
Medical Policy



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***Current Policy Effective Date: 3/1/24**
(See policy history boxes for previous effective dates)

Title: Genetic Testing - Preimplantation

Description/Background

PREIMPLANTATION GENETIC TESTING

Preimplantation genetic testing describes various adjuncts to an assisted reproductive procedure in which either maternal or embryonic DNA is sampled and genetically analyzed, thus permitting deselection of embryos harboring a genetic defect before implantation of the embryo into the uterus. 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 (eg, some authors use PGD 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 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 (ie, 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 (eg, microdeletions, duplications) and, thus, single-gene defects can be recognized with this technique.

A more recent approach for preimplantation genetic screening is with comprehensive chromosome screening using techniques such as array comparative genome hybridization and next generation sequencing.

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 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 in 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. A limitation of FISH is that analysis is restricted to a number of proteins. More recently, newer preimplantation genetic screening methods have been developed. 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.

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 (CLIA). Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration (FDA) has chosen not to require any regulatory review of these tests.

Medical Policy Statement

Preimplantation genetic *diagnosis* may be considered established as an adjunct to in-vitro fertilization (IVF) in individuals or couples who have the IVF benefit, and who meet specific criteria. (See Inclusions)

Preimplantation genetic *screening* as an adjunct to in-vitro fertilization (IVF) is considered experimental/ investigational.

Inclusionary and Exclusionary Guidelines

In order to access benefits for preimplantation genetic testing, the definition of infertility *must be met. A benefit document (certificate of coverage or rider) may specify that the definition of infertility is not a requirement for preimplantation genetic services; ONLY in this case is the requirement of meeting the definition of infertility waived.

**Refer to the medical policy "Infertility Diagnosis" for infertility definition and criteria.*

Note: Member benefit needs to be verified for coverage or exclusion of preimplantation genetic testing.

Inclusions:

1. For preimplantation genetic diagnosis in an embryo identified as at elevated risk of a significant genetic disorder, the individual or couple must:
 - Have the benefit for in-vitro fertilization (IVF) and meet criteria to access the benefit (ie, have a diagnosis of infertility); AND
 - Meet one of the following criteria:
 - 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
2. For preimplantation genetic diagnosis in an embryo identified as at elevated risk for a structural chromosomal abnormality, the individual or couple must:
 - Have the benefit for in-vitro fertilization (IVF) and meet criteria to access the benefit (ie, have a diagnosis of infertility); AND
 - One partner with balanced or unbalanced chromosomal translocation
3. Individual consideration may be given to the individual or couple who has the in-vitro fertilization (IVF) benefit, and meets at least one criterion under 1. or 2. (above) but does not have a diagnosis of infertility.

Exclusions:

- All other situations than those specified above.

Preimplantation genetic *screening* (PGS) as an adjunct to IVF is considered **experimental/ investigational**.

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 individual or couple and the physician.

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)*

Established codes:

81161-81479	88271	88272	88273	88274	88275
88291	89290	89291			

Other codes (investigational, not medically necessary, etc.):

0254U	0396U
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Note: Code(s) may not be covered by all contracts or certificates. Please consult customer or provider inquiry resources at BCBSM or BCN to verify coverage.

Rationale

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 1 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 policy. However, in general, to assure adequate sensitivity and specificity for the genetic test guiding the embryo deselection process, the genetic defect must be well-characterized. For example, the gene or genes responsible for some genetic disorders may be quite large, with 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 in individuals 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 diagnosis of an IVF embryo from individuals with 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 (eg, 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 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.

REVIEW OF EVIDENCE

Systematic Reviews

lews 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.² 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 genetic diagnosis compared with intracytoplasmic sperm injection with preimplantation genetic diagnosis.³ 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, 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.⁴ 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).⁵ 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 preimplantation genetic diagnosis cycles resulted in embryo transfer, with an ongoing pregnancy rate (beyond 8 to 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.⁶ 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 clinical outcomes of 312 cycles performed for 142 couples with reciprocal translocations.⁷ 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.⁸ 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 (ie, 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 genetic 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 Therapy Purpose

The purpose of preimplantation genetic screening in individuals 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 following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals without an 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 includes older methods using fluorescent in situ hybridization (FISH) or newer methods with comprehensive chromosomal screening. Preimplantation genetic screening 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, fetal anomalies and neonatal outcomes.

Study Selection Criteria

Methodologically credible studies were selected as described in the previous section.

Review of Evidence

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 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. 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; $I^2=54\%$). 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; $I^2=16\%$); 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; $I^2=45\%$). 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% CI, 0.51 to 0.90; 5 RCTs; n=1121; $I^2=60\%$) and clinical pregnancy rate (OR, 0.60; 95% CI, 0.45 to 0.81; 5 RCTs; n=1131; $I^2=0\%$) 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 $I^2 >50$).

Shi et al (2021) conducted a systematic review and meta-analysis of 9 RCTs (N=2113) evaluating IVF with or without PGT-A in women of advanced maternal age.⁹ Six of the included trials used FISH-based technology while comprehensive chromosomal screening was applied in 3 trials. Overall, PGT-A did not improve the live birth rate (risk ratio [RR], 1.01; 95% CI, 0.75 to 1.35); however, when the analysis was limited to the 3 trials evaluating comprehensive chromosomal screening (see Rubio et al 2017¹⁰, Verpoest et al 2018¹¹, and Munne et al 2019¹², trials below) the live birth rate was significantly higher in those randomized to IVF with PGT-A than those without PGT-A (RR, 1.30; 95% CI, 1.03 to 1.65). Clinical pregnancy and miscarriage rates were not significantly different between those receiving PGT-A and those without in the general population or subgroups. Although live birth rates were improved in advanced maternal age patients using comprehensive chromosomal screening for PGT-A, studies assessing the overall benefit of PGT-A with newer screening methods are needed. Additional limitations of the individual trials included in this meta-analysis are noted below.

In a meta-analysis limited to PGT-A with comprehensive chromosomal screening conducted on day 3 or day 5, Simopoulou et al (2021) identified 11 RCTs.¹³ In the overall population PGT-A did not improve live birth rates (RR 1.11; 95% CI, 0.87 to 1.42; 6 trials; n=1513; $I^2=75\%$). However, in a subgroup of patients over 35 years of age, live birth rates improved with PGT-A (RR 1.29; 95% CI, 1.05 to 1.60; 4 trials; n=629). Clinical pregnancy rates were also not significantly improved in the overall population (RR 1.14; 95% CI, 0.95 to 1.37; 9 trials; n=1824); however, miscarriage rates were improved with PGT-A (RR 0.36; 95% CI, 0.17 to 0.73; 7 trials; n=912). The authors concluded that PGT-A with comprehensive chromosomal screening did not generally improve outcomes, but when performed on blastocyst stage embryos in women over 35 years of age live birth rates were improved.

Randomized Controlled Trials

Several RCTs for evaluating comprehensive chromosomal screening in patients undergoing PGT-A have been published and are included in the above systematic reviews^{14,15,16,11,12,10}. One additional RCT was published in 2021 and was not incorporated in the above reviews.¹⁷ The characteristics of the RCTs are described in Table 1. Two trials (Yang et al [2012]; Rubio et al [2017]) used array comparative genetic hybridization, 2 used quantitative PCR, 1 (Verpoest et al [2018]) used comprehensive chromosome screening, and 2 used next-generation sequencing (NGS) (Munne et al [2019]; Yan et al [2021]). 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, Yan et al (2021) included good prognosis patients undergoing their first IVF and who were 20 to 37 years of age, 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 21 and 42 years of age 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) and Yan et al (2021) were noninferiority trials.

Table 1. Characteristics of Randomized Controlled Trials Evaluating Comprehensive Chromosomal Screening

Study	Countries	Sites	Dates	Participants	Interventions	
					PGS	Control
Yang et al (2012) ¹⁴	China, U.S.	2	NR	Female partner <35y with no history of spontaneous abortion and with normal karyotype	<ul style="list-style-type: none"> n=56 Blastocyst biopsy (day 5/6) analyzed via aCGH Single euploid embryo selected for transfer based on PGS 	<ul style="list-style-type: none"> n=56 Single embryo selected for transfer on day 5/6 based on morphologic assessment
Forman et al 2013) ¹⁵	U.S.	1	2011-2012	Female partner <43y with no more than 1 failed IVF attempt	<ul style="list-style-type: none"> n=89 Blastocyst biopsy (day 5/6) analyzed via qPCR Single euploid embryo selected for transfer based on PGS 	<ul style="list-style-type: none"> n=86 2 embryos selected for transfer on day 5/6 based on morphologic assessment
Scott et al (2013) ¹⁶	U.S.	1	2009-2012	Female partner between 21y and 42y with no more than 1 failed IVF attempt	<ul style="list-style-type: none"> n=72 Blastocyst biopsy (day 5) analyzed via qPCR Up to 2 euploid embryo(s) selected for transfer on day 6 based on PGS 	<ul style="list-style-type: none"> n=83 2 embryos selected for transfer on day 5 based on morphologic assessment
Rubio et al (2017) ¹⁰	Spain	4	2012-2014	Female partner between 38y and 41y with normal karyotypes who were on their 1st or 2nd cycle of ICSI	<ul style="list-style-type: none"> n=138 Blastocyst biopsy (day 3) analyzed via aCHG Unclear number of euploid embryos selected for transfer or vitrification (day 5) based on PGS 	<ul style="list-style-type: none"> n=140 Conventional ICSI cycle with morphologic embryo selection at blastocyst stage, unclear how many embryos were selected for transfer
Verpoest et al (2018) ¹¹	EU, Israel	9	2012-2016	Female partner between 36y and 40y with < 3 previously unsuccessful IVF attempts, < 3 miscarriages, and without poor ovarian response or reserve	<ul style="list-style-type: none"> n=205 Polar body biopsy (6-9 hr after insemination); analysis method varied by site Up to 2 euploid embryos selected from transfer on day of development decided by site policy 	<ul style="list-style-type: none"> n=191 Conventional ICSI cycle with up to 2 embryos selected for transfer on day of development decided by site policy

Munne et al (2019) Single Embryo Transfer of Euploid Embryo (STAR) study; NCT02268786 ¹²	Australia, Canada, U.S., UK	34	2014-2016	Female partner between 25y and 40y with < 2 previously unsuccessful IVF attempts, ≤ 1 miscarriage, and without azoospermia, or severe oligospermia	<ul style="list-style-type: none"> n=330 Blastocyst biopsy (day 5/6); NGS-based assay (Veriseq PGS) Single euploid embryo selected for transfer based on PGS 	<ul style="list-style-type: none"> n=331 Single embryo selected for transfer on day 5/6 based on morphologic assessment
Yan et al (2021) ¹⁷	China	14	2017-2018	Female partner 20-27y undergoing first IVF cycle with ≥ 3 blastocysts of good quality	<ul style="list-style-type: none"> n=606 Blastocyst biopsy (day 5); NGS-based assay (Illumina Next Seq 550 or Ion PGM/Proton) Single euploid embryo selected for transfer based on PGS 	<ul style="list-style-type: none"> n=606 Single embryo selected for transfer based on morphologic assessment

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 7 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. 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 using Comprehensive Chromosomal Screening

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) ¹⁴						
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) ¹⁵						
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); 0.20	NR (NR); <.001

Scott et al (2013) ¹⁶				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) ¹⁰				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) ¹¹				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	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) ¹²						
N	NR	587	587 ^c	587	587	NR
PGS, %		89.4	50.0	50.0	9.9	
Control, %		91.7	45.7	45.7	9.6	
p-value		NR	.3177	.3177	.8979	
Yan et al (2021) ¹⁷				Live Birth Rate		
N	NR	1061	993 ^d	964	118	24
PGS, %		83.3	79.0	77.2	8.7	1.0
Control, %		91.7	84.8	81.8	12.6	3.0
Rate ratio (95% CI)		0.91 (0.87 to 0.95)	0.93 (0.88 to 0.98)	0.94 (0.89 to 1.00)	0.69 (0.49 to 0.98)	0.33 (0.13 to 0.83)

CI: confidence interval; NR: not reported; OR: odds ratio; PSG: 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) ¹⁴			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) ¹⁵				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) ¹⁶				1. Few delivery or postdelivery outcomes 6. No justification for 20% clinically important difference	1,2. No follow-up of postdelivery outcomes
Rubio et al (2017) ¹⁰		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) ¹¹				1. Few delivery or postdelivery outcomes	1,2. No follow-up of postdelivery outcomes
Munne et al (2019) ¹²	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.	
Yan et al (2021) ¹⁷	4. Good prognosis patients				

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) ¹⁴ —	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) ¹⁵		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) ¹⁶		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) ¹⁰	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) ¹¹	3. Allocation concealment not described	2. Not blinded outcome assessment				
Munne et al (2019) ¹²					3. Magnitude of difference that power calculation was based on was unspecified; targeted sample size of 300 transfers in each arm was not achieved	

Yan et al (2021) ¹⁷	3.Allocation concealment not described	1.Blinding not mentioned				
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ITT: intention to treat; PGS: preimplantation genetic screening.

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

^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.¹⁸ 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 (eg, 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.¹⁹ 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 genetic 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 intelligence quotient (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. A meta-analysis in women of advanced maternal age undergoing

preimplantation genetic screening including both FISH-based technology and comprehensive chromosomal screening did not find an overall improvement in live birth rates, but when analysis was limited to those trials employing comprehensive chromosomal screening, improved live birth rates were found. Similarly, a meta-analysis limited to comprehensive chromosomal screening found improved outcomes in women over 35 years of age, but there was no difference in live birth rates with preimplantation genetic testing in the general population. 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 (eg, 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 (eg, 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 in vitro fertilization (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 is associated with 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 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 randomized controlled trials (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 (eg, fluorescent in situ hybridization [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. Recent meta-analyses of newer methods have found some benefit in subgroups of patients (eg, advanced maternal age); however, the evidence is limited, and larger trials specific to these patient populations are needed. Well-conducted RCTs evaluating preimplantation genetic screening in the various target populations (eg, 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 effects of the technology result 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 College of Obstetricians and Gynecologists

In 2020, the American College of Obstetricians and Gynecologists (ACOG) issued Committee Opinion #799 on Preimplantation Genetic Testing.²⁰ 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 "patients 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."²¹

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.²² 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.”²³

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."²⁴

U.S. Preventive Services Task Force

Not applicable.

Ongoing and Unpublished Clinical Trials

Some currently ongoing and 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
<i>Ongoing</i>			
NCT02941965	Preimplantation Genetic Screening in Patients With Male Factor Infertility	450	June 2023
NCT05009745	Preimplantation Genetic Testing for Aneuploidy (PGT-A) in in Vitro Fertilisation (IVF) Treatment: Pilot Phase of a Randomised Controlled Trial	100	Feb 2023

NCT: national clinical trial.

^a Denotes industry-sponsored or cosponsored trial.

Government Regulations

National:

There is no national coverage determination (NCD) on this topic.

Local:

There is no local coverage determination (LCD) on this topic.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

Assisted Reproductive Techniques

References

1. Cornelisse S, Zagers M, Kostova E, et al. Preimplantation genetic testing for aneuploidies (abnormal number of chromosomes) in in vitro fertilisation. *Cochrane Database Syst Rev*. Sep 08 2020; 9: CD005291. PMID 32898291
2. Ieşu M, Tan J, Taskin O, et al. Bedaiwy MA. Does preimplantation genetic diagnosis improve reproductive outcome in couples with recurrent pregnancy loss owing to structural chromosomal rearrangement? A systematic review. *Reprod Biomed Online*. 2018 Jun;36(6):677-685. PubMed PMID: 29627226.
3. Hasson J, Limoni D, Malcov M, et al. Obstetric and neonatal outcomes of pregnancies conceived after preimplantation genetic diagnosis: cohort study and meta-analysis. *Reprod Biomed Online*. Aug 2017;35(2):208-218. PMID 28576301
4. Kato K, Aoyama N, Kawasaki N, et al. Reproductive outcomes following preimplantation genetic diagnosis using fluorescence in situ hybridization for 52 translocation carrier couples with a history of recurrent pregnancy loss. *J Hum Genet*. May 19 2016. PMID 27193217
5. Chow JF, Yeung WS, Lee VC, et al. Experience of more than 100 preimplantation genetic diagnosis cycles for monogenetic diseases using whole genome amplification and linkage analysis in a single centre. *Hong Kong Med J*. Aug 2015;21(4):299-303. PMID 26044869
6. Scriven PN, Flinter FA, Khalaf Y, et al. Benefits and drawbacks of preimplantation genetic diagnosis (PGD) for reciprocal translocations: lessons from a prospective cohort study. *Eur J Hum Genet*. Feb 6 2013. PMID 23386032
7. Keymolen K, Staessen C, Verpoest W, et al. Preimplantation genetic diagnosis in female and male carriers of reciprocal translocations: clinical outcome until delivery of 312 cycles. *Eur J Hum Genet*. Apr 2012;20(4):376- 380. PMID 22071893
8. Strom CM, Strom S, Levine E, et al. Obstetric outcomes in 102 pregnancies after preimplantation genetic diagnosis. *Am J Obstet Gynecol*. Jun 2000;182(6):1629-1632. PMID 10871489
9. Shi WH, Jiang ZR, Zhou ZY, et al. Different Strategies of Preimplantation Genetic Testing for Aneuploidies in Women of Advanced Maternal Age: A Systematic Review and Meta-Analysis. *J Clin Med*. Aug 30 2021; 10(17). PMID 34501345

10. Rubio C, Bellver J, Rodrigo L, et al. In vitro fertilization with preimplantation genetic diagnosis for aneuploidies in advanced maternal age: a randomized, controlled study. *Fertil Steril*. May 2017; 107(5): 1122-1129. PMID 28433371
11. Verpoest W, Staessen C, Bossuyt PM, et al. Preimplantation genetic testing for aneuploidy by microarray analysis of polar bodies in advanced maternal age: a randomized clinical trial. *Hum Reprod*. Sep 01 2018; 33(9): 1767-1776. PMID 30085138
12. Munne S, Kaplan B, Frattarelli JL, et al. Preimplantation genetic testing for aneuploidy versus morphology as selection criteria for single frozen-thawed embryo transfer in good-prognosis patients: a multicenter randomized clinical trial. *Fertil Steril*. Dec 2019; 112(6): 1071-1079.e7. PMID 31551155
13. Simopoulou M, Sfakianoudis K, Maziotis E, et al. PGT-A: who and when? systematic review and network meta-analysis of RCTs. *J Assist Reprod Genet*. Aug 2021; 38(8): 1939-1957. PMID 34036455
14. Yang Z, Liu J, Collins GS, et al. Selection of single blastocysts for fresh transfer via standard morphology assessment alone and with array CGH for good prognosis IVF patients: results from a randomized pilot study. *Mol Cytogenet*. May 02 2012;5(1):24. PMID 22551456
15. Forman EJ, Hong KH, Ferry KM, et al. In vitro fertilization with single euploid blastocyst transfer: a randomized controlled trial. *Fertil Steril*. Jul 2013;100(1):100-107 e101. PMID 23548942
16. Scott RT, Jr., Upham KM, Forman EJ, et al. Blastocyst biopsy with comprehensive chromosome screening and fresh embryo transfer significantly increases in vitro fertilization implantation and delivery rates: a randomized controlled trial. *Fertil Steril*. Sep 2013;100(3):697-703. PMID 23731996
17. Yan J, Qin Y, Zhao H, et al. Live Birth with or without Preimplantation Genetic Testing for Aneuploidy. *N Engl J Med*. Nov 25 2021; 385(22): 2047-2058. PMID 34818479
18. Beukers F, van der Heide M, Middelburg KJ, et al. Morphologic abnormalities in 2-year-old children born after in vitro fertilization/intracytoplasmic sperm injection with preimplantation genetic screening: follow-up of a randomized controlled trial. *Fertil Steril*. Feb 2013;99(2):408-413. PMID 23127590
19. Schendelaar P, Middelburg KJ, Bos AF, et al. The effect of preimplantation genetic screening on neurological, cognitive and behavioural development in 4-year-old children: follow-up of a RCT. *Hum Reprod*. Jun 2013;28(6):1508-1518. PMID 23535872
20. Preimplantation Genetic Testing: ACOG Committee Opinion Summary, Number 799. *Obstet Gynecol*. Mar 2020; 135(3): 752-753. PMID 32080047
21. Committee Opinion No. 643: Identification and Referral of Maternal Genetic Conditions in Pregnancy. *Obstet Gynecol*. Oct 2015; 126(4): e49-e51. PMID 26393459
22. Amato P, Brzyski R, Braverman A, et al. Use of preimplantation genetic diagnosis for serious adult onset conditions: a committee opinion. *Fertil Steril*. Jul 2013;100(1):54-57. PMID 23477677
23. Penzias A, Bendikson K, Butts S, et al. The use of preimplantation genetic testing for aneuploidy (PGT-A): a committee opinion. *Fertil Steril*. Mar 2018;109(3):429-436. PMID 29566854
24. Practice Committee and Genetic Counseling Professional Group (GCPG) of the American Society for Reproductive Medicine. Electronic address: asrm@asrm.org. Clinical management of mosaic results from preimplantation genetic testing for aneuploidy (PGT-A) of blastocysts: a committee opinion. *Fertil Steril*. Aug 2020; 114(2): 246-254. PMID 32741460

The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through 11/1/23, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
9/1/16	8/22/16	7/13/16	Joint policy established
9/1/17	6/20/17	6/20/17	Routine maintenance Procedure code range, references and rationale updated
9/1/18	6/19/18	6/19/18	Routine maintenance
9/1/19	6/18/19		Routine maintenance
9/1/20	6/16/20		Routine maintenance, policy guidelines updated
9/1/21	6/15/21		Routine maintenance, clarification to MPS and inclusions, ref 20 added
3/1/22	1/19/22		Code update: addition of 0254U Routine maintenance Inclusion verbiage revised. IC will be given to those with IVF benefit who meet criteria but do not have diagnosis of infertility. Ref 1,26,28 added
3/1/23	12/20/22		Routine maintenance Is Ref 9,13,17 added
3/1/24	12/20/23		Routine maintenance (jf) Vendor Managed: NA 2 nd Qtr PLA code update. Added code 0396U to policy as E/I. -Edits to inclusions and description of policy.

Next Review Date: 4th Qtr, 2024

**BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: GENETIC TESTING - PREIMPLANTATION**

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Covered; policy criteria apply
BCNA (Medicare Advantage)	See Government Regulations section of policy.
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.