



# ACOG COMMITTEE OPINION

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## Committee on Genetics

*This Committee Opinion was developed by the American College of Obstetricians and Gynecologists' Committee on Genetics in collaboration with Susan Klugman, MD and Nanette Rollene, MD.*

## Preimplantation Genetic Testing

**ABSTRACT:** Preimplantation genetic testing comprises a group of genetic assays used to evaluate embryos before transfer to the uterus. Preimplantation genetic testing-monogenic is targeted to single gene disorders, and preimplantation genetic testing-aneuploidy is a broader test that screens for aneuploidy in all chromosomes, including the 22 pairs of autosomes and the sex chromosomes X and Y. To test embryos that are at risk for chromosome gains and losses related to parental structural chromosomal abnormalities (eg, translocations, inversions, deletions, and insertions), preimplantation genetic testing-structural rearrangements is used. Independent of the preimplantation genetic testing modality employed, false-positive and false-negative results are possible. Patients and health care providers should be aware that a "normal" or negative preimplantation genetic test result is not a guarantee of a newborn without genetic abnormalities. Traditional diagnostic testing or screening for aneuploidy should be offered to all patients who have had preimplantation genetic testing-aneuploidy, in accordance with recommendations for all pregnant patients. It is especially important to offer diagnostic testing or screening for aneuploidy after preimplantation genetic testing-monogenic or preimplantation genetic testing-structural rearrangements if concurrent preimplantation genetic testing-aneuploidy is not performed. Many limitations exist to preimplantation genetic testing and include challenges in detecting microdeletions and microduplications, de novo variants, and imprinting disorders. An emerging problem has been detection of mosaicism during preimplantation genetic testing-aneuploidy. The clinical utility of preimplantation genetic testing-monogenic and preimplantation genetic testing-structural rearrangements is firmly established; however, the best use of preimplantation genetic testing-aneuploidy remains to be determined. Future research is necessary to establish the overall clinical utility for preimplantation genetic testing-aneuploidy, the subset of patients that may benefit from preimplantation genetic testing-aneuploidy, the clinical significance of mosaicism, and residual risk for aneuploidy in preimplantation genetic testing-aneuploidy screened embryos.

## Recommendations

- Preimplantation genetic testing comprises a group of genetic assays used to evaluate embryos before transfer to the uterus. Preimplantation genetic testing-monogenic (known as PGT-M) is targeted to single gene disorders. Preimplantation genetic testing-monogenic uses only a few cells from the early embryo, usually at the blastocyst stage, and misdiagnosis is possible but rare with modern techniques. Confirmation of preimplantation genetic testing-monogenic results with chorionic villus sampling (CVS) or amniocentesis should be offered.
- To detect structural chromosomal abnormalities such as translocations, preimplantation genetic testing-structural rearrangements (known as PGT-SR) is used. Confirmation of preimplantation genetic testing-structural rearrangements results with CVS or amniocentesis should be offered.
- The main purpose of preimplantation genetic testing-aneuploidy (known as PGT-A) is to screen embryos for whole chromosome abnormalities. Traditional diagnostic testing or screening for aneuploidy should

be offered to all patients who have had preimplantation genetic testing-aneuploidy, in accordance with recommendations for all pregnant patients.

## Introduction

As preimplantation genetic technologies are increasingly used with in vitro fertilization, obstetric care providers should become familiar with these tests as well as their benefits and limitations. Preimplantation genetic testing comprises a group of genetic assays used to evaluate embryos before transfer to the uterus. Preimplantation genetic testing-monogenic is targeted to single gene disorders, and preimplantation genetic testing-aneuploidy is a broader test that screens for aneuploidy in all chromosomes, including the 22 pairs of autosomes and the sex chromosomes, X and Y. To detect structural chromosomal abnormalities such as translocations, preimplantation genetic testing-structural rearrangements is used

Preimplantation genetic testing has been performed on polar bodies, a single blastomere from a cleavage-stage embryo, and a group of cells from the trophectoderm at the blastocyst stage. The latter has become the most common methodology used. In this methodology, preimplantation genetic testing is performed on approximately 5–10 cells derived from the trophectoderm layer that gives rise to the placenta and does not require a biopsy of the inner cell mass, which ultimately gives rise to the fetus. Because of possible mosaicism, preimplantation genetic testing results from the trophectoderm may not reflect the genetic constitution of the inner cell mass (1). Independent of the preimplantation genetic testing modality employed, false-positive and false-negative results are possible.

Preimplantation genetic testing raises several ethical issues that are beyond the scope of this document. For example, there are complexities to offering preimplantation genetic testing to screen for adult-onset disorders or to determine transplantation compatibility for ill family members (2). Such issues are addressed extensively in the bioethics literature as well as documents from ACOG (3) and the American Society of Reproductive Medicine (ASRM) (4).

## Preimplantation Genetic Testing for Monogenic Disorders

Preimplantation genetic testing-monogenic is used to test for a specific genetic pathogenic variant (mutation) associated with a known diagnosis or known predisposition within a family. Preimplantation genetic testing-monogenic does not test for all single gene disorders at once and will not detect de novo pathogenic variants. This technique examines embryos using either cytogenetic or molecular techniques for (1) single-gene disorders (eg, Huntington disease, cystic fibrosis, fragile X

syndrome), including those that are autosomal dominant and recessive or X-linked, or (2) hereditary cancer syndromes (eg, hereditary breast and ovarian cancer, Lynch syndrome). Additionally, preimplantation genetic testing-monogenic can be used to identify human leukocyte antigen-compatible, unaffected embryos gestated with the goal of allowing ill family members to receive compatible bone marrow transplants or cord blood transfusions. Preimplantation genetic testing-monogenic uses only a few cells from the early embryo, usually at the blastocyst stage, and misdiagnosis is possible but rare with modern techniques. Laboratories often quote a small risk for misdiagnosis; however, no cases of misdiagnosis were reported in the data from the European Society of Human Reproduction and Embryology Consortium (5). Regardless, confirmation of preimplantation genetic testing-monogenic results with CVS or amniocentesis should be offered.

## Preimplantation Genetic Testing for Structural Rearrangements

To test embryos that are at risk for chromosome gains and losses related to parental structural chromosomal abnormalities (eg translocations, inversions, deletions, and insertions), preimplantation genetic testing-structural rearrangements is used. Genetic counseling and discussion of possible preimplantation genetic testing should be offered when a structural rearrangement is discovered in a parent. At this time, preimplantation genetic testing-structural rearrangements cannot differentiate between an embryo that has a normal karyotype and an embryo that carries a balanced form of the familial chromosome rearrangement. Individuals who carry a balanced chromosome rearrangement involving imprinted genes (eg, 13;14 robertsonian translocation) are at risk for abnormalities related to uniparental disomy, which cannot be excluded by all methods of preimplantation genetic testing analysis. Because of these limitations, and the fact that this testing method uses only a few trophectoderm cells, confirmation of preimplantation genetic testing-structural rearrangements results with CVS or amniocentesis should be offered.

## Preimplantation Genetic Testing for Aneuploidy

The main purpose of PGT-A is to screen embryos for whole chromosome abnormalities. Before its use, the selection of embryos for transfer was based mainly on morphologic criteria, but many women failed to achieve pregnancy despite transfer of morphologically optimal embryos. Preimplantation genetic testing-aneuploidy was proposed as a way to detect whole chromosome aneuploidy before transfer and thus potentially increase live birth rates and decrease early pregnancy failure rates (6, 7). The original technique used fluorescence in situ hybridization but was limited to just a few chromosomes.

Preimplantation genetic testing-aneuploidy has now expanded to include assessment of all the chromosomes, through various techniques such as array comparative genomic hybridization and next generation sequencing. (8).

The initial interest in preimplantation genetic testing-aneuploidy through fluorescence in situ hybridization was tempered by the publication of randomized studies that did not find improved in vitro fertilization (IVF) outcomes (9, 10). Proposed explanations included the fact that biopsy of the early cleavage stage embryo (day 3) appears to negatively affect implantation potential (11) and single-cell biopsy precludes confirmatory testing. At the time, several major medical societies subsequently released opinions discouraging routine use of preimplantation genetic testing-aneuploidy (12, 13).

In an effort to continue the quest toward higher live birth rates and lower multiple gestation rates in IVF, ongoing research pursued emerging techniques. These involved biopsy of the multiple cell trophoctoderm (future placenta) of the blastocyst. In addition, several platforms capable of testing all chromosomes have been developed. These platforms differ in their ability to identify other anomalies simultaneously, such as structural abnormalities, single gene mutations, mitochondrial copy number, and mosaicism (8).

A systematic review examined the clinical effectiveness of preimplantation genetic testing-aneuploidy and found three randomized controlled trials that reported higher pregnancy rates in younger patients with no previous failed IVF attempts; however, these were small studies with substantial limitations (14). Another randomized controlled trial found that women aged 38–41 had significantly higher live birth rates and lower miscarriage rates after preimplantation genetic testing-aneuploidy, as well as a shorter time to pregnancy. However, the comparison is problematic because in the preimplantation genetic testing-aneuploidy group, 32% of patients did not have an embryo to transfer (15). After a comprehensive review, ASRM published a practice guideline in March of 2018 concluding that “there is insufficient evidence to recommend the routine use of preimplantation genetic testing-aneuploidy in all infertile women.” In addition, the ideal genetic testing platform to analyze all chromosomes has not yet been established (16). Worldwide randomized controlled trials are needed to determine which patient cohorts, if any, may benefit from preimplantation genetic testing-aneuploidy.

Traditional diagnostic testing or screening for aneuploidy should be offered to all patients who have had preimplantation genetic testing-aneuploidy, in accordance with recommendations for all pregnant patients.

### **Prenatal Genetic Screening and Testing After Preimplantation Genetic Testing**

Because preimplantation genetic testing cannot identify all genetic abnormalities in a fetus, counseling about

prenatal genetic screening or testing should be a process of shared decision making with a focus on the patient’s individual risk, reproductive goals, and preferences. For example, current preimplantation genetic testing cannot detect all microdeletions or microduplications, nor will it detect *de novo* pathogenic variants. Patients and health care providers should be aware that a negative preimplantation genetic test result is not a guarantee of a newborn without genetic abnormalities. False-positive and false-negative results can occur with preimplantation genetic testing, therefore, prenatal diagnostic testing (through CVS or amniocentesis) should be offered to all patients who have achieved pregnancy after preimplantation genetic testing. However, there are patients who, because of the associated risk of miscarriage, decline diagnostic testing and choose prenatal screening (first-trimester and second-trimester serologic testing, nuchal translucency screening, or cell-free DNA testing), as do many patients who have not elected preimplantation genetic testing-aneuploidy. Patients who choose screening after preimplantation genetic testing-aneuploidy should be made aware of the substantial limitations of this strategy and the potential for a false-positive test result. It is especially important to offer diagnostic testing or screening for aneuploidy after preimplantation genetic testing-aneuploidy or preimplantation genetic testing-structural rearrangements if concurrent preimplantation genetic testing-aneuploidy is not performed. As preimplantation genetic testing is used more over time, data will be available to help determine the optimal prenatal testing and screening strategies for this patient population. For a full discussion of screening and diagnostic testing for aneuploidy in pregnancy, see ACOG Practice Bulletin Number 162, *Prenatal Diagnostic Testing for Genetic Disorders*, and ACOG Practice Bulletin Number 163, *Screening for Fetal Aneuploidy*.

### **Preimplantation Genetic Testing and Mosaicism, an Emerging Conundrum**

Many limitations exist to preimplantation genetic testing and include challenges in detecting microdeletions and microduplications, *de novo* variants, and imprinting disorders. An emerging problem has been detection of mosaicism during preimplantation genetic testing-aneuploidy. *Mosaicism* is defined as two or more cell populations with different chromosomal complements present within the same embryo (16). Traditionally, embryos with mosaicism detected on preimplantation genetic testing-aneuploidy have not been used for transfer in IVF because it is assumed they will not develop into euploid fetuses at term. It is important to understand that preimplantation genetic testing-aneuploidy testing was not originally intended to confirm a diagnosis of mosaicism. Recent application of advanced genetic technologies, such as next generation sequencing, has allowed mosaicism to be detected with greater sensitivity,

with an incidence as high as 20% of tested embryos (17). Numerous reasons for the apparent mosaicism exist, and some are more likely to result in a healthy live-born infant than others. (18). Several studies have shown term delivery of euploid fetuses after mosaic embryo transfer, albeit with lower pregnancy rates. Proposed etiologies for this success include self-correction of the mosaicism or inaccuracy of the initial embryo biopsy (19, 20). Given this data, some patients may choose to implant select embryos with mosaicism detected on preimplantation genetic testing-aneuploidy, after detailed consent and counseling. Referral to a specialist with genetic training and expertise should be considered, and prenatal diagnosis with CVS or amniocentesis should be strongly encouraged.

## Future Directions

The clinical utility of preimplantation genetic testing-monogenic and preimplantation genetic testing-structural rearrangements is firmly established; however, the best use of preimplantation genetic testing-aneuploidy remains to be determined. At this time, in concordance with ASRM recommendations, there is insufficient evidence to recommend the routine use of preimplantation genetic testing-aneuploidy in all infertile women.

The cost effectiveness of preimplantation genetic testing-aneuploidy is difficult to quantify because of the intangible costs of failed implantation and spontaneous loss, as well as variability in treatment costs. In addition, preimplantation genetic testing-aneuploidy may prove to be a factor in decreasing the multiple gestation associated with IVF because of the current recommendation of single euploid embryo transfer regardless of age (21, 22). Future research is necessary to establish the overall clinical utility for preimplantation genetic testing-aneuploidy, the subset of patients that may benefit from preimplantation genetic testing-aneuploidy, the clinical significance of mosaicism, and the residual risk for aneuploidy in preimplantation genetic testing-aneuploidy screened embryos.

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