



## Medical Policy

# Preimplantation Genetic Testing

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### Policy Number: 088

BCBSA Reference Number: 4.02.05

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### Related Policies

- Assisted Reproductive Services, #[086](#)

### Policy

## Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity Medicare HMO Blue<sup>SM</sup> and Medicare PPO Blue<sup>SM</sup> Members

### Overview of Covered Services

For all members (female, male and other gender identities), preimplantation genetic testing services are considered to be medically necessary when policy criteria are met for the time period that fertility is naturally expected. In addition, for all members, services will no longer be covered if the treatment being requested is considered to be “futile” or has a “very poor prognosis,” as defined by the American Society for Reproductive Medicine. Futile treatments are defined as having a <1% chance of achieving a live birth. Treatments with a very poor prognosis are defined as having a 1-5% chance of achieving a live birth.

The determination of whether or not a treatment is futile or has a very poor prognosis is specific to each patient and takes into account medical history, physical exam findings, lab work, prior infertility treatments, and other factors such as population and national society of assisted reproductive techniques (SART) annual statistics.

### **Preimplantation genetic testing for monogenic/single gene diseases (PGT-M)**

Preimplantation genetic testing for monogenic/single gene defects (PGT-M) may be **MEDICALLY NECESSARY** including IVF with or without ICSI, even if the member is not infertile, when **ALL** of the following criteria are met:

1. The member/couple has undergone genetic counseling, **AND**
2. The member has a > 5% chance of live birth per cycle of IVF with or without ICSI, **AND**
3. PGT-M is for evaluation of an embryo at an identified elevated risk for one of the following:

- a. A genetic disorder that is associated with severe disability or has a lethal natural history, such as when:
  - i. Both partners are known carriers of a single gene autosomal recessive disorder,
  - ii. One partner is a known carrier of a single gene autosomal recessive disorder and the partners have one offspring that has been diagnosed with that recessive disorder,
  - iii. One partner is a known carrier of a single gene autosomal dominant disorder, or
  - iv. One partner is a known carrier of a single X-linked disorder.
- b. A structural chromosomal abnormality such as for a parent with balanced or unbalanced chromosomal translocation.

Preimplantation genetic testing for monogenic/single gene diseases (PGT-M) in conjunction with IVF is **INVESTIGATIONAL** in patients/couples who are undergoing IVF in all situations other than those specified above.

Examples of **MEDICALLY NECESSARY** diagnoses include but **are not limited to** the following:

Single gene autosomal recessive disorders	Single gene autosomal dominant disorders	Single gene x-linked recessive disorders
<ul style="list-style-type: none"> <li>• B-Thalassemia Syndromes</li> <li>• Canavan Disease</li> <li>• Cystic Fibrosis</li> <li>• Epidermolysis Bullosa Simplex (autosomal recessive type)</li> <li>• Fanconi Anemia</li> <li>• Familial Dysautonomia</li> <li>• Gaucher Disease</li> <li>• Hurler Syndrome</li> <li>• Metabolic disorders (e.g., methylmalonic acidemia or propionic acidemia)</li> <li>• Sickle Cell Anemia</li> <li>• Spinal Muscular Atrophy Type I</li> <li>• Spinocerebellar Ataxia (autosomal recessive type)</li> <li>• Tay-Sachs Disease</li> </ul>	<ul style="list-style-type: none"> <li>• Epidermolysis Bullosa (autosomal dominant type)</li> <li>• Huntington's Disease</li> <li>• Marfan's Syndrome</li> <li>• Myotonic Dystrophy</li> <li>• Neurofibromatosis Type I &amp; II</li> <li>• Retinoblastoma</li> <li>• Spinocerebellar Ataxia (autosomal dominant type)</li> <li>• Tuberous Sclerosis</li> </ul>	<ul style="list-style-type: none"> <li>• Adrenoleukodystrophy</li> <li>• Alport Syndrome</li> <li>• Choroideremia</li> <li>• Fabry's Disease</li> <li>• Fragile X Syndrome</li> <li>• Hemophilia A &amp; B</li> <li>• Hunter Syndrome</li> <li>• Incontinentia pigmenti</li> <li>• Lesch-Nyhan Syndrome</li> <li>• Muscular Dystrophy</li> <li>• X-linked Mental Retardation</li> </ul>

Preimplantation genetic testing for monogenic/single gene diseases (PGT-M) in conjunction with in vitro fertilization (IVF) in couples not known to be infertile may be considered **MEDICALLY NECESSARY** when used to evaluate human leukocyte antigen (HLA) status alone in families with a child with a bone marrow disorder requiring a stem cell transplant, and in whom there is no other source of a compatible bone marrow donor other than an HLA matched sibling.

**Preimplantation genetic testing for a chromosomal rearrangements or size of the chromosome (PGT-SR)** abnormality may be **MEDICALLY NECESSARY** including IVF with or without ICSI, even if the member is not infertile, when **ALL** of the following criteria are met:

1. The member/couple has undergone genetic counseling, **AND**
2. The member has a > 5% chance of live birth per cycle of IVF with or without ICSI, **AND**
3. Is for the evaluation of an embryo at an identified elevated risk of being affected by a genetic disorder involving the rearrangement or size of a chromosome,
  - i. such as for a parent with a balanced or unbalanced chromosomal translocation.

### **Preimplantation genetic testing for aneuploidies (PGT-A)**

Preimplantation genetic testing for aneuploidies (PGT-A)/the correct number and size of all chromosomes in an embryo in conjunction with IVF with or without ICSI is **INVESTIGATIONAL** in patients/couples who are undergoing IVF in all situations.

### **Prior Authorization Information**

#### **Inpatient**

- For services described in this policy, precertification/preauthorization **IS REQUIRED** for all products if the procedure is performed **inpatient**.

#### **Outpatient**

- For services described in this policy, see below for products where prior authorization **might be required** if the procedure is performed **outpatient**.

	<b>Outpatient</b>
<b>Commercial Managed Care (HMO and POS)</b>	Prior authorization is <b>required</b> .
<b>Commercial PPO and Indemnity</b>	Prior authorization is <b>required</b> .
<b>Medicare HMO Blue<sup>SM</sup></b>	Prior authorization is <b>required</b> .
<b>Medicare PPO Blue<sup>SM</sup></b>	Prior authorization is <b>required</b> .

### **CPT Codes / HCPCS Codes / ICD Codes**

*Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member.*

*Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.*

*The following codes are included below for informational purposes only; this is not an all-inclusive list.*

**The above medical necessity criteria MUST be met for the following codes to be covered for Commercial Members: Managed Care (HMO and POS), PPO, Indemnity, Medicare HMO Blue and Medicare PPO Blue:**

#### **CPT Codes**

<b>CPT codes:</b>	<b>Code Description</b>
89290	Biopsy, oocyte polar body or embryo blastomere, microtechnique (for pre-implantation genetic diagnosis); less than or equal to 5 embryos
89291	Biopsy, oocyte polar body or embryo blastomere, microtechnique (for pre-implantation genetic diagnosis); greater than 5 embryos

### **Description**

#### **Preimplantation Genetic Testing**

Preimplantation genetic testing describes various adjuncts to an assisted reproductive procedure (see [MP 086, Assisted Reproductive Services Infertility Services](#)) in which either maternal or embryonic DNA is sampled and genetically analyzed, thus permitting deselection of embryos harboring a genetic defect before implantation of an embryo into the uterus. The ability to identify preimplantation embryos with genetic defects before implantation provides an alternative to amniocentesis, chorionic villus sampling, and selective pregnancy termination of affected fetuses. Preimplantation genetic testing is generally categorized as either diagnostic (preimplantation genetic diagnosis [PGD]) or screening (preimplantation genetic screening [PGS]). PGD is used to detect genetic evidence of a specific inherited disorder, in the oocyte or embryo, derived from mother or couple, respectively, that has a high-risk of transmission. PGS is not used to detect a specific abnormality but instead uses similar techniques to identify a number of genetic abnormalities in the absence of a known heritable disorder. This terminology, however, is not

used consistently (eg, some authors use PGD when testing for a number of possible abnormalities in the absence of a known disorder).

### **Biopsy**

Biopsy for PGD can take place at 3 stages: the oocyte, cleavage stage embryo, or the blastocyst. In the earliest stage, both the first and second polar bodies are extruded from the oocyte as it completes the meiotic division after ovulation (first polar body) and fertilization (second polar body). This strategy thus focuses on maternal chromosomal abnormalities. If the mother is a known carrier of a genetic defect and genetic analysis of the polar body is normal, then it is assumed that the genetic defect was transferred to the oocyte during meiosis.

Biopsy of cleavage stage embryos or blastocysts can detect genetic abnormalities arising from either the maternal or paternal genetic material. Cleavage stage biopsy takes place after the first few cleavage divisions when the embryo is composed of 6 to 8 cells (ie, blastomeres). Sampling involves aspiration of 1 and sometimes 2 blastomeres from the embryo. Analysis of 2 cells may improve diagnosis but may also affect the implantation of the embryo. In addition, a potential disadvantage of testing at this phase is that mosaicism might be present. Mosaicism refers to genetic differences among the cells of the embryo that could result in an incorrect interpretation if the chromosomes of only a single cell are examined.

The third option is sampling the embryo at the blastocyst stage when there are about 100 cells. Blastocysts form 5 to 6 days after insemination. Three to 10 trophoctoderm cells (outer layer of the blastocyst) are sampled. A disadvantage is that not all embryos develop to the blastocyst phase in vitro and, when they do, there is a short time before embryo transfer needs to take place. Blastocyst biopsy has been combined with embryonic vitrification to allow time for test results to be obtained before the embryo is transferred.

### **Analysis and Testing**

The biopsied material can be analyzed in a variety of ways. Polymerase chain reaction or other amplification techniques can be used to amplify the harvested DNA with subsequent analysis for single genetic defects. This technique is most commonly used when the embryo is at risk for a specific genetic disorder such as Tay-Sachs disease or cystic fibrosis. Fluorescent in situ hybridization (FISH) is a technique that allows direct visualization of specific (but not all) chromosomes to determine the number or absence of chromosomes. This technique is most commonly used to screen for aneuploidy, sex determination, or to identify chromosomal translocations. FISH cannot be used to diagnose single genetic defect disorders. However, molecular techniques can be applied with FISH (eg, microdeletions, duplications) and, thus, single-gene defects can be recognized with this technique. Performing PGS using FISH is known as PGS version 1.

Another more recent approach is array comparative genome hybridization testing at either the 8-cell or, more often, the blastocyst stage, also known as PGS version 2. Unlike FISH analysis, hybridization allows for 24 chromosome aneuploidy screening, as well as more detailed screening for unbalanced translocations and inversions and other types of abnormal gains and losses of chromosomal material. Other PGS version 2 methods include single nucleotide variant microarrays and quantitative polymerase chain reaction.<sup>1,2</sup> Next-generation sequencing such as massively parallel signature sequencing has potential applications to prenatal genetic testing and is grouped with PGS version 2 techniques in some literature and referred to as PGS version 3 in other literature.

### **Embryo Classification**

Three general categories of embryos have undergone preimplantation genetic testing, which is discussed in the following subsections.

#### **Embryos at Risk for a Specific Inherited Single-Gene Defect**

Inherited single-gene defects fall into 3 general categories: autosomal recessive, autosomal dominant, and X-linked. When either the mother or father is a known carrier of a genetic defect, embryos can undergo PGD to deselect embryos harboring the defective gene. Sex selection of a female embryo is another strategy when the mother is a known carrier of an X-linked disorder for which there is no specific

molecular diagnosis. The most common example is female carriers of fragile X syndrome. In this scenario, PGD is used to deselect male embryos, half of which would be affected. PGD could also be used to deselect affected male embryos. While there is a growing list of single-gene defects for which molecular diagnosis is possible, the most common indications include cystic fibrosis,  $\beta$ -thalassemia, muscular dystrophy, Huntington disease, hemophilia, and fragile X disease. It should be noted that when PGD is used to deselect affected embryos, the treated couple is not technically infertile but is undergoing an assisted reproductive procedure for the sole purpose of PGD. In this setting, PGD may be considered an alternative to selective termination of an established pregnancy after diagnosis by amniocentesis or chorionic villus sampling.

### **Embryos at a Higher Risk of Translocations**

Balanced translocations occur in 0.2% of the neonatal population but at a higher rate in infertile couples or those with recurrent spontaneous abortions. PGD can be used to deselect embryos carrying the translocations, thus leading to an increase in fecundity or a decrease in the rate of spontaneous abortion.

### **Identification of Aneuploid Embryos**

Implantation failure of fertilized embryos is common in assisted reproductive procedures; aneuploidy of embryos is thought to contribute to implantation failure and may also be the cause of recurrent spontaneous abortion. The prevalence of aneuploid oocytes increases in older women. These age-related aneuploidies are mainly due to nondisjunction of chromosomes during maternal meiosis. Therefore, PGS has been explored as a technique to deselect aneuploid oocytes in older women and is also known as PGD for aneuploidy screening. FISH analysis of extruded polar bodies from the oocyte or no blastomeres at day 3 of embryo development was initially used to detect aneuploidy (PGS version 1). A limitation of FISH is that analysis is restricted to a number of proteins. More recently, newer PGS methods have been developed (PGS version 2). These methods allow for all chromosomes analysis with genetic platforms including array comparative genomic hybridization and single nucleotide variant chain reaction analysis. Moreover, in addition to older women, PGS has been proposed for women with repeated implantation failures.

## **Summary**

### **Description**

Preimplantation genetic testing involves analysis of biopsied cells as part of an assisted reproductive procedure. It is generally considered to be divided into 2 categories. Preimplantation genetic diagnosis is used to detect a specific inherited disorder in conjunction with in vitro fertilization (IVF) and aim to prevent the birth of affected children to couples at high-risk of transmitting a disorder. Preimplantation genetic screening may also involve testing for potential genetic abnormalities in conjunction with IVF for couples without a specific known inherited disorder.

### **Summary of Evidence**

For individuals who have an identified elevated risk of a genetic disorder undergoing IVF who receive preimplantation genetic diagnosis, the evidence includes observational studies and systematic reviews. Relevant outcomes are health status measures and treatment-related morbidity. Data from observational studies and systematic reviews have suggested that preimplantation genetic diagnosis is associated with the birth of unaffected fetuses when performed for detection of single genetic defects and is associated with a decrease in spontaneous abortions for patients with structural chromosomal abnormalities. Moreover, preimplantation genetic diagnosis performed for single-gene defects does not appear to be associated with an increased risk of obstetric complications. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have no identified elevated risk of a genetic disorder undergoing IVF who receive preimplantation genetic screening (PGS), the evidence includes randomized controlled trials (RCTs) and meta-analyses. Relevant outcomes are health status measures and treatment-related morbidity. RCTs and meta-analyses of RCTs on initial PGS methods (eg, fluorescent in situ hybridization) have found lower or similar ongoing pregnancy and live birth rates compared with IVF without PGS. There are fewer RCTs on newer PGS methods, and findings are mixed. Meta-analyses of RCTs have found higher implantation rates with PGS than with standard care but improvements in other outcomes

are inconsistent. Well-conducted RCTs evaluating PGS in the various target populations (eg, women of advanced maternal age, women with recurrent pregnancy loss) are needed before conclusions can be drawn about the impact on the net health benefit. The evidence is insufficient to determine the effects of the technology on health outcomes.

## Policy History

Date	Action
10/2020	BCBSA National medical policy review. Description, summary, and references updated. Policy statements unchanged.
5/2020	Added overview of covered services section to policy. Policy statements unchanged. 5/1/2020.
10/2019	BCBSA National medical policy review. Description, summary and references updated. Policy statements unchanged.
6/2019	Terminology clarified: Preimplantation genetic screening (PGS) changed to preimplantation genetic testing for aneuploidies (PGT-A); Preimplantation genetic diagnosis (PGD) changed to preimplantation genetic testing for monogenic/single gene diseases (PGT-M) and defined coverage criteria for preimplantation genetic testing for structural rearrangements (PGT-SR).
10/2018	BCBSA National medical policy review. No changes to policy statements. New references added. Background and summary clarified.
3/2017	Policy statements clarified.
10/2016	New references added from BCBSA National medical policy.
1/2016	Clarified medical necessity criteria.
11/2015	Clarified medical necessity criteria.
8/2015	New references added from BCBSA National medical policy.
9/2015	Revised medical necessity language to include IVF for PGT-M and a list of covered diagnoses. Clarified language in investigational statements. Effective 9/1/2015.
9/2014	New references added from BCBSA National medical policy.
1/2014	BCBSA National medical policy review. Medically necessary statement clarified. Effective 1/1/2014.
9/2013	New investigational indications described. Effective 9/1/2013.
2/2013	BCBSA National medical policy review. No change in medical policy statement. Effective 2/4/2013.
11/2011-4/2012	Medical policy ICD 10 remediation: Formatting, editing and coding updates. No changes to policy statements.
9/2011	Reviewed - Medical Policy Group - Urology and Obstetrics/Gynecology. No changes to policy statements.
12/15/2010	Updated to add infertility treatment for a member with recurrent pregnancy loss in accordance with Massachusetts law (M.G.L.c. 175, section 47H and 211 C.M.R 37.09). Effective December 15, 2010.
11/2009	BCBSA National medical policy review. Changes to policy statements.
10/2009	Reviewed - Medical Policy Group - Urology and Obstetrics/Gynecology. No changes to policy statements.
10/2009	Revised to include benefit coverage information in the header section of the document that addresses infertility services when a healthy female member is age 35 or older and has not been able to conceive after a period of six months of actively trying.
3/2009	BCBSA National medical policy review. No changes to policy statements.
1/2009	Updated to remove information regarding requirement of 3 FSH IUI prior to receiving IVF treatment for those that meet the definition of unexplained infertility; this change is effective January 2009 as published in the December '08 Provider Focus.
11/2008	BCBSA National medical policy review. Changes to policy statements.
10/2008	Reviewed - Medical Policy Group - Urology and Obstetrics/Gynecology. No changes to policy statements.

2/2008	Policy edited with the removal of coverage references for preimplantation genetic diagnosis which is now addressed in a new medical policy document, #088.
10/2007	Reviewed - Medical Policy Group - Urology and Obstetrics/Gynecology. No changes to policy statements.

## Information Pertaining to All Blue Cross Blue Shield Medical Policies

Click on any of the following terms to access the relevant information:

[Medical Policy Terms of Use](#)

[Managed Care Guidelines](#)

[Indemnity/PPO Guidelines](#)

[Clinical Exception Process](#)

[Medical Technology Assessment Guidelines](#)

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