT-A samples with <20% aneuploidy be classified as euploid, 20–80% as mosaic, and >80% as aneuploid.<sup>6-7</sup> PGT-A by NGS can reliably detect mosaicism within this range.<sup>1\*</sup>



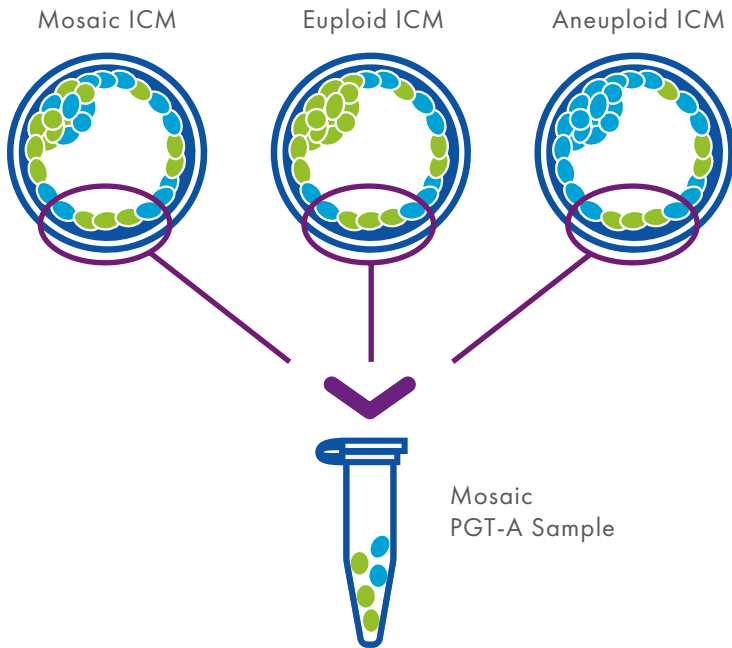
| % Aneuploidy | Classification |
|--------------|----------------|
| <20%         | Euploid        |
| 20–80%       | Mosaic         |
| >80%         | Aneuploid      |

\*Quality dependent.

## Whole embryo concordance

It is possible for mosaicism to either appear throughout an embryo or be confined to specific parts. Blastocyst biopsies are taken from the trophectoderm (TE), which goes on to form the placenta; the inner cell mass (ICM), which goes on to form the fetus, is left untouched. Mosaicism in a trophectoderm sample may or may not indicate the presence of mosaicism in the ICM and may or may not lead to mosaicism in a fetus or live birth.<sup>1,3</sup>

### Mosaicism in the TE



### Mosaicism in the ICM

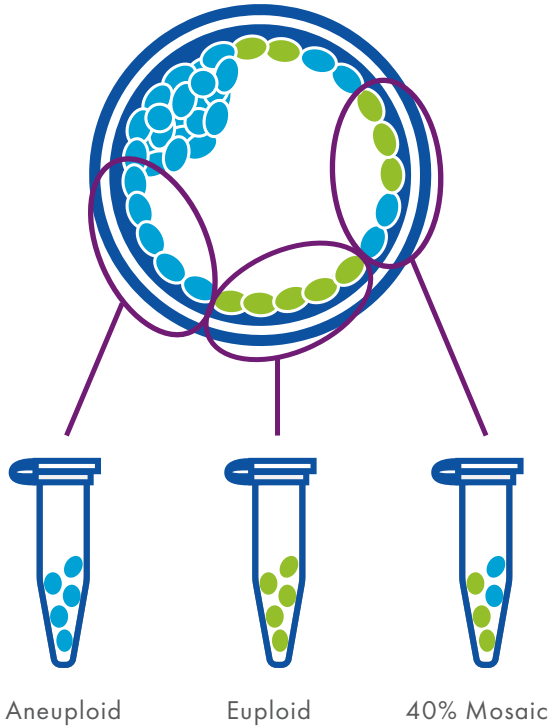
It is also possible that mosaicism could exist in only the ICM and not the TE. An embryo with a mosaic ICM but euploid TE would be called "euploid" by PGT-A, and could result in an adverse outcome. It is important to share POC test results and follow-up data with PGT-A laboratories to help improve PGT-A testing.





## Re-biopsy of mosaic embryos

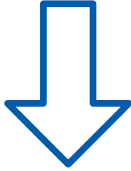
Because blastocyst biopsies are taken from the TE, re-biopsy of an embryo with a mosaic result will not provide any additional information about the ICM and thus is not recommended. Additionally, the results of a re-biopsy do not negate the initial results, even if they differ. Rather, different results would be characteristic of the mosaic classification.



There may or may not be parallels between embryonic mosaicism and prenatal mosaicism. Confined placental mosaicism occurs when the genetic makeup of the placenta (typically determined by a chorionic villus sampling, or CVS) does not match that of the fetus. This is observed in about 2% of pregnancies and is one reason why PGT-A follow-up testing is recommended by amniocentesis rather than CVS.<sup>1,3</sup>

## Clinical impact

When mosaic embryos are transferred, **implantation rates are lower** and **miscarriage rates are higher** (as compared to euploid embryo transfer), **but live births have been reported.**<sup>1-7</sup>



Implantation  
rates decreased



Miscarriage  
rates increased



Live births  
reported

According to Munne & Wells (2017), "There are no detailed studies following up [on] babies resulting from the transfer of mosaic embryos, but to our knowledge more than 100 such babies have been born. So far, there have been no reports of abnormal karyotypes, although it is likely that few pregnancies/children have been subjected to a detailed cytogenetic assessment."<sup>1</sup>

Mosaic embryos have likely been transferred unknowingly for years, as previous PGT-A technologies only allowed for classification as euploid or aneuploid. Because some mosaic embryos may produce viable pregnancies, the practice of excluding all mosaic embryos from transfer may lead to embryo wastage and a decrease in overall pregnancy rates.<sup>1</sup> Genetic counseling is recommended for all patients prior to transferring or discarding mosaic embryos.



## Approaching mosaic results

When no euploid embryos are available, current studies and guidelines suggest prioritizing mosaic embryos based on the percent aneuploidy in the biopsied sample and number of chromosomes involved, as shown below.<sup>1,5</sup> Prioritization based on which chromosomes are impacted may also be considered, but the direction of the change (monosomy vs trisomy) is of less importance.<sup>1,3,5-7</sup>



### Low-level mosaics (20–40% abnormal cells)

have been shown to more frequently have euploid ICMs and result in a 50% ongoing pregnancy rate (n=102).\* Samples with low-level mosaicism involving a single chromosome may be prioritized when no euploid embryos are available.



### High-level mosaics (>40–80% abnormal cells)

have been shown to result in a 30% ongoing pregnancy rate (n=44).\* Samples with high-level mosaicism, as well as samples with low-level mosaicism involving two chromosomes, may be given lower priority.



### Complex mosaics<sup>†</sup> (mosaicism in $\geq 3$ chromosomes)

have been shown to result in a 6% ongoing pregnancy rate (n=32).\* Complex mosaics may be given lowest priority.

Appropriate counseling by a physician and/or genetic counselor is recommended for all PGT-A cases. Prenatal diagnosis by amniocentesis should be offered for all resulting pregnancies.

\*CooperSurgical & Genoma internal data (2015-2016)

<sup>†</sup>Complex mosaics are reported as “Complex Abnormal” on CooperGenomics PGT-A reports.

CooperGenomics' PGT-A reliably detects mosaicism and results are reported in accordance with society recommendations.

We are committed to performing clinically actionable research and we invite you to share any follow-up data you have on outcomes of mosaic transfers.

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## References

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