4.02.05	**Preimplantation Genetic Testing**		
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Section:	4.0 OB/Gyn/Reproduction	**Page:**	Page 1 of 23

Policy Statement

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** of the criteria listed below:
For evaluation of an embryo at an identified elevated risk of a genetic disorder such as when:

I. For evaluation of an embryo at an identified elevated risk of a genetic disorder such as when:
   A. Both partners are known carriers of a single-gene autosomal recessive disorder
   B. 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
   C. One partner is a known carrier of a single-gene autosomal dominant disorder
   D. One partner is a known carrier of a single X-linked disorder, or

II. For evaluation of an embryo at an identified elevated risk of structural chromosomal abnormality such as for a:
   A. Parent with balanced or unbalanced chromosomal translocation.

Preimplantation genetic *diagnosis* (PGD) as an adjunct to IVF is considered **not medically necessary** 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 **not medically necessary** in patients or couples who are undergoing IVF in all situations.

NOTE: Refer to Appendix A to see the policy statement changes (if any) from the previous version.

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 of ethical issues associated with preimplantation genetic testing that should be carefully discussed between the treated couple and the physician.

Certain custom benefits allow for preimplantation genetic testing (either diagnostic or screening; which may be either with or without an elevated risk of a genetic disorder). Benefits should be confirmed prior to denial notifications.

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 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 PG1. Nomenclature to Report on Variants Found in DNA

Previous	Updated	Definition
Mutation	Disease-associated variant	Disease-associated change in the DNA sequence
	Variant	Change in the DNA sequence
	Familial variant	Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives

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

Variant Classification	Definition
Pathogenic	Disease-causing change in the DNA sequence
Likely pathogenic	Likely disease-causing change in the DNA sequence
Variant of uncertain significance	Change in DNA sequence with uncertain effects on disease
Likely benign	Likely benign change in the DNA sequence
Benign	Benign change in the DNA sequence

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

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) or screening (preimplantation genetic screening). Preimplantation genetic diagnosis 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. Preimplantation genetic screening 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 preimplantation genetic diagnosis when testing for a number of possible abnormalities in the absence of a known disorder), following a terminology change from 'preimplantation genetic screening' to 'preimplantation genetic testing' in 2017.[1,]

Biopsy

Biopsy for preimplantation genetic diagnosis 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 1 and sometimes 2 blastomeres from the embryo. Analysis of 2 cells may improve diagnosis but may also affect the implantation of the embryo. In addition, a potential disadvantage of testing at this phase is that mosaicism might be present. Mosaicism refers to genetic differences among the cells of the embryo that could result in an incorrect interpretation if the chromosomes of only a single cell are examined.

The third option is sampling the embryo at the blastocyst stage when there are about 100 cells. Blastocysts form 5 to 6 days after insemination. Three to 10 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. Fluorescent in situ hybridization 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 preimplantation genetic screening using FISH is known as version 1.

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

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

Embryos at Risk for a Specific Inherited Single-Gene Defect
Inherited single-gene defects fall into 3 general categories: autosomal recessive, autosomal dominant, and X-linked. When either the mother or father is a known carrier of a genetic defect, embryos can undergo preimplantation genetic diagnosis 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, preimplantation genetic diagnosis is used to deselect male embryos, half of which would be affected. Preimplantation genetic diagnosis 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 preimplantation genetic diagnosis 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 preimplantation genetic diagnosis. In this setting, preimplantation genetic diagnosis 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. Preimplantation genetic diagnosis 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, preimplantation genetic screening has been explored as a technique to deselect aneuploid oocytes in older women and is also known as preimplantation genetic diagnosis for aneuploidy screening. Analysis of extruded polar bodies from the oocyte or no blastomeres at day 3 of embryo development using Fish was initially used to detect aneuploidy (preimplantation genetic screening version 1). A limitation of FISH is that analysis is restricted to a number of proteins. More recently, newer preimplantation genetic screening methods have been developed (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, preimplantation genetic screening has been proposed for women with repeated implantation failures.

Literature Review
Evidence reviews assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are the 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 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 technology, 2 domains are examined: the relevance, and 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
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 the

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 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 Test Purpose

The purpose of preimplantation genetic diagnosis in patients who have an identified elevated risk of a genetic disorder undergoing in vitro fertilization (IVF) 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 preimplantation genetic testing of an IVF embryo from individuals with an identified elevated risk of a genetic disorder improve pregnancy outcomes and net health outcomes?

The following PICO was used to select literature to inform this review.

Populations

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 preimplantation genetic diagnosis using methods such as polymerase chain reaction (PCR), array comparative genomic hybridization, 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. Preimplantation genetic diagnosis 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.

Comparators

The comparator of interest is IVF without preimplantation genetic diagnosis and prenatal genetic testing.

Outcomes

The outcomes of interest include test accuracy, health status measures, and treatment-related morbidity, including pregnancy and neonatal outcomes such as implantation rates and time to successful implantation, spontaneous abortion or miscarriage rates, length of gestation, live birth rates, birth weight, fetal anomalies, and neonatal outcomes.

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 long-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.

Review of Evidence

Systematic Reviews

Iews et al (2018) conducted a systematic review examining the outcomes of preimplantation genetic diagnosis for couples with recurrent pregnancy loss due to structural chromosomal rearrangement.[4] Twenty studies were identified, mostly retrospective and case-control, therefore, a meta-analysis was not performed due to significant heterogeneity among the studies. The primary outcome for the systematic review was live birth rate. The authors identified 3 study types among the 20 studies: (1) 10 evaluated reproductive outcomes for genetic testing with natural conception, (2) 8 compared outcomes after IVF and preimplantation genetic diagnosis, and (3) 2 directly compared differences in live birth rates between couples who conceived naturally versus those who conceived after IVF and preimplantation genetic diagnosis. The pooled total of 847 couples who conceived naturally had a live birth rate of 25% to 71% as opposed to 26.7% to 87% for the 562 couples who underwent IVF and preimplantation genetic diagnosis - a small difference. One strength of this study is the variety of populations included in the selected studies, which encompassed a range of geographic and ethnic groups, thus reducing the risk of selection bias. Also, case reports and case series were excluded, further lessening the risk of bias. However, most of the studies included in this systematic review were retrospective, nonrandomized, and without a well-defined population.

Hasson et al (2017) published a meta-analysis of studies comparing obstetric and neonatal outcomes after intracytoplasmic sperm injection without preimplantation diagnosis compared with intracytoplasmic sperm injection with preimplantation genetic diagnosis.[5] 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 preimplantation genetic diagnosis group than in the non-testing group (relative risk [RR], 0.84; 95% confidence interval [CI], 0.72 to 1.00; p=.04).

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 Robertsonian translocation (n=6) in at least 1 partner.[6] 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 preimplantation genetic diagnosis in 76 couples with monogenetic diseases (X-linked recessive, autosomal recessive, autosomal dominant).[7] The most common genetic conditions were a-thalassemia (64 cycles) and β-thalassemia (23 cycles). Patients were not required to have a history of miscarriage. A total of 92 preimplantation genetic diagnosis 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 preimplantation genetic diagnosis for couples carrying reciprocal translocations.[8] This prospective analysis included the first 59 consecutive couples who completed treatment at a single center. Thirty-two (54%) of the 59 couples previously 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.[9] Seventy-five (53%) of 142 couples had preimplantation genetic diagnosis 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 preimplantation genetic diagnosis 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 preimplantation genetic diagnosis with genetic material from the polar body.[10] All preimplantation genetic diagnoses were confirmed postnatally; there were no diagnostic errors. The incidence of multiple gestations was similar to that seen with IVF. Preimplantation genetic diagnosis 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 a biopsy of the polar body is considered a biopsy of extra-embryonic material, and thus one might not expect an impact on obstetric outcomes. Patients in this study had undergone preimplantation genetic diagnosis for both unspecified chromosomal disorders and various disorders associated with a single-gene defect (e.g., cystic fibrosis, sickle cell disease).

Section Summary: Preimplantation Genetic Diagnosis

Two systematic reviews of observational studies were identified. One of the systematic reviews found a median live birth rate of 31% after preimplantation genetic diagnosis compared with 55.5% after natural conception. The median miscarriage rate was 0% after preimplantation genetic diagnosis and 34% after natural conception. The findings of this review apply only to patients with recurrent miscarriages. The other systematic review found a significant rate of low birth weight in the preimplantation genetic diagnosis group compared with a non-preimplantation diagnosis group, but no significant differences in other outcomes. Studies in the review focused on parents with known genetic aberrations.

Preimplantation Genetic Screening

Clinical Context and Test Purpose

The purpose of preimplantation genetic screening in patients with no identified elevated risk of a genetic disorder undergoing IVF 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 preimplantation genetic screening of an IVF embryo from individuals with no identified elevated risk of a genetic disorder improve pregnancy outcomes and net health outcomes?

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with no identified elevated risk of a genetic disorder who are undergoing IVF. Although preimplantation genetic screening may be used in any patient undergoing IVF, in particular, preimplantation genetic screening 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 preimplantation genetic screening. Preimplantation genetic screening version 1 uses fluorescent in situ hybridization (FISH) on polar bodies or cleavage stage embryos. Preimplantation genetic screening version 2 uses techniques such as array comparative genomic hybridization, single nucleotide variant microarrays, and quantitative PCR. Next-generation sequencing is grouped with preimplantation genetic screening version 2 techniques in some literature and referred to as preimplantation genetic screening version 3 in other literature.

Preimplantation genetic diagnosis 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.

Comparators

The comparator of interest is IVF without preimplantation genetic screening.

Outcomes

The outcomes of interest include test accuracy, health status measures, and treatment-related morbidity, including pregnancy and neonatal outcomes such as implantation rates, spontaneous abortion or miscarriage rates, live birth rates, gestational age, birth weight, and fetal anomalies, and neonatal outcomes.

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 long-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.

Preimplantation Genetic Screening Version 1 (Fluorescent in situ Hybridization)

Systematic Reviews

A number of RCTs evaluating preimplantation genetic screening using FISH-based technology have been published, and these findings have been summarized in several systematic reviews and a meta-analysis. The most recent and comprehensive meta-analysis was a Cochrane review by Cornelisse et al (2020), which included RCTs comparing participants undergoing IVF with preimplantation genetic testing for aneuploides (PGT-A) versus IVF without PGT-A.[1] A total of 13 trials were included (N=2794 women), of which 11 used FISH for the genetic analysis. The Cochrane review also included 2 studies that used genome-wide analysis (Verpoest et al 2018 and Munne et al 2019); however, pooled analyses were not performed due to heterogeneity in testing methods, and each study is discussed separately later in this review. Of the 13 included RCTs, studies included patients with advanced maternal age (n=7 studies) and repeated IVF failure (n=3 studies), as well as good prognosis patients (n=5 studies). In a pooled analysis of RCTs using FISH for genetic analysis, live birth rate after the first embryo transfer was lower in patients undergoing PGT-A compared to the control group (odds ratio [OR], 0.62; 95% CI, 0.43 to 0.91; 10 RCTs; n=1680; I2=54%). No difference in miscarriage rate per woman randomized was observed between PGT-A and control groups (OR, 1.03; 95% CI, 0.75 to 1.41; 10 RCTs; n=1680; I2=16%); however rate of miscarriage per clinical pregnancy was reduced in the control group (OR, 1.77; 95% CI, 1.10 to 2.86; 5 RCTs, n=288; I2=45%). Only 1 study utilizing FISH evaluated cumulative live birth rate per woman, which did not detect a difference in patients undergoing PGT-A compared with the control (OR, 0.59; 95% CI, 0.35 to 1.01; 1 RCT; n=408). Ongoing pregnancy rate (OR, 0.68; 95%0.51 to 0.90; 5 RCTs; n=1121; I2=60%) and clinical pregnancy rate (OR, 0.60; 95% CI, 0.45 to 0.81; 5 RCTs; n=1131; I2=0%) were also reported to be lower in patients undergoing PGT-A compared with the control group. The authors noted a risk of publication bias, a limited quantity of studies and events, inconsistency in estimates between studies, and high heterogeneity for certain analyses (considered I2 >50).

Preimplantation Genetic Screening Versions 2 and 3

Systematic Reviews

More recently, studies of newer preimplantation genetic screening methods have been published. There are several systematic reviews.[11,12,13,14,15] 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 single nucleotide variant 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 et al (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 preimplantation genetic screening 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 preimplantation genetic screening 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 nonsignificantly 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 reduced miscarriage rates (RR, 0.31; 95% CI, 0.21 to 0.46; 5 studies), but no improvement in 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

Several RCTs have been published, 3 of which (Rubio et al [2017], Verpoest et al [2018], and Munne et al [2019]) were published after the systematic reviews described in the previous section.[16,17,18,19,20,21] The characteristics of the RCTs are described in Table 1, which includes the 3 published RCTs in the Chen et al (2015) meta-analysis (Yang et al [2012], Forman et al [2013], Scott et al [2013]). Four trials conducted embryo biopsies on day 5 or 6 of development, while the Rubio et al (2017) trial performed a biopsy in the preimplantation genetic screening group on day 3. Two trials (Yang et al [2012] and Rubio et al [2017]) used array comparative genetic hypridization, 2 used quantitative PCR, 1 (Verpoest et al [2018]) used comprehensive chromosome screening, and 1 used next-generation sequencing (Veriseq PGS; Munne et al [2019]). The majority of trials did not target women of advanced maternal age or women with repeated implantation failure. Instead, the majority of trials targeted good prognosis patients. For example, 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 Scott 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) and Verpoest et al (2018) trials did target women of advanced maternal age (36-41 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. The majority of studies were superiority trials. 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

Study	Countries	Sites	Dates	Participants	Interventions	
					PGS	Control
Yang et al (2012)[16]	China, U.S.	2	NR	Female partner <35 y with no history of spontaneous abortion and with normal karyotype	• n=56 • Blastocyst biopsy (day 5/6) analyzed via aCGH • Single euploid embryo selected	• n=56 • Single embryo selected for transfer on day 5/6 based on morphologic assessment

Study	Countries	Sites	Dates	Participants	Interventions	
					for transfer based on PGS	
Forman et al (2013)[17]	U.S.	1	2011-2012	Female partner <43 y with no more than 1 failed IVF attempt	• n=89 • Blastocyst biopsy (day 5/6) analyzed via qPCR • Single euploid embryo selected for transfer based on PGS	• n=86 • 2 embryos were selected for transfer on day 5/6 based on morphologic assessment
Scott et al (2013)[18]	U.S.	1	2009-2012	Female partner between 21 y and 42 y with no more than 1 failed IVF attempt	• n=72 • Blastocyst biopsy (day 5) analyzed via qPCR • Up to 2 euploid embryo(s) were selected for transfer on day 6 based on PGS	• n=83 • 2 embryos were selected for transfer on day 5 based on morphologic assessment
Rubio et al (2017)[21]	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 • Blastocyst biopsy (day 3) analyzed via aCHG • An unclear number of euploid embryos 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
Verpoest et al (2018)[19]	EU, Israel	9	2012-2016	Female partner between 36 y and 40 y with < 3 previously unsuccessful IVF attempts, < 3 miscarriages, and without poor ovarian response or reserve	• n=205 • Polar body biopsy (6-9 hr after insemination); analysis method varied by site • Up to 2 euploid embryos selected from transfer on the day of development decided by site policy	• n=191 • Conventional ICSI cycle with up to 2 embryos selected for transfer on the day of development decided by site policy
Munne et al (2019); Single Embryo Transfer of Euploid Embryo (STAR) study; NCT02268786 [20]	Australia, Canada, U.S., UK	34	2014-2016	Female partner between 25 y and 40 y with < 2 previously unsuccessful IVF attempts, ≤ 1 miscarriage, and without azoospermia, or severe oligospermia	• n=330 • Blastocyst biopsy (day 5/6); NGS-based assay (Veriseq PGS) • Single euploid embryo selected for transfer based on PGS	• n=331 • Single embryo selected for transfer on day 5/6 based on morphologic assessment

aCGH: array comparative genomic hybridization; ICSI: intracytoplasmic sperm injection; IVF: in vitro fertilization; NGS: Next-Generation Sequencing; NR: not reported; 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 6 RCTs with preimplantation genetic screening compared with the control group. The pregnancy rate in preimplantation genetic screening was 37% in the study including women of advanced maternal age and from 70% to 90% in the studies including good prognosis couples. Findings were mixed across 3 studies (Yang et al [2012], Forman et al [2013], and Munne et al [2019]) reporting ongoing pregnancy rate (≥ 20 or 24 weeks gestation). Yang et al (2012) reported higher rates in the preimplantation screening group compared to control (71% vs. 46%).[16] Forman et al (2013) reported lower rates in the preimplantation genetic screening group (61% vs. 65%), but the CI for the risk difference excluded the noninferiority margin.[17] Munne et al (2019) reported similar (50.0% versus 45.7%) ongoing pregnancy rates (≥ 20 weeks gestation) for next-generation sequencing-based preimplantation genetic screening versus morphology in good-prognosis patients.[20] However, in the subgroup of 267 women aged 35 to 40 years, next-generation sequencing-based preimplantation genetic sequencing improved ongoing pregnancy rates (50.8% versus 37.2%; p=.0349). Scott et al (2013) reported a statistically significantly higher delivery rate in the preimplantation genetic screening group compared with control (85% vs. 68%).[18] Similarly, Rubio et al (2017) reported a statistically significant higher live birth rate (32% vs. 19%).[21] None of the studies provided justification for clinically meaningful improvements in the outcomes reported. Few neonatal or post-delivery outcomes were reported.

Table 2. Results of Randomized Controlled Trials Evaluating Preimplantation Genetic Screening Versions 2 and 3

Study	Implantation Rate	Clinical Pregnancy Rate	Ongoing Pregnancy Rate (≥24 Wk of Gestation)	Delivery Rate or Live Births	Miscarriage Rate	Multiple Pregnancy Rate
Yang et al (2012)[16]						
N	NR	103	103	NR	NR	103
PGS, %		70.9	69.1		2.6	0
Control, %		45.8	41.7		9.1	0
TE (95% CI); p		NR (NR);.017	NR (NR);.009		NR (NR);.60	
Forman et al (2013)[17]						
N	259[a]	175	175	NR	131[b]	115[b]
PGS, %	63.2	69	60.7		11.5	0
Control, %	51.7	81	65.1		20.0	53
TE (95% CI); p	NR (NR); .08	NR	RD = -4.4 (-18.7 to 9.9); noninferior but p NR		NR (NR);.20	NR (NR); <.001
Scott et al (2013)[18]				Delivery Rate		
N	297[a]	155	NR	155	NR	NR
PGS, %	79.8	93.1		84.7		
Control, %	63.2	80.7		67.5		
RR (95% CI); p	1.26 (1.04 to 1.39);.002	1.15 (1.03 to 1.43);.03		1.26 (1.06 to.1.53);.01		
Rubio et al (2017)[21]				Live Birth Rate		
N	263[a]	205	NR	278	78[b]	78[b]
PGS, %	52.8	37		31.9	2.7	22
Control, %	27.6	39		18.6	39.0	13
OR (95% CI); p	2.9 (1.7 to 5.0); <.001	NR		2.4 (1.3 to 4.2);.003	0.06 (0.008 to 0.48); <.001	NR
Verpoest et al (2018)[19]				Live Birth Rate		
N	396[a]	136	NR	95	41	38
PGS, %	73	31		24	7	7
Control, %	90	37		24	14	13
RR (95% CI); p-value	0.81 (0.74 to 0.89); <.001	0.85 (0.65 to 1.12);.25		1.07 (0.75 to 1.51);.71	0.48 (0.26 to 0.90);.02	NR
Munne et al (2020)[20]						
N	NR	587	587[c]	587	587	NR

Study	Implantation Rate	Clinical Pregnancy Rate	Ongoing Pregnancy Rate (≥24 Wk of Gestation)	Delivery Rate or Live Births	Miscarriage Rate	Multiple Pregnancy Rate
PGS, %		89.4	50.0	50.0	9.9	
Control, %		91.7	45.7	45.7	9.6	
p-value		NR	.3177	.3177	.8979	

CI: 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.
[c] Ongoing pregnancy at 20 weeks' gestation

Tables 3 and 4 display notable limitations identified in each study.

Table 3. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
Yang et al (2012)[16]			2. Only single embryos transferred in control	1. No delivery or postdelivery outcomes 5, 6. No discussion of clinically important difference	1,2. No follow-up of delivery or postdelivery outcomes
Forman et al (2013)[17]				1. No delivery or postdelivery outcomes 6. No justification for 20% noninferiority margin	1,2. No follow-up of delivery or postdelivery outcomes
Scott et al (2013)[18]				1. Few delivery or postdelivery outcomes6. No justification for 20% clinically important difference	1,2. No follow-up of postdelivery outcomes
Rubio et al (2017)[21]		1. Not clear how many embryos were transferred	1. Not clear how many embryos were transferred	1. Few delivery or postdelivery outcomes 6. No justification for 15% clinically important difference	1,2. No follow-up of postdelivery outcomes
Verpoest et al (2018)[19]				1. Few delivery or postdelivery outcomes	1,2. No follow-up of postdelivery outcomes
Munne et al (2019)[20]	4. Good prognosis patients	4. More embryos of poor quality were biopsied and vitrified because of study participation that otherwise may have been discarded in standard clinic practice		1. Few delivery or postdelivery outcomes; no discussion of clinical importance of 20-week timepoint.	

The study limitations 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.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4.Not the intervention of interest.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.

[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 4. Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Yang et al (2012)[16]	3. Allocation concealment not described		1. Registration not described	5,6. No ITT analysis reported, patients not completing intervention were excluded (1 in PGS, 8 in control)	1. No power calculations described, "pilot study"	4. Treatment effect estimate not provided
Forman et al (2013)[17]		1. Blinding not possible because different no. of embryos implanted in 2 treatment groups			3. Noninferiority margin of 20% may not exclude clinically important differences	
Scott et al (2013)[18]		1. Blinding not mentioned but perhaps not possible because transfer occurred on different days			3. Not clear how the clinically important difference was determined	2. Multiple embryos per patient analyzed as independent
Rubio et al (2017)[21]	3. Allocation concealment not described	1. Blinding not mentioned		6. ITT analysis not reported for most outcomes, patients were excluded for many reasons (38 in PGS, 35 in control)	3. Not clear how the clinically important difference was determined	
Verpoest et al (2018)[19]	3. Allocation concealment not described	2. Not blinded outcome assessment				
Munne et al (2019) [20]					3. Magnitude of difference that power calculation was based on was unspecified; targeted sample size of 300 transfers in each arm was not achieved	

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
ITT: intention to treat; PGS: preimplantation genetic screening.
[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.
[b] Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[d] 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).
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.
[f] 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 Preimplantation Genetic Screening

Several RCTs have reported long-term outcomes after preimplantation genetic screening. Beukers et al (2013) reported morphologic abnormalities in surviving children at 2 years.[22] Women included in the trial were ages 35 to 41 years scheduled for IVF or intracytoplasmic sperm injection treatment. Data were available on 50 children born after preimplantation genetic screening and 72 children born without preimplantation genetic screening. Fourteen (28%) of 50 children in the preimplantation genetic screening group and 25 (35%) of 72 children in the non-screening group had at least 1 major abnormality; the between-group difference was not statistically significant (p=.43). Skin abnormalities (e.g., capillary hemangioma, hemangioma plana) were the most common, affecting 5 children after preimplantation genetic screening and 10 children in the non-screening 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.[23] 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 preimplantation genetic screening and 64 children (42 singletons, 11 sets of twins) born after IVF without preimplantation genetic screening. 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 preimplantation genetic screening and the non-screening groups. However, among twins, the fluency score was significantly lower among those in the preimplantation screening group (mean score, 10.6; 95% CI, 9.8 to 11.3) and non-screening 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 groups.

Section Summary: Preimplantation Genetic Screening

Randomized controlled trials and meta-analyses are available. A meta-analysis of preimplantation genetic screening using FISH-based technology found a significantly lower live birth rate after preimplantation genetic screening compared with controls in women of advanced maternal age, and there was no significant between-group difference in good prognosis patients. Randomized controlled trials assessing newer methods found higher implantation rates with preimplantation genetic screening than with standard care. Randomized controlled trials evaluating newer preimplantation genetic screening methods tended to include good prognosis patients, and results might not be generalizable to other populations. Two of these RCTs included women of advanced maternal age. Moreover, individual RCTs on newer preimplantation genetic screening methods had potential biases (e.g., lack of blinding, choice of noninferiority margin, imprecision). Several RCTs have been completed but have not yet been published, so publication bias cannot be excluded. Well-conducted RCTs evaluating preimplantation genetic screening 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 preimplantation genetic diagnosis, the evidence includes observational studies and systematic reviews. Relevant outcomes are health status measures and treatment-related morbidity. Data from observational studies and systematic reviews have suggested that preimplantation genetic diagnosis is associated with the birth of unaffected fetuses when performed for detection of single genetic defects and a decrease in spontaneous abortions for patients with structural chromosomal abnormalities. Moreover, preimplantation genetic diagnosis performed for single-gene defects does not appear to be associated with an increased risk of obstetric complications. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have no identified elevated risk of a genetic disorder undergoing IVF who receive preimplantation genetic screening, the evidence includes RCTs and meta-analyses. Relevant outcomes are health status measures and treatment-related morbidity. Randomized controlled trials and meta-analyses of RCTs on initial preimplantation genetic screening methods (e.g., FISH) have found lower or similar ongoing pregnancy and live birth rates compared with IVF without preimplantation genetic screening. There are fewer RCTs on newer preimplantation genetic screening methods, and findings are mixed. Meta-analyses of RCTs have found higher implantation rates with preimplantation genetic screening than with standard care, but improvements in other outcomes are inconsistent. Well-conducted RCTs evaluating preimplantation genetic screening 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 that the technology results in an improvement in the net health outcome.

Supplemental Information

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American Society for Reproductive Medicine

In 2013, the American Society for Reproductive Medicine (ASRM) published an opinion on the use of preimplantation genetic diagnosis for serious adult-onset conditions.[24] 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.

In 2018, the ASRM issued an opinion on the use of preimplantation genetic testing for aneuploidy 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 in vitro fertilization (IVF) patients has yet to be determined."[25]

In 2020, the ASRM issued an opinion on the clinical management of mosaic results from preimplantation genetic testing for aneuploidy of blastocytes; however, this policy states that the document "does not endorse nor does it suggest that PGT-A (preimplantation genetic testing for aneuploidy) is appropriate for all cases of IVF."[26]

American College of Obstetricians and Gynecologists

In 2020, the American College of Obstetricians and Gynecologists (ACOG) issued Committee Opinion #799 on Preimplantation Genetic Testing.[27] Recommendations are as follows:

- "Preimplantation genetic testing comprises a group of genetic assays used to evaluate embryos before transfer to the uterus. Preimplantation genetic testing-monogenic (known as PGT-M) is targeted to single gene disorders. Preimplantation genetic testing-monogenic uses only a few cells from the early embryo, usually at the blastocyst stage, and misdiagnosis is possible but rare with modern techniques. Confirmation of preimplantation genetic testing-monogenic results with chorionic villus sampling (CVS) or amniocentesis should be offered."
- "To detect structural chromosomal abnormalities such as translocations, preimplantation genetic testing-structural rearrangements (known as PGT-SR) is used. Confirmation of preimplantation genetic testing-structural rearrangements results with CVS or amniocentesis should be offered."
- "The main purpose of preimplantation genetic testing-aneuploidy (known as PGT-A) is to screen embryos for whole chromosome abnormalities. Traditional diagnostic testing or screening for aneuploidy should be offered to all patients who have had preimplantation genetic testing-aneuploidy, in accordance with recommendations for all pregnant patients."

The ACOG (2015, reaffirmed 2017) issued an opinion that recommends "[p]atients with established causative mutations for a genetic condition who are undergoing in vitro fertilization and desire prenatal genetic testing should be offered the testing, either preimplantation or once pregnancy is established."[28]

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

NCT No.	Trial Name	Planned Enrollment	Completion Date
Unpublished			
NCT02223221	Effects of Preimplantation Genetic Screening for Aneuploidies in Infertile Female Patients With Recurrent Spontaneous Abortion History	189	Apr 2017 (completed)

NCT No.	Trial Name	Planned Enrollment	Completion Date
NCT02941965	Preimplantation Genetic Screening in Patients With Male Factor Infertility	480	Dec 2018 (unknown)
NCT02868528	A Prospective Randomized Controlled Study of Preimplantation Genetic Screening With Next Generation Sequencing Technology on Advanced Age Women	238	Aug 2019 (unknown)
NCT03371745	A Prospective, Randomized, Controlled Clinical Trial Evaluating the Superiority of Preimplantation Genetic Screening (PGS) and Deferred Transfer of Cryopreserved Embryos Over "Freeze-Only" Deferred Transfer Without PGS or Immediate Embryo Transfer During a "Fresh" In Vitro Fertilization Cycle	32	Dec 2019
NCT03173885	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 Undergoing IVF	276	Feb 2020 (terminated)
NCT03118141	Cumulative Live Birth Rate With eSET After In-vitro Fertilization With Preim-plantation Genetic Screening by Next Generation Sequencing Versus Conventional In-vitro Fertilization: A Pragmatic Randomized Controlled Clinical Trial	1215	Jun 2020 (last updated Sep 2019)

NCT: national clinical trial.
[a] Denotes industry-sponsored or cosponsored trial.

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Documentation for Clinical Review

Please provide the following documentation:

- 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.

The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.

Type	Code	Description
CPT®	0254U	Reproductive medicine (preimplantation genetic assessment), analysis of 24 chromosomes using embryonic DNA genomic sequence analysis for aneuploidy, and a mitochondrial DNA score in euploid embryos, results reported as normal (euploidy), monosomy, trisomy, or partial deletion/duplication, mosaicism, and segmental aneuploidy, per embryo tested ***(Code effective 7/1/2021)***
	81161 - 81479	Molecular pathology code range ***(Code revision effective 1/1/2022)***
	88271	Molecular cytogenetics; DNA probe, each (e.g., FISH)
	88272	Molecular cytogenetics; chromosomal in situ hybridization, analyze 3-5 cells (e.g., for derivatives and markers)
	88273	Molecular cytogenetics; chromosomal in situ hybridization, analyze 10-30 cells (e.g., for microdeletions)
	88274	Molecular cytogenetics; interphase in situ hybridization, analyze 25-99 cells
	88275	Molecular cytogenetics; interphase in situ hybridization, analyze 100-

Type	Code	Description
		300 cells
	88291	Cytogenetics and molecular cytogenetics, interpretation and report
	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
HCPCS	None	

Policy History

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

Effective Date	Action
08/29/2014	BCBSA Medical Policy adoption
11/01/2017	Policy revision without position change
10/01/2018	Policy revision without position change
12/01/2019	Policy revision with position change
11/01/2020	Annual review. No change to policy statement. Literature review updated.
01/01/2021	Coding Update
11/01/2021	Annual review. No change to policy statement. Literature review updated. Coding Update.
02/01/2022	Coding Update.

Definitions of Decision Determinations

Medically Necessary: Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the Member's illness, injury, or disease.

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 at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 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.

Appendix A

<table>
<tr><th colspan="2">POLICY STATEMENT
(No changes)</th></tr>
<tr><th>BEFORE</th><th>AFTER</th></tr>
<tr><td>Preimplantation Genetic Testing 4.02.05

Policy Statement:
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 of the criteria listed below:
I. For evaluation of an embryo at an identified elevated risk of a genetic disorder such as when:
A. Both partners are known carriers of a single-gene autosomal recessive disorder
B. 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
C. One partner is a known carrier of a single-gene autosomal dominant disorder
D. One partner is a known carrier of a single X-linked disorder, or
II. For evaluation of an embryo at an identified elevated risk of structural chromosomal abnormality such as for a:
A. Parent with balanced or unbalanced chromosomal translocation.

Preimplantation genetic diagnosis (PGD) as an adjunct to IVF is considered not medically necessary 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 not medically necessary in patients or couples who are undergoing IVF in all situations.</td><td>Preimplantation Genetic Testing 4.02.05

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