GENETIC TESTING: PREIMPLANTATION GENETIC TESTING

OVERVIEW

Preimplantation genetic testing involves analysis of biopsied cells from an embryo as a part of an assisted reproductive procedure. Preimplantation genetic testing for monogenic disorders (PGT-M) and preimplantation genetic testing for structural rearrangements (PGT-SR) are used to detect a specific inherited disorder in conjunction with in vitro fertilization (IVF) and aims to prevent the birth of affected children to couples at an increased risk of transmitting either a gene mutation(s) or an unbalanced structural chromosomal rearrangement that can be typically targeted in this context. Preimplantation genetic testing for aneuploidy (PGT-A) is used to screen for potential chromosomal or subchromosomal abnormalities (e.g., chromosomal aneuploidy) in conjunction with IVF for couples; in this case testing is untargeted.

POLICY REFERENCE TABLE

Below is a list of higher volume tests and the associated laboratories for each coverage criteria section. This list is not all inclusive.

Coverage Criteria Sections	Example Tests (Labs)	Common CPT Codes	Common ICD Codes	Ref
Preimplantation Genetic Testing for Aneuploidy (PGT-A)	Spectrum PGT-A (Natera)	89290, 89291, 81479	N97.0, N97.9, Z31	2, 3, 4
	Preimplantation Genetic Testing for Chromosomal Aneuploidy (Invitae)			
	SMART PGT-A (Preimplantation Genetic Testing - Aneuploidy) (Igenomix)	0254U		
Preimplantation Genetic Testing for Monogenic	Spectrum PGT-M (Natera)	89290, 89291, 81479	N97.0, N97.9, Z14.8, Z31	1, 2
	PGT-M (Cooper Genomics)	81403		

Disorders (PGT-M)				
Preimplantation Genetic Testing for Structural Rearrangements (PGT-SR)	Preimplantation Genetic Testing for Structural Chromosomal Rearrangements/Translocations (Invitae)	89290, 89291, 81479, 81403, 81228, 88291	N97.0, N97.9, Z14.8, Z31	2
	Spectrum PGT-SR (Natera)	81479		

OTHER RELATED POLICIES

This policy document provides coverage criteria for preimplantation genetic testing. Please refer to:

- ***Genetic Testing: Prenatal and Preconception Carrier Screening*** for coverage criteria related to carrier screening.
- ***Genetic Testing: Prenatal Diagnosis (via amniocentesis, CVS, or PUBS) and Pregnancy Loss*** for coverage related to diagnostic genetic testing during pregnancy or for a pregnancy loss.
- ***Genetic Testing: Noninvasive Prenatal Screening (NIPS)*** for coverage criteria related to prenatal cell-free DNA screening tests.
- ***Genetic Testing: Multisystem Inherited Disorders, Intellectual Disability, and Developmental Delay*** for coverage criteria related to diagnostic genetic testing in the postnatal period.
- ***Genetic Testing: General Approach to Genetic Testing*** for coverage criteria related to preimplantation genetic testing that is not specifically discussed in this or another non-general policy.

COVERAGE CRITERIA

PREIMPLANTATION GENETIC TESTING FOR ANEUPLOIDY (PGT-A)

I. Preimplantation genetic testing for aneuploidy (PGT-A) (89290, 89291, 0254U, 81479) is considered **investigational**.

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PREIMPLANTATION GENETIC TESTING FOR MONOGENIC DISORDERS (PGT-M)

I. Preimplantation genetic testing for monogenic disorders (PGT-M) (89290, 89291, 81479, 81403) may be considered **medically necessary** when:

   A. The embryo is at an elevated risk of a genetic disorder due to one of the following:

      1. Both biological parents are known carriers for the same autosomal recessive disorder, **OR**

      2. One biological parent is a known carrier of an autosomal dominant disorder, **OR**

      3. One biological parent is a known carrier of an X-linked recessive disorder.

II. Preimplantation genetic testing for monogenic disorders (PGT-M) (89290, 89291, 81479, 81403) is considered **investigational** for all other indications.

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PREIMPLANTATION GENETIC TESTING FOR STRUCTURAL REARRANGEMENTS (PGT-SR)

I. Preimplantation genetic testing for structural rearrangements (PGT-SR) (81228, 88291, 89290, 89291, 81479, 81403) may be considered **medically necessary** when:

   A. The embryo is at an elevated risk of a genetic disorder because one biological parent has a chromosomal rearrangement.

II. Preimplantation genetic testing for structural rearrangements (PGT-SR) (81228, 88291, 89290, 89291, 81479, 81403) is considered **investigational** for all other indications.

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NOTES AND DEFINITIONS

1. Close relatives include first, second, and third degree blood relatives on the same side of the family:

   a. **First-degree relatives** are parents, siblings, and children

   b. **Second-degree relatives** are grandparents, aunts, uncles, nieces, nephews, grandchildren, and half siblings

   c. **Third-degree relatives** are great grandparents, great aunts, great uncles, great grandchildren, and first cousins

2. Preimplantation genetic testing for monogenic disorders (**PGT-M**) and Preimplantation genetic testing for structural rearrangements (**PGT-SR**) are used to detect a specific single-gene inherited disorder or chromosome rearrangement in conjunction with in vitro fertilization (IVF)

3. Preimplantation genetic testing for aneuploidy (**PGT-A**) is used to screen for chromosomal aneuploidy in conjunction with IVF for couples.

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CLINICAL CONSIDERATIONS

Genetic counseling is highly encouraged for patients considering and undergoing in vitro fertilization. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods, such as a genetic counselor, medical geneticist, or advanced practice practitioner specializing in genetics.

All patients who undergo PGT-M or PGT-SR should be offered diagnostic testing via chorionic villus sampling (CVS) or amniocentesis for confirmation of results.

All patients who undergo PGT-A should be offered traditional diagnostic testing or screening for aneuploidy in accordance with recommendations for all pregnant patients.

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BACKGROUND AND RATIONALE

Preimplantation Genetic Testing for Aneuploidy (PGT-A)

American Society of Reproductive Medicine

The American Society for Reproductive Medicine issued an opinion on the use of preimplantation genetic testing (PGS) for aneuploidy (2018) which concluded, "Large, prospective, well-controlled studies evaluating the combination of multiple approaches (genomics, time-lapse imaging, transcriptomics, proteomics, metabolomics, etc.) for enhanced embryo selection applicable in a more inclusive IVF population are needed to determine not only the effectiveness, but also the safety and potential risks of these technologies. PGT-A will likely be part of a future multidimensional approach to embryo screening and selection. At present, however, there is insufficient evidence to recommend the routine use of blastocyst biopsy with aneuploidy testing in all infertile patients."

This position was reaffirmed in a 2020 committee opinion regarding clinical management of mosaic results from preimplantation genetic testing for aneuploidy of blastocysts, stating, “It should be recognized that this document does not endorse nor does it suggest that PGT-A is appropriate for all cases of IVF.”

American College of Obstetricians and Gynecologists (ACOG)

The American College of Obstetricians and Gynecologists issued Committee Opinion No. 799 (2020) regarding Preimplantation Genetic Testing. The recommendations include the following:

"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."

The American College of Obstetricians and Gynecologists (2015, reaffirmed 2017) issued an opinion that recommends “[p]atients with established causative mutations for a genetic condition” who are undergoing in vitro fertilization and desire prenatal genetic testing should be offered the testing, either preimplantation or once pregnancy is established.

Preimplantation Genetic Testing for Monogenic Disorders (PGT-M)

American Society for Reproductive Medicine

The American Society for Reproductive Medicine published an opinion on the use of preimplantation genetic diagnosis (PGD) for serious adult-onset conditions (2013). The statement includes the following:

- "Preimplantation genetic diagnosis (PGD) for adult-onset conditions is ethically justifiable when the conditions are serious and when there are no known interventions for the conditions or the available interventions are either inadequately effective or significantly burdensome.”
- “For conditions that are less serious or of lower penetrance, PGD for adult[-]onset conditions is ethically acceptable as a matter of reproductive liberty. It should be discouraged, however, if the risks of PGD are found to be more than merely speculative."

The opinion also stated that physicians and patients should be aware that much remains unknown about the long-term effects of embryo biopsy on the developing fetus and that experienced genetic counselors should be involved in the decision process.

American College of Obstetricians and Gynecologists (ACOG)

The American College of Obstetricians and Gynecologists issued Committee Opinion No. 799 (2020) regarding Preimplantation Genetic Testing. The recommendations include the following:

"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."

The American College of Obstetricians and Gynecologists (2015, reaffirmed 2017) issued an opinion that recommends “[p]atients with established causative mutations for a genetic condition” who are undergoing in vitro fertilization and desire prenatal genetic testing should be offered the testing, either preimplantation or once pregnancy is established.

Preimplantation Genetic Testing for Structural Rearrangements (PGT-SR)

American College of Obstetricians and Gynecologists (ACOG)

The American College of Obstetricians and Gynecologists issued Committee Opinion No. 799 (2020) regarding Preimplantation Genetic Testing. The recommendations include the following: "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."

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REFERENCES

1. Ethics Committee of American Society for Reproductive Medicine. Use of preimplantation genetic diagnosis for serious adult onset conditions: a committee opinion. Fertil Steril. 2013;100(1):54-57. doi:10.1016/j.fertnstert.2013.02.043
2. Preimplantation Genetic Testing: ACOG Committee Opinion, Number 799. Obstet Gynecol. 2020;135(3):e133-e137. doi:10.1097/AOG.0000000000003714
3. Practice Committees of the American Society for Reproductive Medicine and the Society for Assisted Reproductive Technology. Electronic address: ASRM@asrm.org; Practice Committees of the American Society for Reproductive Medicine and the Society for Assisted Reproductive Technology. The use of preimplantation genetic testing for aneuploidy (PGT-A): a committee opinion. Fertil Steril. 2018;109(3):429-436. doi:10.1016/j.fertnstert.2018.01.002
4. Practice Committee and Genetic Counseling Professional Group (GCPG) of the American Society for Reproductive Medicine. Electronic address: asrm@asrm.org. Clinical management of mosaic results from preimplantation genetic testing for aneuploidy (PGT-A) of blastocysts: a committee opinion. Fertil Steril. 2020;114(2):246-254. doi:10.1016/j.fertnstert.2020.05.014

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