

**Policy #: 088**

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**Title**

**Preimplantation Genetic Testing**

**Description**

Preimplantation genetic testing (PGT) describes a variety of adjuncts to an assisted reproductive procedure in which either maternal or embryonic DNA is sampled and genetically analyzed, thus permitting deselection of embryos harboring a genetic defect prior to implantation of the embryo into the uterus. The ability to identify preimplantation embryos with genetic defects before the initiation of pregnancy provides an attractive alternative to amniocentesis or chorionic villous sampling (CVS) with selective pregnancy termination of affected fetuses. Preimplantation genetic testing can be viewed as either diagnostic (PGD) or 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 genetic abnormalities to identify embryos at risk.

Two different sources of genetic material may be sampled in PGT; either the first or second polar body of the oocyte may be sampled or the preimplantation embryo may be biopsied. The first and second polar bodies are extruded from the oocyte as it completes 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. Alternatively, single cells from the preimplantation embryo can also be sampled. Typically, pre-embryos are biopsied after the first few cleavage divisions, although some researchers have performed biopsies of blastocytes containing 120 cells. At both of these stages, the cells are totipotent, and there is no damage to the resulting embryo. Biopsy of pre-embryos or blastocytes can detect genetic abnormalities arising from the maternal or paternal genetic material.

The biopsied material can be analyzed in a variety of ways. Polymerase chain reaction (PCR) 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 (PGD), such as Tay Sach's 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 (PGS) for aneuploidy, gender determination, or to identify chromosomal translocations. FISH cannot be used to diagnose single genetic defect disorders. However, molecular techniques can be applied with FISH (such as microdeletions and duplications) and thus, single-gene defects can be recognized with this technique.

Three general categories of embryos have undergone PGT:

1. Embryos at risk for a specific inherited single genetic defect (PGD)

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. Gender selection of a female embryo is another strategy when the mother is a known carrier of an X-linked disorder for which there is not yet a 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 genetic defects for which molecular diagnosis is possible, the most common indications include cystic fibrosis, beta thalassemia, muscular dystrophy, Huntington's 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 are 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.

## 2. Identification of aneuploid embryos

Implantation failure of fertilized embryos is a common cause for failure of 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 of the extruded polar bodies from the oocyte has been explored as a technique to deselect aneuploid oocytes in older women. The FISH technique is most commonly used to detect aneuploidy.

## 3. 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 in those with recurrent spontaneous abortions. PGD can be used to deselect those embryos carrying the translocations, thus leading to an increase in fecundity or a decrease in the rate of spontaneous abortion.

As PGT has been developed, additional issues have been raised. One important issue is that of mosaicism of the embryo, whereby examining chromosomes of a single cell may be misleading with respect to the rest of the embryo.

### **When services are covered for all Products (including Medicare HMOB, Medicare PPO Blue and Blue Medicare PFFS Plus Rx Products)**

We cover **preimplantation genetic diagnosis (PGD)** as an adjunct to In Vitro Fertilization (IVF) in patients/couples who are undergoing IVF due to infertility who have a history of 3 prior failed IVF cycles.

We cover **preimplantation genetic diagnosis (PGD)** as an adjunct to IVF in fertile and infertile couples for evaluation of an embryo at an identified elevated risk of a genetic disorder, such as when:<sup>1</sup>

- Both partners are known carriers of a single autosomal recessive gene disorder, or
- One partner is a known carrier of a single autosomal recessive disorder and the partners have one offspring that has been diagnosed with that recessive disorder, or
- One partner is a known carrier of a single gene autosomal dominant disorder, or
- One partner is a known carrier of a single X-linked disorder.

We cover **preimplantation genetic diagnosis (PGD)** as an adjunct to IVF in fertile and infertile couples for evaluation of an embryo at an identified elevated risk of a specific chromosomal abnormality, e.g. unbalanced translocation, microdeletion/duplication, aneuploidy, such as for a parent with a balanced or unbalanced chromosomal translocation.<sup>1</sup>

- Prior parental history of offspring with aneuploidy
- Advanced maternal age, i.e., age greater than 35 years, in the egg donor.

### **When services are not covered for all Products (including Medicare HMOB, Medicare PPO Blue and Blue Medicare PFFS Plus Rx Products)**

We do not cover **preimplantation genetic diagnosis (PGD)** as an adjunct to in vitro fertilization (IVF) in patients/couples who are undergoing IVF due to infertility when there is no identified elevated risk of genetic disorder or chromosomal abnormality in the embryo (as noted above.) or no history of at least 3 prior failed IVF cycles.

We do not cover **preimplantation genetic screening (PGS)** as an adjunct to IVF since it is considered investigational in patients/couples who are undergoing IVF<sup>1</sup> and does not meet our BCBSMA Medical Technology Assessment Guidelines, #350.

#### Individual consideration

All our medical policies are written for the majority of people with a given condition. Each policy is based on medical science. For many of our medical policies, each individual's unique clinical circumstances may be considered in light of current scientific literature. For consideration of an individual patient, physicians may send relevant clinical information to:

#### For services already billed

Blue Cross Blue Shield of Massachusetts  
Provider Appeals  
PO Box 986065  
Boston, MA 02298

#### Prior to performance of service

Blue Cross Blue Shield of Massachusetts  
Case Creation/Medical Policy  
One Enterprise Drive  
Quincy, MA 02171  
Tel: 1-800-327-6716  
Fax: 1-888-641-5330

#### Coordination of care guidelines for all Products

- Any specialist visit requires a referral for Medicare HMO Blue.
- For all other Managed Care plans, any specialist visit requires a referral, except for visits performed by OB/GYN specialists.
- Authorizations are required for all plans.

#### Coding information

*Procedure codes are from current CPT, HCPCS Level II, Revenue Code, and/or ICD-9-CM manuals, as recommended by the American Medical Association, Centers for Medicare and Medicaid Services and American Hospital Associations. Blue Cross Blue Shield Association national codes may be developed when appropriate.*

*The following codes are included below for informational purposes. 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.*

#### CPT codes:

- **89290:** biopsy, oocyte polar body or embryo blastomere, microtechnique (for pre-implantation genetic diagnosis); less than or equal to five embryo
- **89291:** biopsy, oocyte polar body or embryo blastomere, microtechnique (for pre-implantation genetic diagnosis); greater than five embryo

#### Other information

In some cases involving a single X-linked disorder, determination of the gender of the embryo provides sufficient information for excluding or confirming the disorder.

The complicated technical and ethical issues associated with preimplantation genetic testing will frequently require case by case consideration. For example, such consideration may be required, particularly for couples who are known carriers of potentially lethal or disabling genetic mutations and are seeking preimplantation genetic diagnosis as an alternative to conventional conception, with the possibility of an elective abortion if a subsequent amniocentesis identifies an affected fetus. The diagnostic performance of the individual laboratory tests used to analyze the biopsied genetic material is rapidly evolving, and evaluation of each specific genetic test for each abnormality is beyond the scope of this policy. However, in general, to assure adequate sensitivity

and specificity for the genetic test guiding the embryo deselection process, the genetic defect must be well characterized. For example, the gene or genes responsible for some genetic disorders may be quite large, with mutations spread along the entire length of the gene. The ability to detect all or some of these genes, and an understanding of the clinical significance of each mutation (including its penetrance, i.e., the probability that an individual with the mutation will express the associated disorder) will affect the diagnostic performance of the test. An ideal candidate for genetic testing would be a person who has a condition that is associated with a single well-characterized mutation for which a reliable genetic test has been established. In some situations, preimplantation genetic testing (PGT) may be performed in couples in which the mother is a carrier of an X-linked disease, such as fragile X syndrome. In this case, the genetic test could focus on merely deselecting male embryos.

The severity of the genetic disorder is also a consideration. At the present time, many cases of preimplantation genetic diagnosis (PGD) have involved lethal or severely disabling conditions with limited treatment opportunities, such as Huntington's chorea or Tay Sach's disease. Cystic fibrosis is another condition for which PGD has been frequently performed. However, cystic fibrosis has a variable presentation and can be treatable. The range of genetic testing that is performed on amniocentesis samples as a possible indication for elective abortion may serve as a guide.

This policy does not attempt to address the myriad ethical issues associated with PGT that, it is hoped, have involved careful discussion between the treated couple and the physician. For some couples, the decision may involve the choice between the risks of an IVF procedure and deselection of embryos as part of the PGT treatment versus normal conception with the prospect of amniocentesis and an elective abortion.

#### **Definitions**

**assisted reproductive techniques:** the use of medical techniques, such as drug therapy, artificial insemination, or in vitro fertilization, to enhance fertility.

**aneuploid:** an embryo with the wrong number of chromosomes. Aneuploidy is nearly always incompatible with life, and is the cause of most early miscarriages.

**autosomal dominant:** autosomal dominant is one of several ways that a trait or disorder can be passed down through families. If a disease is autosomal dominant, it means a child only needs to get the abnormal gene from one parent in order for that child to inherit the disease. One of the parents may often have the disease.

**autosomal recessive:** autosomal recessive is one of several ways that a trait, disorder, or disease can be passed down through families. An autosomal recessive disorder means two copies of an abnormal gene must be present in order for the disease or trait to develop.

**chromosomal translocation:** the combining of part of one chromosome onto part of another chromosome

**embryos:** the organism in the early stages of growth and differentiation from fertilization to, in humans, the beginning of the third month of pregnancy. After that point in time, it is termed a fetus.

**FISH:** (fluorescence in situ hybridization), a molecular clinical lab technique used in the study of chromosomes. This technique is useful for identifying chromosomal abnormalities and gene mapping.

**genetic defects:** defects of function or structure passed on from parents to offspring. Inherited defects.

**In Vitro Fertilization (IVF):** a laboratory procedure in which sperm are placed with an unfertilized egg in a petri dish to achieve fertilization. The embryo is then transferred into the uterus to begin a pregnancy or cryopreserved (frozen) for future use.

**oocytes:** eggs produced by the ovary before fertilization.

**polar bodies:** one of the small cells that are produced during the development of an oocyte (egg) and ultimately degenerates

**preimplantation genetic diagnosis (PGD):** the genetic material (DNA) of the mother or of the embryo is sampled and analyzed. This information could be used to choose some embryos and not others, before putting the embryo into the uterus.

**X-linked:** a trait or disease tied to genes on the X chromosome, one of the sex chromosomes that determine gender of an organism.

## Policy update history

Updated 10/99 to exclude coverage for preimplantation genetic diagnosis (PGD). Updated 10/03 to include coverage for PGD, effective January 2004. Updated 5/05 to clarify coverage guidelines for PGD Updated 5/05 to include the 2005 rationale and references on PGD from the BCBSA National policy. 5/06 Updated to reflect recent review of National Policy pertaining to Preimplantation Genetic Diagnosis (PGD). Reviewed 1/09 based on a comparison of BCBSA national medical policy, Preimplantation Genetic Diagnosis; no policy coverage changes which BCBSMA benchmarks. Issuance of separate Preimplantation Genetic Diagnosis (PGD) medical policy document, 2/2009 (previously addressed on BCBSMA medical policy #86.) Updated 7/09, clarified language based on the BCBSA national medical policy, Preimplantation Genetic Testing: the medical policy has been retitled, "When services are covered" includes- "one partner is a known carrier of a single autosomal recessive disorder and the partners have one offspring that has been diagnosed with that recessive disorder", and clarified "When services are not covered" states: "preimplantation genetic screening (PGS) is considered investigational in patients/couples who are undergoing IVF." References added to include 34-36, and guideline information added to the Other Information section.

## Footnotes

<sup>1</sup> Based on the Blue Cross Blue Shield Association medical policy, Preimplantation Genetic Testing, 4.02.05.

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