Preimplantation genetic diagnosis (PGD) may be considered medically necessary as an adjunct to in vitro fertilization (IVF) in couples not known to be infertile who meet one or more of the following criteria:

- For evaluation of an embryo at an identified elevated risk of a genetic disorder such as any of the following:
  - 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

- For evaluation of an embryo at an identified elevated risk of structural chromosomal abnormality, i.e., a parent with balanced or unbalanced chromosomal translocation

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

Preimplantation genetic screening (PGS) as an adjunct to IVF is considered investigational in patients or couples who are undergoing IVF in all situations.

Policy Guidelines

In some cases involving a single X-linked disorder, determination of the sex 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 preimplantation genetic diagnosis 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 that should have been carefully discussed 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 preimplantation genetic testing treatment versus normal conception with the prospect of amniocentesis and an elective abortion.

Genetics Nomenclature Update

The Human Genome Variation Society nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. It is being implemented for genetic testing medical evidence review updates starting in 2017 (see Table PG1). The Society’s nomenclature is recommended by the Human Variome Project, the HUman Genome Organization, and by the Human Genome Variation Society itself.

The American College of Medical Genetics and Genomics and the Association for Molecular Pathology standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations, in addition to the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including...
Table PG1. Nomenclature to Report on Variants Found in DNA

<table>
<thead>
<tr>
<th>Previous</th>
<th>Updated</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mutation</td>
<td>Disease-associated variant</td>
<td>Disease-associated change in the DNA sequence</td>
</tr>
<tr>
<td>Variant</td>
<td>Change in the DNA sequence</td>
<td></td>
</tr>
<tr>
<td>Familial variant</td>
<td>Disease-associated variant</td>
<td>Disease-associated variant identified in a proband for use in</td>
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<tr>
<td></td>
<td></td>
<td>subsequent targeted genetic testing in first-degree relatives</td>
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</table>

Table PG2. ACMG-AMP Standards and Guidelines for Variant Classification

<table>
<thead>
<tr>
<th>Variant Classification</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathogenic</td>
<td>Disease-causing change in the DNA sequence</td>
</tr>
<tr>
<td>Likely pathogenic</td>
<td>Likely disease-causing change in the DNA sequence</td>
</tr>
<tr>
<td>Variant of uncertain significance</td>
<td>Change in DNA sequence with uncertain effects on disease</td>
</tr>
<tr>
<td>Likely benign</td>
<td>Likely benign change in the DNA sequence</td>
</tr>
<tr>
<td>Benign</td>
<td>Benign change in the DNA sequence</td>
</tr>
</tbody>
</table>

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.

Coding

There are specific CPT codes describing the embryo biopsy procedure:

- **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

Additional CPT codes will be required for the genetic analysis. CPT codes used will vary by technique used to perform the genetic analysis.

As appropriate, specific codes from the CPT molecular pathology section or molecular cytogenetics section would be reported:

- **81161-81479**: Molecular pathology code range
- **88271-88275**: Molecular cytogenetics code range

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

Preimplantation genetic screening (PGS) involves testing for potential genetic abnormalities in conjunction with in vitro fertilization (IVF) for couples without a specific known inherited disorder.
Related Policies

- General Approach to Evaluating the Utility of Genetic Panels
- General Approach to Genetic Testing
- Reproductive Techniques

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates [e.g., Federal Employee Program (FEP)] prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

Regulatory Status

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

Rationale

Background

Preimplantation Genetic Testing

Preimplantation genetic testing describes various adjuncts to an assisted reproductive procedure (see Blue Shield of California Medical Policy: Reproductive Techniques) 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 (e.g., 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 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 (i.e., blastomeres). Sampling involves aspiration of one 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 trophectoderm 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 (e.g., microdeletions, duplications) and, thus, single-gene defects can be recognized with this technique.

Another approach becoming more common is array comparative genome hybridization testing at either the 8-cell or, more often, the blastocyst stage. 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 abnomal gains and losses of chromosomal material. Next-generation sequencing such as massively parallel signature sequencing has potential applications to prenatal genetic testing. These techniques are being actively studied, but their use is in a relatively early stage of development compared with other methods of analyzing biopsied material.1,2

Three general categories of embryos have undergone preimplantation genetic testing, which are 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 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-gene 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 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. 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 failures.

Literature Review
The complicated technical and ethical issues associated with preimplantation genetic testing frequently require case-by-case consideration. 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 evidence review. 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 variants 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 variant (including its penetrance, i.e., the probability that an individual with the variant 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 associated with a single well-characterized variant for which a reliable genetic test has been established. In some situations, preimplantation genetic testing 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. This review does not consider every possible genetic defect. Therefore, implementation will require a case-by-case approach to address the many specific technical and ethical considerations inherent in testing for genetic disorders, based on an understanding of the penetrance and natural history of the genetic disorder in question and the technical capability of genetic testing to identify affected embryos.

The following is a summary of the key literature to date.

Preimplantation Genetic Diagnosis with In Vitro Fertilization
Systematic Reviews
In 2011, Franssen et al conducted a systematic review of the literature on reproductive outcomes in couples with recurrent miscarriage (at least 2) who had a known structural chromosome abnormality; reviewers compared live birth rates after preimplantation genetic diagnosis (PGD) with natural conception. No controlled studies were identified. Reviewers identified 4 observational studies on reproductive outcomes for 469 couples after natural conception and 21 studies on reproductive outcomes for 126 couples after PGD. The live birth rates per couple ranged from 33% to 60% (median, 55.5%) after natural conception and between 0% and 100% (median, 31%) after PGD. Miscarriage rate was a secondary outcome. After natural conception, miscarriage rates ranged from 21% to 40% (median, 34%); after PGD,
miscarriage rates ranged from 0% to 50% (median, 0%). Findings of this review apply only to couples with both recurrent miscarriage and a known structural chromosome abnormality.

In 2017, Hasson et al published a meta-analysis of studies comparing obstetric and neonatal outcomes after intracytoplasmic sperm injection without PGD compared with intracytoplasmic sperm injection with PGD. Studies focused on cases in which there were known parental genetic aberrations. Reviewers identified 6 studies, including data published by the investigators in the same article. Pooled analysis found no significant differences between the 2 groups for 4 of the 5 reported outcomes: mean birth weight, mean gestational age at birth, the rate of preterm delivery, and the rate of malformations. There was a significantly lower rate of low birth weight neonates (<2500 g) in the PGD group than in the non-PGD group (relative risk [RR], 0.84; 95% confidence interval [CI], 0.72 to 1.00; p=0.04).

Randomized Controlled Trials
In 2017, Rubio et al published a randomized controlled trial (RCT) comparing outcomes in women of advanced maternal age who underwent PGD for aneuploidy before blastocyst transfer compared with blastocyst transfer without PGD. The trial included women between 38 and 41 years old with normal karyotypes who were on their first or second cycle of intracytoplasmic sperm injection. A total of 138 patients were randomized to the PGD group and 140 to the non-PGD control group. Of these, 100 patients in the PGD group and 105 in the non-PGD group completed the intervention. In an intention-to-treat analysis, there was a significantly higher live birth rate in the PGD group (31.9%) than in the control group (18.6%; odds ratio [OR], 2.4; 95% CI, 1.3 to 4.2; p=0.003). In the per-protocol analysis, there was a significantly higher rate of live birth in the PGD group than in the control group, both in the per transfer and per patient analyses. Per transfer, there were live births in 65% of the PGD group and 27% of the control group (OR=4.86; 95% CI, 2.49 to 9.53; p<0.001). Per patient, there were live births in 44% of the PGD group and 25% of the control group (OR=2.39; 95% CI, 1.32 to 4.32; p=0.005). In addition, the implantation rate was significantly higher in the PGD group (53%) than in the control group (43% p<0.001) and the miscarriage rate was significantly lower in the PGD group (3%) than in the control group (39% p=0.007).

Observational Studies
Selected recent observational studies reporting on pregnancy rates or live birth rates are described next. For example, a 2016 study by Kato et al included 52 couples with a reciprocal translocation (n=46) or Robertsonian translocation (n=6) in at least 1 partner. All couples had a history of at least 2 miscarriages. The average live birth rate was 76.9% over 4.6 oocyte retrieval cycles. In the subgroups of young (<38 years) female carriers, young male carriers, older (≥38 years) female carriers, and older male carriers, live birth rates were 77.8%, 72.7%, 66.7%, and 50.0%, respectively.

In 2015, Chow et al reported on 124 cycles of PGD in 76 couples with monogenetic diseases (X-linked recessive, autosomal recessive, autosomal dominant). The most common genetic conditions were α-thalassemia (64 cycles) and β-thalassemia (23 cycles). Patients were not required to have a history of miscarriage. A total of 92 PGD cycles resulted in embryo transfer, with an ongoing pregnancy rate (beyond 8-10 weeks of gestation) in 28.2% of initiated cycles and an implantation rate of 35%. The live birth rate was not reported.

In 2012, Keymolen et al in Belgium reported on clinical outcomes for 312 cycles performed for 142 couples with reciprocal translocations. Seventy-five (53%) of 142 couples had PGD for infertility, 40 (28%) couples for a history of miscarriage, and the remainder had other reasons. The live birth rate per cycle was 12.8% (40/312), and the live birth rate per cycle with embryo transfer was 26.7% (40/150).

A 2013 study by Scriven et al in the United Kingdom evaluated PGD for couples carrying reciprocal translocations. This prospective analysis included the first 59 consecutive couples who completed treatment at a single center. Thirty-two (54%) of the 59 couples had had
recurrent miscarriages. The 59 couples underwent a total of 132 cycles. The estimated live birth rate per couple was 51% (30/59) after 3 to 6 cycles. The live birth rate estimate assumed that couples who were unsuccessful and did not return for additional treatment would have had the same success rate as couples who returned.

**Adverse Events**

An important general clinical issue is whether PGD is associated with adverse obstetric outcomes, specifically fetal malformations related to the biopsy procedure. Strom et al (2000) addressed this issue in an analysis of 102 pregnant women who had undergone PGD with genetic material from the polar body.10 All PGDs were confirmed postnatally; there were no diagnostic errors. The incidence of multiple gestations was similar to that seen with in vitro fertilization (IVF). PGD did not appear to be associated with an increased risk of obstetric complications compared with the risk of obstetric outcomes reported in data for IVF. However, it should be noted that biopsy of the polar body is considered biopsy of extra-embryonic material, and thus one might not expect an impact on obstetric outcomes. Patients in this study had undergone PGD for both unspecified chromosomal disorders and various disorders associated with a single-gene defect (i.e., cystic fibrosis, sickle cell disease, others).

**Section Summary: Preimplantation Genetic Diagnosis with In Vitro Fertilization**

Two systematic reviews of observational studies were identified. One of the systematic reviews found a median live birth rate of 31% after PGD compared with 55.5% after natural conception. The median miscarriage rate was 0% after PGD and 34% after natural conception. Findings of this review apply only to patients with recurrent miscarriage. The other systematic review found a significant rate of low birth weight in the PGD group compared with a non-PGD group and no significant differences in other outcomes. Studies in the review focused on parents with known genetic aberrations. One RCT was identified; it found that outcomes were significantly better after PGD for aneuploidy in women of advanced maternal age than assisted reproduction without PGD. In particular, there were higher implantation rates, lower miscarriage rates, and higher live birth rates.

**Preimplantation Genetic Screening with In Vitro Fertilization**

**Systematic Reviews and Randomized Controlled Trials**

A number of RCTs evaluating preimplantation genetic screening (PGS) using fluorescent in situ hybridization-based technology have been published, and these findings have been summarized in a systematic review. In 2011, a systematic review by Mastenbroek et al included RCTs that compared the live birth rates in women undergoing IVF with and without PGS for aneuploidies.11 Fourteen potential trials were identified; 5 trials were excluded, leaving 9 eligible trials (total N=1589 women). Five trials included women of advanced maternal age; three included “good prognosis” patients, and one included women with repeated implantation failure. When data from the 5 trials including women with advanced maternal age were pooled, the live birth rate was significantly lower in the PGS group (18%) than in the control group (26%; p<0.001). There was no significant difference between live birth rates when data from the 3 studies with good prognosis patients were pooled; rates were 32% in the PGS group and 42% in the control group (p=0.12). Reviewers concluded that there was no evidence of a benefit of PGS as currently applied in practice; they noted potential reasons for inefficacy, including possible damage from the biopsy procedure and the mosaic nature of analyzed embryos.

**New Methods of Preimplantation Genetic Screening**

More recently, studies on newer methods of PGS have been published. There are several systematic reviews, including a 2015 review of RCTs on PGS by Dahdouh et al.12 RCTs were eligible for inclusion if they compared women undergoing IVF with PGS using one of the newer techniques on trophectodermic blastocyst cells with standard care without PGS. Reviewers did not distinguish between studies using fresh or frozen embryos, or between the various PGS version 2 techniques. Three RCTs met eligibility criteria.13-15 The characteristics and results of the RCTs are described in Table 1. All trials conducted embryo biopsies on day 5 or 6 of development. One trial (Yang et al) used array comparative genomic hybridization, and the
other two used quantitative polymerase chain reaction. None targeted women of advanced maternal age or women with repeated implantation failure. Instead, Yang et al included good prognosis patients younger than age 35 with no history of spontaneous abortion, Foman et al included women younger than age 43, and Scott et al included women between the ages of 21 and 42 years with no more than 1 failed IVF attempt. One of the trials (Foman et al) transferred 1 embryo in the intervention group and 2 embryos in the control group, which might have introduced bias. Two studies were superiority trials and the other (Foman et al) a noninferiority trial. Forman used a 20% noninferiority margin, which may not be the most appropriate approach for evaluating the impact of PGS on health outcomes.

### Table 1. Randomized Controlled Trials Evaluating Preimplantation Genetic Screening Methods

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<tr>
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<tbody>
<tr>
<td><strong>Design</strong></td>
<td>Superiority trial</td>
<td>Noninferiority trial</td>
<td>Superiority trial</td>
</tr>
<tr>
<td><strong>Sample size</strong></td>
<td>112 couples</td>
<td>205 couples</td>
<td>155 patients</td>
</tr>
<tr>
<td><strong>Patient population</strong></td>
<td>Female partner &lt;35 y with no history of spontaneous abortion and with normal karyotype</td>
<td>Female partner &lt;43 y</td>
<td>Female partner between 21 and 42 y with no more than 1 failed IVF attempt</td>
</tr>
</tbody>
</table>
| **Intervention**           | • Blastocyst biopsy (day 5/6) and analyzed via aCGH  
                           • Single euploid embryo selected for transfer based on PGS | • Blastocyst biopsy (day 5/6) and analyzed via qPCR  
                           • Single euploid embryo selected for transfer based on PGS | • Blastocyst biopsy (day 5/6) and analyzed via qPCR  
                           • Single euploid embryo selected for transfer based on PGS |
| **Comparator**             | Single embryo selected for transfer on day 5/6 based on morphologic assessment | Two embryos selected for transfer on day 5/6 based on morphologic assessment | Single embryo selected for transfer on day 5/6 based on morphologic assessment |
| **Implantation rate**      | Not reported      | Intervention group: 63.2%  
                           Control group: 51.7% (p=0.08) | Intervention group: 66.4%  
                           Control group: 47.9% (p<0.001) |
| **Clinical pregnancy rate** | • Intervention group: 70.9%  
                           Control group: 45.8% (p=0.017) | • Intervention group: 69%  
                           Control group: 81% (not inferior) | • Intervention group: 93.1%  
                           Control group: 80.7% (p=0.03) |
| **Ongoing pregnancy rate (≥24 wk of gestation)** | • Intervention group: 69.1%  
                           Control group: 41.7% (p=0.009) | • Intervention group: 60.7%  
                           Control group: 65.1% (not inferior) | Not reported |

aCGH: array comparative genomic hybridization; IVF: in vitro fertilization; PGS: preimplantation genetic screening; qPCR: quantitative polymerase chain reaction.

In a 2015 meta-analysis, Dahdouh et al pooled findings of the above 3 RCTs. Primary outcomes of the meta-analysis were implantation rates and ongoing pregnancy rates (i.e., >20 weeks). In pooled analyses, rates of both primary outcomes were significantly higher after use of the newer PGS techniques compared with standard care without PGS. For clinical implantation rate, the pooled RR was 1.29 (95% CI, 1.15 to 1.45); for sustained implantation rate, the pooled RR was 1.39 (95% CI, 1.21 to 1.60). The meta-analysis did not address the live birth rate or adverse obstetric outcomes.

In 2015, Chen et al published a meta-analysis of RCTs and cohort studies on newer PGS methods. Four RCTs and 7 cohort studies were identified. In addition to the 3 RCTs described in Table 1, Chen included a 2012 RCT that used single-nucleotide polymorphism microarray analysis. A pooled analysis of the 4 RCTs found a significantly higher implantation rate with PGS than with control (RR=1.32; 95% CI, 1.18 to 1.47). However, in additional pooled analyses of the RCTs, other outcomes were not significantly better with PGS than with control. For example, for the ongoing pregnancy rate, a pooled analysis of 2 RCTs had an RR of 1.31 (95% CI, 0.64 to 2.66). Two RCTs reported a lower miscarriage rate (RR=0.53; 95% CI, 0.24 to 1.15). Meta-analyses of the cohort studies found significantly improved ongoing pregnancy rates (RR=1.61; 95% CI, 1.30 to
2.00; 6 studies) and miscarriage rates (RR=0.31; 95% CI, 0.21 to 0.46; 5 studies), but not live birth rates (RR=1.35; 95% CI, 0.85 to 2.13; 3 studies). The cohort studies were subject to limitations such as selection bias.

**Long-Term Outcomes of Preimplantation Genetic Screening**
Several RCTs have reported longer-term outcomes after PGS. Beukers et al (2013) reported morphologic abnormalities in surviving children at 2 years. Data were available on 50 children born after PGS and 72 children born without PGS. Fourteen (28%) of 50 children in the PGS group and 25 (35%) of 72 children in the non-PGS group had at least 1 major abnormality; the between-groups difference was not statistically significant (p=0.43). Skin abnormalities (e.g., capillary hemangioma, hemangioma plana) were the most common, affecting 5 children after PGS and 10 children in the non-PGS group. In a control group of 66 age-matched children born without assisted reproduction, 20 (30%) children had at least 1 major abnormality.

In 2013, Schendelaar et al reported on outcomes when children were 4 years old. Data were available for 49 children (31 singletons, 9 sets of twins) born after IVF with PGS and 64 children (42 singletons, 11 sets of twins) born after IVF without PGS. The primary outcome was the child’s neurologic condition, as assessed by the fluency of motor behavior. The fluency score ranged from 0 to 15, as measured using a subscale of the Neurological Optimality Score. In the sample, and among singletons, the fluency score did not differ among children in the PGS and the non-PGS groups. However, among twins, the fluency score was significantly lower among those in the PGS group (mean score, 10.6; 95% CI, 9.8 to 11.3) and non-PGS group (mean score, 12.3; 95% CI, 11.5 to 13.1). Cognitive development, as measured by IQ score, and behavioral development, as measured by the total problem score, were similar between PGS and non-PGS groups.

**Section Summary: Preimplantation Genetic Screening with In Vitro Fertilization**
RCTs and meta-analyses are available. A meta-analysis of PGS using fluorescent in situ hybridization-based technology found a significantly lower live birth rate after PGS compared with controls in women of advanced maternal age, and there was no significant between-group difference in good prognosis patients. Meta-analyses of RCTs on newer methods found higher implantation rates with PGS than with standard care, but not live birth rates. One meta-analysis, but not the other, found a significantly higher ongoing pregnancy rate after PGS than with standard care. The RCTs on newer PGS methods tended to include good prognosis patients, and results may not be generalizable to other populations. An analysis of national data found that the live birth rate was significantly lower after PGS than without PGS in the entire cohort. Moreover, individual RCTs on newer PGS methods had potential biases (e.g., lack of blinding, choice of noninferiority margin). Well-conducted RCTs evaluating PGS in the target population (e.g., women of advanced maternal age) are needed before conclusions can be drawn about the impact on the net health benefit.

**Summary of Evidence**
For individuals who have an identified elevated risk of a genetic disorder undergoing IVF who receive PGD, 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 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 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 PGS, the evidence includes RCTs and meta-analyses. Relevant outcomes are health status measures and treatment-related morbidity. RCTs and meta-analyses of RCTs on initial PGS methods (e.g., fish 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 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 (e.g., 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.

Supplemental Information
Practice Guidelines and Position Statements

American Society for Reproductive Medicine
In 2013, the American Society for Reproductive Medicine published an opinion on the use of preimplantation genetic diagnosis (PGD) for serious adult-onset conditions.20 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 (PGS) 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.21

American College of Obstetricians and Gynecologists
In 2009 (reaffirmed 2014), the American College of Obstetricians and Gynecologists issued an opinion on PGS for aneuploidy.22 The College stated that current data did 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 was limited to research studies.

U.S. Preventive Services Task Force Recommendations
Not applicable.

Medicare National Coverage
There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials
Some currently unpublished trials that might influence this review are listed in Table 2.

Table 2. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCTNo.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ongoing</td>
<td>Single Embryo TrAnseR of Euploid Embryo (STAR)</td>
<td>600</td>
<td>Jun 2017 (ongoing)</td>
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<tr>
<td>NCT No.</td>
<td>Trial Name</td>
<td>Planned Enrollment</td>
<td>Completion Date</td>
</tr>
<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.

**References**


**Documentation for Clinical Review**

Please provide the following documentation (if when requested):

- History and physical and/or consultation notes including:
  - Reason for performing test
  - Signs/symptoms/test results related to reason for genetic testing
  - Family history if applicable
  - How test result will impact clinical decision making
- Lab results documenting one/both partners carrier status or genetic disorder
- Physician order for genetic test
- Name and description of genetic test
- CPT codes billed for the particular genetic test

**Coding**

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement.

**MN/IE**

The following services may be considered medically necessary in certain instances and investigational in others. Services may be considered medically necessary when policy criteria are met. Services may be considered investigational when the policy criteria are not met or when the code describes application of a product in the position statement that is investigational.
### CPT®

<table>
<thead>
<tr>
<th>Type</th>
<th>Code</th>
<th>Description</th>
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<td>81161-81479</td>
<td>Molecular pathology code range</td>
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<tr>
<td></td>
<td>88271</td>
<td>Molecular cytogenetics; DNA probe, each (e.g., FISH)</td>
</tr>
<tr>
<td></td>
<td>88272</td>
<td>Molecular cytogenetics; chromosomal in situ hybridization, analyze 3-5 cells (e.g., for derivatives and markers)</td>
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<tr>
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<td>88273</td>
<td>Molecular cytogenetics; chromosomal in situ hybridization, analyze 10-30 cells (e.g., for microdeletions)</td>
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<tr>
<td></td>
<td>88274</td>
<td>Molecular cytogenetics; interphase in situ hybridization, analyze 25-99 cells</td>
</tr>
<tr>
<td></td>
<td>88275</td>
<td>Molecular cytogenetics; interphase in situ hybridization, analyze 100-300 cells</td>
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<tr>
<td></td>
<td>88291</td>
<td>Cytogenetics and molecular cytogenetics, interpretation and report</td>
</tr>
<tr>
<td></td>
<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></td>
<td>89291</td>
<td>Biopsy, oocyte polar body or embryo blastomere, microtechnique (for pre-implantation genetic diagnosis); greater than 5 embryos</td>
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<tr>
<td>HCPCS</td>
<td>None</td>
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<tr>
<td>ICD-10</td>
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<tr>
<td>ICD-10</td>
<td>All Diagnoses</td>
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</table>

### Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

<table>
<thead>
<tr>
<th>Effective Date</th>
<th>Action</th>
<th>Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>08/29/2014</td>
<td>BCBSA Medical Policy adoption</td>
<td>Medical Policy Committee</td>
</tr>
<tr>
<td>11/01/2017</td>
<td>Policy revision without position change</td>
<td>Medical Policy Committee</td>
</tr>
</tbody>
</table>

### Definitions of Decision Determinations

**Medically Necessary:** A treatment, procedure, or drug is medically necessary only when it has been established as safe and effective for the particular symptoms or diagnosis, is not investigational or experimental, is not being provided primarily for the convenience of the patient or the provider, and is provided at the most appropriate level to treat the condition.

**Investigational/Experimental:** A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

**Split Evaluation:** Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

### Prior Authorization Requirements (as applicable to your plan)
Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department. Please call (800) 541-6652 or visit the provider portal at www.blueshieldca.com/provider.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.