Introduction

In vitro fertilization is the process of combining eggs and sperm in a lab dish to create a fertilized egg (an embryo) and later implanting it into the uterus to complete the pregnancy. Before implantation, one or more cells from the embryo may be tested to see if there are problems with its genes or chromosomes. "Preimplantation genetic diagnosis" testing looks at the genes to see if the embryo carries a genetic disease such as cystic fibrosis. "Preimplantation genetic screening" looks to see if there are too few or too many chromosomes. This policy describes when either type of preimplantation genetic testing may be considered medically necessary.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.
**Policy Coverage Criteria**

**Note:** Preimplantation genetic diagnosis (PGD) is performed on embryos created as a result of in vitro fertilization (IVF) cycles. This procedure tests for specific diseases such as cystic fibrosis and would be covered as part of the member's infertility benefit, if applicable. Please check member contract and benefit descriptions for coverage.

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Medical Necessity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preimplantation genetic diagnosis (PGD)</td>
<td>The procedure to obtain the cell sample for PGD (ie, the embryo biopsy) is considered medically necessary when the criteria below for PGD are met. However, the IVF procedure (ie, the procedures and services, including intracytoplasmic sperm injection [ICSI], required to create the embryos to be tested and the transfer of the appropriate embryos back to the uterus after testing) is covered only for persons with assisted fertility benefits for IVF. Please check the member contract and benefit descriptions for coverage of assisted fertility techniques such as IVF.</td>
</tr>
</tbody>
</table>

Preimplantation genetic diagnosis (PGD) may be considered medically necessary as an alternative to amniocentesis or chorionic villus sampling in fertile couples undergoing IVF who meet one of the following criteria:

- For evaluation of an embryo at an identified elevated risk of a genetic disorder such as when:
  - Both partners are known carriers of a single-gene autosomal recessive disorder
  - One partner is a known carrier of a single-gene autosomal recessive disorder and the partners have an offspring who has been diagnosed with that recessive disorder
  - One partner is a known carrier of a single-gene autosomal dominant disorder
  - One partner is a known carrier of a single X-linked disorder

OR

- For evaluation of an embryo at an identified elevated risk of structural chromosomal abnormality such as if one parent has a
### Procedure

**Medical Necessity**

- balanced or unbalanced chromosomal translocation

**Preimplantation genetic screening (PGS), gender selection**

Preimplantation genetic screening (PGS) is considered not medically necessary when testing embryos solely for nonmedical gender selection or selection of other nonmedical traits.

### Procedure

**Investigational**

**Preimplantation genetic diagnosis (PGD)**

Preimplantation genetic diagnosis (PGD) as an alternative to amniocentesis or chorionic villus sampling is considered investigational in patients/couples who are undergoing IVF in all situations other than those specified above.

**Preimplantation genetic screening (PGS)**

Preimplantation genetic screening (PGS) as an alternative to amniocentesis or chorionic villus sampling is considered investigational in patients/couples who are undergoing IVF in all situations when used to screen for potential genetic abnormalities in couples without a specific known inherited disorder.

### Coding

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>81200</td>
<td>ASPA (aspartoacylase) (eg, Canavan disease) gene analysis, common variants (e.g., E285A, Y231X)</td>
</tr>
<tr>
<td>81223</td>
<td>CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene analysis; full gene sequence</td>
</tr>
<tr>
<td>81255</td>
<td>HEXA (hexosaminidase A [alpha polypeptide]) (eg, Tay-Sachs disease) gene analysis, common variants (eg, 1278insTATC, 1421+1G&gt;C, G269S)</td>
</tr>
<tr>
<td>81257</td>
<td>HBA1/HBA2 (alpha globin 1 and alpha globin 2) (eg, alpha thalassemia, Hb Bart hydrops fetalis syndrome, HbH disease), gene analysis, for common deletions or variant (eg, Southeast Asian, Thai, Filipino, Mediterranean, alpha3.7, alpha4.2, alpha20.5, and Constant Spring)</td>
</tr>
<tr>
<td>81599</td>
<td>Unlisted multianalyte assay with algorithmic analysis</td>
</tr>
<tr>
<td>Code</td>
<td>Description</td>
</tr>
<tr>
<td>--------</td>
<td>-----------------------------------------------------------------------------</td>
</tr>
<tr>
<td>89290</td>
<td>Biopsy, oocyte polar body or embryo blastomere, microtechnique (for pre-implantation genetic diagnosis); less than or equal to 5 embryos</td>
</tr>
<tr>
<td>89291</td>
<td>Biopsy, oocyte polar body or embryo blastomere, microtechnique (for pre-implantation genetic diagnosis); greater than 5 embryos</td>
</tr>
<tr>
<td>89398</td>
<td>Unlisted reproductive medicine laboratory procedure</td>
</tr>
</tbody>
</table>

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Specific CPT codes describe the embryo biopsy procedure (89290-89291). Additional CPT codes will be required for the genetic analysis and will vary by technique used to perform the genetic analysis.

Related Information

Definition of Terms

**Benign**: Not harmful to the DNA sequence.

**Disease-associated variant**: A disease-associated change in the DNA sequence (also known as a mutation).

**Familial variant**: A disease-associated variant identified in an index patient for use in subsequent targeted genetic testing of first-degree relatives.

**Likely benign**: Unlikely to be a disease-causing change to the DNA sequence.

**Likely pathogenic**: Likely a disease-causing change in the DNA sequence.

**Pathogenic**: Disease-causing change in the DNA sequence.

**Preimplantation genetic diagnosis (PGD)**: Genetic testing to look for a specific disease, eg, cystic fibrosis.

**Preimplantation genetic screening (PGS)**: Genetic testing to see if the embryo has the normal number of chromosomes

**Preimplantation genetic testing (PGT)**: An umbrella term including preimplantation genetic diagnosis and preimplantation genetic screening
**Variant of uncertain significance:** A change in the DNA sequence with uncertain effects on disease.

**Variant:** A change in the DNA sequence. Formerly called a mutation.

*Source: ACMG: American College of Medical Genetics and Genomics; AMP: Association for Molecular Pathology*

### Genetic Counseling

Genetic counseling is primarily aimed at patients who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual's family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

### Additional 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 severity of the genetic disorder is also a consideration. At present, many cases of preimplantation genetic diagnosis (PGD) have involved lethal or severely disabling conditions with limited treatment opportunities, such as Huntington chorea or Tay-Sachs 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 address the myriad ethical issues associated with preimplantation genetic testing (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 in vitro fertilization procedure and deselection of embryos as part of the PGT treatment versus normal conception with the prospect of amniocentesis and an elective abortion.
Description

Preimplantation genetic testing (PGT) involves analysis of biopsied cells as part of an assisted reproductive procedure. It is generally considered to be divided into two categories:

1. Preimplantation genetic diagnosis (PGD) is used to detect a specific inherited disorder and aims to prevent the birth of affected children in couples at high risk of transmitting a disorder.

2. Preimplantation genetic screening (PGS) is used to screen for chromosomal aneuploidy in conjunction with in vitro fertilization for couples without a specific known inherited disorder.

Background

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 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 (CVS), and selective pregnancy termination of affected fetuses. PGT 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).

Embryos at Risk for a Specific Inherited Single Genetic 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 genetic defects for which molecular diagnosis is possible, the most common indications include cystic fibrosis, β-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 CVS.

**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 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. FISH analysis of extruded polar bodies from the oocyte or no blastomeres at day 3 of embryo development was the initial method used to detect aneuploidy. A limitation of FISH is that analysis is limited to a restricted number of proteins. More recently, newer PGS methods have been developed and are known collectively as 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 failure.
Summary of Evidence

For individuals who have an identified elevated risk of a genetic disorder undergoing in vitro fertilization who receive preimplantation genetic diagnosis (PGD), the evidence includes observational studies and systematic reviews. Relevant outcomes are health status measures and treatment-related morbidity. Data from observational studies and a systematic review have suggested that PGD 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, PGD performed for single gene defects does not appear to be associated with increased risk of obstetric complications. The evidence is sufficient to determine qualitatively 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 in vitro fertilization 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, fish in situ hybridization) have found lower or similar ongoing pregnancy and live birth rates compared with in vitro fertilization 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 not live birth rates. One meta-analysis, but not the other, found significantly higher ongoing pregnancy rates after PGS than after standard care. Well-conducted RCTs evaluating PGS in the target population (eg, women of advanced maternal age) 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.

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 1.

Table 1. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ongoing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT02268786</td>
<td>Single Embryo TrAnsfeR of Euploid Embryo (STAR)</td>
<td>600</td>
<td>Jun 2017</td>
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<tr>
<td>NCT No.</td>
<td>Trial Name</td>
<td>Planned Enrollment</td>
<td>Completion Date</td>
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<tr>
<td>--------------</td>
<td>----------------------------------------------------------------------------</td>
<td>--------------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>NCT02868528</td>
<td>A Study of Preimplantation Genetic Screening With Next Generation Sequencing Technology on Advanced Age Women</td>
<td>239</td>
<td>Aug 2019</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.

* Denotes industry-sponsored or cosponsored trial.

**Practice Guidelines and Position Statements**

**American Society for Reproductive Medicine (ASRM)**

In 2013, the American Society for Reproductive Medicine published an opinion on the use of preimplantation genetic diagnosis (PGD) for serious adult onset conditions. The main points included:

- 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.

Previously, in 2007, the Society issued an opinion that concluded the available evidence did not support the use of preimplantation genetic screening as currently performed to improve live birth rates in patients with advanced maternal age, previous implantation failure, or recurrent pregnancy loss, or to reduce miscarriage rates in patients with recurrent pregnancy loss related to aneuploidy.
American College of Obstetricians and Gynecologists (ACOG)

In 2009 (reaffirmed in 2014), the ACOG issued an opinion on PGS for aneuploidy. The College stated that current data do not support the use of PGS to screen for aneuploidy due solely to maternal age. The College also did not recommend PGS for recurrent unexplained miscarriage and recurrent implantation failures in the clinical setting; it recommended that use be limited to research studies.

Medicare National Coverage

There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

Regulatory Status

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

References


<table>
<thead>
<tr>
<th>Date</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>08/11/09</td>
<td>Replace Policy - Policy updated with literature search. Policy statement revised to delete medically necessary bullet: “Prior parental history of offspring with aneuploidy. Advanced maternal age, i.e., age greater than 35 years in the egg donor. Prior history of recurrent spontaneous abortion with uncertain genetic karyotype”. References added.</td>
</tr>
<tr>
<td>02/09/10</td>
<td>Code Update - New 2010 code added.</td>
</tr>
<tr>
<td>08/10/10</td>
<td>Replace Policy - Policy updated with literature search. Rationale updated. References added. No change to policy statement.</td>
</tr>
<tr>
<td>07/12/11</td>
<td>Replace Policy - Policy updated with literature search. Rationale updated. Reference added. No change to policy statement.</td>
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<tr>
<td>01/11/12</td>
<td>Codes 81200, 81220 – 81224, 81243 – 81244, 81255 and 81257 added.</td>
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<tr>
<td>09/11/12</td>
<td>Replace policy. Policy changed to BCBSA 4.02.05 (replacing 4.02.500) and renumbered 12.04.305, moving to the Genetic Testing section. Policy title changed to Preimplantation Genetic Testing. Policy updated with literature search through May 2012. Two medical necessary statements added: When 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 and when there is partner with documented history of aneuploidy in a previous pregnancy. Statement added that PGD is investigational in all instances other than those listed. PGS, previously considered not medically necessary in patients/couples when used to screen for potential genetic abnormalities in couples without a specific known inherited disorder, is now considered investigational. Other policy statements unchanged. References 1, 2, 3, 4, 6 and 7 added; other references renumbered or removed.</td>
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<tr>
<td>01/14/13</td>
<td>Coding update. CPT codes 83890 – 83913 deleted as of 12/31/12; CPT codes 81200 – 81479 and 81599, effective 1/1/13, are added to the policy.</td>
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<tr>
<td>05/14/13</td>
<td>Update Related Policies. Add 12.04.91.</td>
</tr>
<tr>
<td>09/09/13</td>
<td>Replace policy. Policy statement revised to delete “Partner with documented history of aneuploidy in a previous pregnancy” as indication for elevated risk of chromosomal abnormality. Description and Rationale revised. References added.</td>
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<tr>
<td>12/19/13</td>
<td>Update Related Policies. Add 12.04.75.</td>
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<tr>
<td>07/24/14</td>
<td>Update Related Policies. Remove 12.04.91.</td>
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<tr>
<td>Date</td>
<td>Comments</td>
</tr>
<tr>
<td>------------</td>
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<tr>
<td>12/03/14</td>
<td>Update Related Policies. Add 12.04.104.</td>
</tr>
<tr>
<td>09/08/15</td>
<td>Annual Review. Severity of genetic disorder determination paragraph deleted from policy guidelines as beyond the scope of this policy. Policy updated with literature review through June 3, 2015. References 17-21 added; others renumbered/removed. Policy statements unchanged. Coding update: Deleted CPT codes 88384-86 removed; 89290, 89291 and 88275 removed – reviewed under fertility benefit; 81220-81222, 81224, 81243, 81244, and 88271-88274 removed since these are not reviewed pertaining to this policy.</td>
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<tr>
<td>05/04/16</td>
<td>Update related policies. 12.04.109 was deleted and replaced with 12.04.519.</td>
</tr>
<tr>
<td>02/07/17</td>
<td>Coding correction. CPT code 83898 was previously listed on this policy in error. Code corrected to 89398.</td>
</tr>
</tbody>
</table>

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