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.

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.

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 genotyping, single genes, panels, exomes, and genomes. Table PG2 shows the recommended standard terminology—“pathogenic,” “likely pathogenic,” “uncertain significance,” “likely benign,” and “benign”—to describe variants identified that cause Mendelian disorders.

<table>
<thead>
<tr>
<th>Table PG1. Nomenclature to Report on Variants Found in DNA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Previous</strong></td>
</tr>
<tr>
<td>Mutation</td>
</tr>
<tr>
<td>Variant</td>
</tr>
<tr>
<td>Familial variant</td>
</tr>
</tbody>
</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 (i.e., FISH), 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 in conjunction with in vitro fertilization (IVF) 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 also in conjunction with IVF for couples without a specific known inherited disorder.

### Related Policies

- 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 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 (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. 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. 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 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 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 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.

Literature Review
Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function—including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

Preimplantation Genetic Diagnosis with In Vitro Fertilization
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, ie, 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 carries 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.

**Clinical Context and Therapy Purpose**
The purpose of preimplantation genetic diagnosis (PGD) in patients who have an identified elevated risk of a genetic disorder is to provide an alternative to amniocentesis, chorionic villus sampling, and selective pregnancy termination of affected fetuses.

The question addressed in this evidence review is: Does PGD of an in vitro fertilization (IVF) embryo from individuals with identified elevated risk of a genetic disorder improve pregnancy outcomes?

The following PICOTS were used to select literature to inform this review.

**Patients**
The relevant population of interest is individuals with an identified elevated risk of a genetic disorder such as a heritable genetic defect or chromosomal abnormality (e.g., translocations) who are undergoing IVF.

**Interventions**
The therapy being considered is PGD using methods such as polymerase chain reaction (PCR), array comparative genomic hybridization (aCGH), gene sequencing, or single nucleotide variant arrays to identify single-gene defects in cells from a preimplantation embryo or an oocyte polar body single-gene defects.

**Comparators**
The comparator of interest is IVF without PGD potentially with prenatal genetic testing.

**Outcomes**
The outcomes of interest include pregnancy and neonatal outcomes such as implantation rates, spontaneous abortion or miscarriage rates, length of gestation, live birth rates, birth weight, and fetal anomalies.

**Timing**
The timing of the outcomes of interest includes the time to successful implantation, the duration of pregnancy, and the neonatal period.

**Setting**
PGD is performed at specialized reproductive endocrinology services or clinics where comprehensive evaluation is available. This includes the availability of or referral for genetic counseling for prospective parents.

**Study Selection Criteria**
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess longer term outcomes and adverse effects, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

**Systematic Reviews**
Hasson et al (2017) 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 with known parental genetic aberrations.
Reviewers identified 6 studies, including data published by the investigators in the same article. The 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).

Franssen et al (2011) 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 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.

Observational Studies
Selected recent observational studies reporting on pregnancy rates or live birth rates are described next. For example, a study by Kato et al (2016) included 52 couples with a reciprocal translocation (n=46) or Robersonian 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.

Chow et al (2015) reported on 124 cycles of PGD in 76 couples with monogenic 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.

A study by Scriven et al (2013) 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.

Keymolen et al (2012) 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).

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. All PGDs were confirmed postnatally; there were no diagnostic errors. The incidence of multiple gestations was similar to that seen with 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.

Preimplantation Genetic Screening with IVF
Clinical Context and Therapy Purpose
The purpose of preimplantation genetic screening (PGS) in patients without an identified elevated risk of a genetic disorder is to identify genetic abnormalities in the absence of a known heritable disorder, in particular, to identify de novo aneuploidy and identify the embryo with the best potential to result in pregnancy and live birth.

The question addressed in this evidence review is: Does PGS of an IVF embryo from individuals without identified elevated risk of a genetic disorder improve pregnancy outcomes?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant population of interest is individuals without an identified elevated risk of a genetic disorder who are undergoing IVF. Although PGS may be used in any patient undergoing IVF, in particular, PGS may be used in patients with recurrent IVF implantation failure, recurrent early pregnancy loss, and/or of advanced maternal age.

Interventions
The therapy being considered is PGS. PGS version 1 uses fluorescent in situ hybridization (FISH) on polar bodies or cleavage stage embryos. PGS version 2 uses techniques such as aCGH, single nucleotide variant microarrays, and quantitative PCR. Next-generation sequencing is grouped with PGS version 2 techniques in some literature and referred to as PGS version 3 in other literature.

Comparators
The comparator of interest is IVF without PGS.

Outcomes
The outcomes of interest include pregnancy and neonatal outcomes such as implantation rates, spontaneous abortion or miscarriage rates, live birth rates, gestational age, birth weight, and fetal anomalies.

Timing
The timing of the outcomes of interest is the length of pregnancy.

Setting
PGS is performed at specialized reproductive endocrinology services or clinics where comprehensive evaluation is available. This includes the availability of or referral for genetic counseling for prospective parents.
Study Selection Criteria
Methodologically credible studies were selected as described in the previous section.

PGS Version 1 (FISH)
Systematic Reviews
A number of RCTs evaluating PGS using FISH-based technology have been published, and these findings have been summarized in a systematic review. The review by Mastenbroek et al (2011) included RCTs that compared the live birth rates of women undergoing IVF with and without PGS for aneuploidies.10 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.

PGS Versions 2 and 3
Systematic Reviews
More recently, studies of newer PGS methods have been published. There are several systematic reviews.11-14 These reviews all included the same 3 RCTs with the exception that the review by Chen et al (2015) also included a 2012 RCT that used SNV microarray analysis; this RCT was presented as an abstract but does not appear to have been published in full. Given the complete overlap in studies, only the Chen (2015) review is described here.13 Four RCTs and 7 cohort studies were identified. 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.

Randomized Controlled Trials
Four RCTs have been published, one of which (Rubio et al [2017]) was published after the systematic reviews described in the previous section.15-18 The characteristics of the RCTs are described in Table 1. Three trials conducted embryo biopsies on day 5 or 6 of development while the Rubio et al (2017) trial performed a biopsy in the PGS group on day 3. Two trials (Yang et al [2012] and Rubio et al [2017]) used aCGH and the other two used quantitative PCR. The trials conducted in 2012 and 2013 did not target women of advanced maternal age or women with repeated implantation failure. Instead, Yang et al (2012) included good prognosis patients younger than age 35 with no history of spontaneous abortion, Forman et al (2013) included women younger than age 43, and 5cott et al (2013) included women between the ages of 21 and 42 years with no more than 1 failed IVF attempt. The Rubio et al (2017) trial did target women of advanced maternal age (range, 38-41 years). One of the trials (Forman et al [2013]) transferred 1 embryo in the intervention group and 2 embryos in the control group, which might have introduced bias. Three studies were superiority trials and the other (Forman et al [2013]) was a noninferiority trial using a 20% noninferiority margin.
Table 1. Characteristics of Randomized Controlled Trials Evaluating PGS Versions 2 and 3

<table>
<thead>
<tr>
<th>Study</th>
<th>Countries</th>
<th>Sites</th>
<th>Dates</th>
<th>Participants</th>
<th>Interventions</th>
<th>Control</th>
</tr>
</thead>
</table>
| Yang et al (2012)      | China, U.S. | 2     | NR           | Female partner <35 y with no history of spontaneous abortion and with normal karyotype | n=56  
Bl astocyst biopsy (day 5/6) analyzed via aCGH  
Single euploid embryo selected for transfer based on PGS | n=56  
Single embryo selected for transfer on day 5/6 based on morphologic assessment |
| Forman et al (2013)    | U.S.      | 1     | 2011-2012    | Female partner <43 y with no more than 1 failed IVF attempt                   | n=89  
Bl astocyst biopsy (day 5/6) analyzed via qPCR  
Single euploid embryo selected for transfer based on PGS | n=86  
2 embryos selected for transfer on day 5/6 based on morphologic assessment |
| Scott et al (2013)     | U.S.      | 1     | 2009-2012    | Female partner between 21 y and 42 y with no more than 1 failed IVF attempt  | n=72  
Bl astocyst biopsy (day 5) analyzed via qPCR  
Up to 2 euploid embryo(s) selected for transfer on day 6 based on PGS | n=83  
2 embryos selected for transfer on day 5 based on morphologic assessment |
| Rubio et al (2017)     | Spain     | 4     | 2012-2014    | Female partner between 38 y and 41 y with normal karyotypes who were on their 1st or 2nd cycle of ICSI | n=138  
Bl astocyst biopsy (day 3) analyzed via aCHG  
Unclear number of euploid embryo selected for transfer or vitrification (day 5) based on PGS | n=140  
Conventional ICSI cycle with morphologic embryo selection at blastocyst stage, unclear how many embryos were selected for transfer |

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

Results of the RCTs are shown in Table 2. Results were mixed for all outcomes reported across studies. Pregnancy rates were higher in 2 of the 4 RCTs with PGS compared with the control group. The pregnancy rate in PGS was 37% in the study including women of advanced maternal age and from 70% to 90% in the studies including good prognosis couples. Of the 2 studies (Yang et al [2012] and Forman et al [2013]) reporting ongoing pregnancy rate (≥24 weeks gestation), one reported higher rates in the PGS group compared with control (71% vs 46%) while the other reported lower rates in the PGS group (61% vs 65%) but with a confidence interval for the risk difference that excluded the noninferiority margin. Scott et al (2013) reported a statistically significantly higher delivery rate in the PGS compared with control (85% vs 68%) while the other reported lower rates in the PGS group (61% vs 65%) but with a confidence interval for the risk difference that excluded the noninferiority margin. Scott et al (2013) reported a statistically significantly higher live birth rate (32% vs 19%). None of the studies provided justification for clinically meaningful improvements in the outcomes reported. Few neonatal or postdelivery outcomes were reported. Blinding of patients was reported in only 1 study, although blinding would be complicated by operational and ethical considerations in this context.

Table 2. Results of Randomized Controlled Trials Evaluating PGS Versions 2 and 3

<table>
<thead>
<tr>
<th>Study</th>
<th>Implantation Rate</th>
<th>Clinical Pregnancy Rate</th>
<th>Ongoing Pregnancy Rate (≥24 Wk of Gestation)</th>
<th>Delivery Rate or Live Births</th>
<th>Miscarriage Rate</th>
<th>Multiple Pregnancy Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yang et al (2012)</td>
<td>n</td>
<td>NR</td>
<td>103</td>
<td>NR</td>
<td>NR</td>
<td>103</td>
</tr>
<tr>
<td>Control, %</td>
<td></td>
<td>70.9</td>
<td>69.1</td>
<td>2.6</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>TE (95% CI); p</td>
<td></td>
<td>NR (NR); 0.017</td>
<td>NR (NR); 0.009</td>
<td>NR (NR); 0.60</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Table 3. Relevance Gaps

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Outcomes</th>
<th>Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yang et al (2012)</td>
<td></td>
<td></td>
<td>1. No delivery or postdelivery outcomes</td>
<td>1. No follow-up of delivery or postdelivery outcomes</td>
<td></td>
</tr>
<tr>
<td>Forman et al (2013)</td>
<td></td>
<td></td>
<td>1. No delivery or postdelivery outcomes</td>
<td>1. No follow-up of delivery or postdelivery outcomes</td>
<td></td>
</tr>
<tr>
<td>Scott et al (2013)</td>
<td></td>
<td></td>
<td>1. Few delivery or postdelivery outcomes</td>
<td>1. No follow-up of postdelivery outcomes</td>
<td></td>
</tr>
<tr>
<td>Rubio et al (2017)</td>
<td></td>
<td></td>
<td>1. Few delivery or postdelivery outcomes</td>
<td>1. No follow-up of postdelivery outcomes</td>
<td></td>
</tr>
</tbody>
</table>

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

a Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.

---

C: confidence interval; NR: not reported; OR: odds ratio; PGS: preimplantation genetic screening; RD: risk difference; RR: relative risk; TE: treatment effect.

a Analysis performed per embryo transferred.
b Analysis performed per pregnancy.
Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest.

Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.


<table>
<thead>
<tr>
<th>Study</th>
<th>Allocation</th>
<th>Blinding</th>
<th>Selective Reporting</th>
<th>Data Completeness</th>
<th>Power</th>
<th>Statistical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yang et al (2012)15</td>
<td>3. Allocation concealment not described</td>
<td>1. Blinding not possible because different no. of embryos implanted in 2 treatment groups</td>
<td>1. Registration not described</td>
<td>5,6. No ITT analysis reported, patients not completing intervention were excluded (1 in PDS, 8 in control)</td>
<td>1. No power calculations described, “pilot study”</td>
<td>4. Treatment effect estimate not provided</td>
</tr>
<tr>
<td>Forman et al (2013)16</td>
<td>1. Blinding not possible because different no. of embryos implanted in 2 treatment groups</td>
<td>3. Noninferiority margin of 20% may not exclude clinically important differences</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scott et al (2013)17</td>
<td>1. Blinding not mentioned but perhaps not possible because transfer occurred on different days</td>
<td>3. Not clear how the clinically important difference was determined</td>
<td>2. Multiple embryos per patient analyzed as independent</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rubio et al (2017)18</td>
<td>3. Allocation concealment not described</td>
<td>1. Blinding not mentioned</td>
<td>6. ITT analysis not reported for most outcomes, patients were excluded for many reasons (38 in PDS, 35 in control)</td>
<td>3. Not clear how the clinically important difference was determined</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.


Preimplantation Genetic Testing


Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).

Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.

Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

Long-Term Outcomes of PGS

Several RCTs have reported long-term outcomes after PGS. Beukers et al (2013) reported morphologic abnormalities in surviving children at 2 years. Women included in the trial were ages 35 to 41 years scheduled for IVF or ICSI treatment. 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-group 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.

Schendelaar et al (2013) reported on outcomes when the children were 4 years old. Women included in the trial were ages 35 to 41 years. 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 as a whole, 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 IVF

RCTs and meta-analyses are available. A meta-analysis of PGS using FISH-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. RCTs assessing newer methods found higher implantation rates with PGS than with standard care. Three RCTs evaluating newer PGS methods tended to include good prognosis patients, and results might not be generalizable to other populations. One of these RCTs included women of advanced maternal age. Moreover, individual RCTs on newer PGS methods had potential biases (e.g., lack of blinding, choice of noninferiority margin). Several RCTs have been completed but have not yet been published, so publication bias cannot be excluded. Well-conducted RCTs evaluating PGS in a 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 improvements in other outcomes are inconsistent. Well-conducted RCTs evaluating PGS in the various target populations (e.g., 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.

**Supplemental Information**

**Practice Guidelines and Position Statements**

**American Society for Reproductive Medicine**
The American Society for Reproductive Medicine (2013) 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.

The American Society for Reproductive Medicine issued an opinion on the use of preimplantation genetic testing (PGS) for aneuploidy in 2018 which was informed by a literature search for relevant trials. The committee concluded that “The value of preimplantation genetic testing for aneuploidy as a universal screening test for all IVF patients has yet to be determined.”

**American College of Obstetricians and Gynecologists**
In 2009 (reaffirmed 2014), the American College of Obstetricians and Gynecologists issued an opinion on PGS for aneuploidy. 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 be 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 5.
Table 5. 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 Transferee of Euploid Embryo (STAR)</td>
<td>600</td>
<td>Jun 2017 (ongoing)</td>
</tr>
<tr>
<td>NCT02941965</td>
<td>Preimplantation Genetic Screening in Patients With Male Factor Infertility</td>
<td>480</td>
<td>Dec 2018</td>
</tr>
<tr>
<td>NCT02868528</td>
<td>A Study of Preimplantation Genetic Screening With Next Generation Sequencing Technology on Advanced Age Women</td>
<td>238</td>
<td>Aug 2019</td>
</tr>
<tr>
<td>NCT03118141</td>
<td>Cumulative Live Birth Rate With eSET After In-vitro Fertilization With Preimplantation Genetic Screening by Next Generation Sequencing Versus Conventional In-vitro Fertilization: A Pragmatic Randomized Controlled Clinical Trial</td>
<td>1208</td>
<td>Jun 2020</td>
</tr>
<tr>
<td>NCT03173885</td>
<td>An RCT Evaluating the Implantation Potential of Vitrified Embryos Screened by Next Generation Sequencing Following Trophectoderm Biopsy, Versus Vitrified Unscreened Embryos in Good Prognosis Patients</td>
<td>276</td>
<td>Jan 2022</td>
</tr>
<tr>
<td>NCT03371745</td>
<td>A Prospective, Randomized, Controlled Clinical Trial Evaluating the Superiority of Preimplantation Genetic Screening (PGS) and Deferred Transfer of Cryopreserved Embryos Over &quot;Freeze-Only&quot; Deferred Transfer Without PGS or Immediate Embryo Transfer During a &quot;Fresh&quot; In Vitro Fertilization Cycle</td>
<td>1539</td>
<td>Nov 2022</td>
</tr>
<tr>
<td>Unpublished</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT02223221</td>
<td>Effects of Preimplantation Genetic Screening for Aneuploidies in Infertile Female Patients With Recurrent Spontaneous Abortion History</td>
<td>189</td>
<td>Apr 2017 (completed)</td>
</tr>
<tr>
<td>NCT01532284</td>
<td>The Eshre Study Into The Evaluation of Oocyte Euploidy by Microarray Analysis</td>
<td>396</td>
<td>Sep 2017 (completed)</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.
a 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 codes 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.

<table>
<thead>
<tr>
<th>Type</th>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT®</td>
<td>81161 - 81479</td>
<td>Molecular pathology code range</td>
</tr>
<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</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(e.g., for derivatives and markers)</td>
</tr>
<tr>
<td></td>
<td>88273</td>
<td>Molecular cytogenetics; chromosomal in situ hybridization, analyze 10-30</td>
</tr>
<tr>
<td></td>
<td></td>
<td>cells (e.g., for microdeletions)</td>
</tr>
<tr>
<td></td>
<td>88274</td>
<td>Molecular cytogenetics; interphase in situ hybridization, analyze 25-99</td>
</tr>
<tr>
<td></td>
<td></td>
<td>cells</td>
</tr>
<tr>
<td></td>
<td>88275</td>
<td>Molecular cytogenetics; interphase in situ hybridization, analyze 100-300</td>
</tr>
<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</td>
</tr>
<tr>
<td></td>
<td></td>
<td>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</td>
</tr>
<tr>
<td></td>
<td></td>
<td>pre-implantation genetic diagnosis); greater than 5 embryos</td>
</tr>
<tr>
<td>HCPCS</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>ICD-10</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Procedure</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</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>
<tr>
<td>10/01/2018</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.