

Preimplantation Genetic Testing of Embryos

Effective: July 1, 2021

Next Review: March 2022

Last Review: May 2021

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Preimplantation genetic testing (PGT) involves analysis of biopsied cells as part of an assisted reproductive procedure. It is generally considered to be divided into two categories: 1) Preimplantation genetic diagnosis (PGD) is used to detect a specific inherited disorder, and 2) aims to prevent the birth of affected children in couples at high risk of transmitting a disorder. Preimplantation genetic screening (PGS) uses similar techniques to screen for potential genetic abnormalities in conjunction with in vitro fertilization for couples without a specific known inherited disorder.

MEDICAL POLICY CRITERIA

Notes:

- Preimplantation genetic testing is an associated service, an adjunct to in vitro fertilization. Member contracts for covered services vary. Member contract language takes precedent over medical policy.
- This policy does not address whole exome sequencing (WES), whole genome sequencing (WGS), or carrier screening (see Cross References section).

- I. Preimplantation genetic diagnosis (PGD) may be considered **medically necessary** as an adjunct to in vitro fertilization (IVF) in couples who meet at least one of the following

criteria, subject to careful consideration of the technical and ethical issues involved:

- A. For evaluation of an embryo at an identified elevated risk of a genetic disorder such as when:
 - 1. Both partners are known carriers of a single-gene autosomal recessive disorder
 - 2. One partner is a known carrier of a single-gene autosomal recessive disorder and the partners have one offspring that has been diagnosed with that recessive disorder
 - 3. One partner is a known carrier of a single-gene autosomal dominant disorder
 - 4. One partner is a known carrier of a single X-linked disorder
 - B. For evaluation of an embryo at an identified elevated risk of structural chromosomal abnormality, such as for a parent with balanced or unbalanced chromosomal translocation.
- II. Preimplantation genetic diagnosis (PGD) as an adjunct to IVF is considered **investigational** in patients/couples who are undergoing IVF in all situations other than those specified above.
- III. Preimplantation genetic screening (PGS), also known as PGT-A, as an adjunct to IVF is considered **investigational** in patients/couples who are undergoing IVF in all situations.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

LIST OF INFORMATION NEEDED FOR REVIEW

In order to determine the clinical utility of gene test(s), all of the following information must be submitted for review. If any of these items are not submitted, it could impact our review and decision outcome:

- 1. Name of the genetic test(s) or panel test
- 2. Name of the performing laboratory and/or genetic testing organization (more than one may be listed)
- 3. The exact gene(s) and/or variant(s) being tested
- 4. Relevant billing codes
- 5. Brief description of how the genetic test results will guide clinical decisions that would not otherwise be made in the absence testing
- 6. Medical records related to this genetic test:
 - o History and physical exam including any relevant diagnoses related to the genetic testing
 - o Conventional testing and outcomes
 - o Conservative treatments, if any

CROSS REFERENCES

- 1. [Genetic and Molecular Diagnostic Testing](#), Genetic Testing, Policy No. 20
- 2. [Chromosomal Microarray Analysis \(CMA\) or Copy number Analysis for the Genetic Evaluation of Patients with Developmental Delay, Intellectual Disability, Autism Spectrum Disorder, or Congenital Anomalies](#),

- Genetic Testing, Pol. No. 58
3. [Evaluating the Utility of Genetic Panels](#), Genetic Testing, Policy No. 64
 4. [Genetic Testing for Macular Degeneration](#), Genetic Testing, Policy No. 75
 5. [Whole Exome and Whole Genome Sequencing](#), Genetic Testing, Policy No. 76
 6. [Invasive Prenatal \(Fetal\) Diagnostic Testing Using Chromosomal Microarray Analysis \(CMA\)](#), Genetic Testing, Policy No. 78
 7. [Genetic Testing for the Evaluation of Products of Conception and Pregnancy Loss](#), Genetic Testing, Policy No. 79
 8. [Reproductive Carrier Screening for Genetic Diseases](#), Genetic Testing, Policy No. 81
 9. [Maternal Serum Analysis for Risk of Preterm Birth](#), Laboratory, Policy No. 75

BACKGROUND

Preimplantation genetic testing (PGT) describes a variety of adjuncts to an assisted reproductive procedure, in which either maternal or embryonic DNA is sampled and genetically analyzed, thus permitting deselection of embryos harboring a genetic defect prior to implantation of the embryo into the uterus. The ability to identify preimplantation embryos with genetic defects before the initiation of pregnancy provides an attractive alternative to amniocentesis or chorionic villous sampling (CVS) with selective pregnancy termination of affected fetuses. Preimplantation genetic testing can be viewed as either diagnostic (PGD) or screening (PGS). PGD is used to detect genetic evidence of a specific inherited disorder in the oocyte or embryo derived from mother or couple that has a high risk of transmission. PGS is not used to detect a specific abnormality but instead uses similar techniques to identify genetic abnormalities to identify embryos at risk. This terminology, however, is not used consistently (e.g., some authors use the term preimplantation genetic diagnosis when testing for a number of possible abnormalities in the absence of a known disorder).

Biopsy for PGD can take place at three stages; the oocyte, the cleavage stage embryo or the blastocyst. In the earliest stage, 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 six to eight cells (i.e., blastomeres). Sampling involves aspiration of one and sometimes two blastomeres from the embryo. Analysis of two 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 five to six days after insemination. Three to 10 trophoblast cells (outer layer of the blastocyst) are sampled. A disadvantage is that not all embryos develop to the blastocyst phase in vitro and, if 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.

The biopsied material can be analyzed in a variety of ways. Polymerase chain reaction (PCR)

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 (PGD), such as Tay Sachs disease or cystic fibrosis. Fluorescent in situ hybridization (FISH) is a technique that allows direct visualization of chromosomes to determine the number or absence of chromosomes. This technique is most commonly used to screen (PGS) for aneuploidy, gender determination, or to identify chromosomal translocations. FISH cannot be used to diagnose single genetic defect disorders. However, molecular techniques can be applied with FISH (such as micro-deletions and duplications) and thus, single-gene defects can be recognized with this technique.

Another approach is array comparative genome hybridization (aCGH) testing at either the eight-cell or more often, the blastocyst stage. Unlike FISH analysis, this allows for 24 chromosome aneuploidy screening, as well as more detailed screening for unbalanced translocations and inversions and other types of abnormal gains and losses of chromosomal material.

Next-generation sequencing (NGS) such as massively parallel signature sequencing has potential applications to prenatal genetic testing, but use of these techniques is in a relatively early stage of development compared to other methods of analyzing biopsied material.^[1-3] In addition, the use of NGS as a tool for PGD is limited by the presence of false-positive and false-negative single-nucleotide variations (SNVs), which is not acceptable in IVF. This continues to be a major challenge for the use of this application for PGD.^[4]

Three general categories of embryos have undergone PGT:

1. Embryos at risk for a specific inherited single genetic defect (PGD)

Inherited single-gene defects fall into three general categories: autosomal recessive, autosomal dominant, and X-linked. When either the mother or father is a known carrier of a genetic defect, embryos can undergo PGD to deselect embryos harboring the defective gene. Gender selection of a female embryo is another strategy when the mother is a known carrier of an X-linked disorder for which there is not yet a specific molecular diagnosis. The most common example is female carriers of fragile X syndrome. In this scenario, PGD is used to deselect male embryos, half of which would be affected. PGD could also be used to deselect affected male embryos. While there is a growing list of single genetic defects for which molecular diagnosis is possible, the most common indications include cystic fibrosis, beta thalassemia, muscular dystrophy, Huntington's disease, hemophilia, and fragile X disease. It should be noted that when PGD is used to deselect affected embryos, the treated couple is not technically infertile, but are undergoing an assisted reproductive procedure for the sole purpose of PGD. In this setting, PGD may be considered an alternative to selective termination of an established pregnancy after diagnosis by amniocentesis or chorionic villus sampling.

2. Identification of aneuploid embryos

Implantation failure of fertilized embryos is a common cause for failure of assisted reproductive procedures. Aneuploidy of embryos is thought to contribute to implantation failure and may also be the cause of recurrent spontaneous abortion. The prevalence of aneuploid oocytes increases in older women. These age-related aneuploidies are mainly due to nondisjunction of chromosomes during maternal meiosis. Therefore, PGS of the extruded polar bodies from the oocyte has been explored as a technique to deselect aneuploid oocytes in older women and is

also known as PGD for aneuploidy screening. In addition to older women, PGS has been proposed for women with repeated implantation failure.

FISH is most commonly used to detect aneuploidy. A limitation of FISH is that analysis is limited to a restricted number of locations along each chromosome. More recently, newer PGS methods have been developed that allow for a more comprehensive analysis of all chromosomes with genetic platforms including aCGH and single-nucleotide polymorphism (SNP) microarrays, NGS and quantitative PCR (qPCR)-based expression assays. These newer PGS methods are collectively known as PGS version 2 (PGS-v2) or PGS#2 techniques.

3. Embryos at a higher risk of translocations

Balanced translocations occur in 0.2% of the neonatal population but at a higher rate in infertile couples or in those with recurrent spontaneous abortions. PGD can be used to deselect those embryos carrying the translocations, thus leading to an increase in fecundity or a decrease in the rate of spontaneous abortion.

EVIDENCE SUMMARY

Human Genome Variation Society (HGVS) nomenclature^[5] is used to describe variants found in DNA and serves as an international standard. It is being implemented for genetic testing medical evidence review updates starting in 2017. According to this nomenclature, the term “variant” is used to describe a change in a DNA or protein sequence, replacing previously-used terms, such as “mutation.” Pathogenic variants are variants associated with disease, while benign variants are not. The majority of genetic changes have unknown effects on human health, and these are referred to as variants of uncertain significance.

TECHNICAL FEASIBILITY

Preimplantation genetic diagnosis (PGD) has been shown to be a feasible technique to detect genetic defects and to deselect affected embryos. Recent reviews continue to state that PGD using either polymerase chain reaction (PCR) or FISH can be used to identify numerous single gene disorders and unbalanced chromosomal translocation.^[6, 7] According to a PGD registry initiated by the European Society of Hormone Reproduction and Embryology (ESHRE), the most common indications for PGD were thalassemia, sickle cell syndromes, cystic fibrosis (CF), spinal muscular disease, and Huntington’s disease.^[8]

In 2007 the ESHRE PGD registry reported PGD testing on 3,753 oocyte retrievals, resulting in 729 with chromosomal abnormalities, 110 with X-linked diseases, 1,203 with with monogenic diseases, and 92 for social sexing.^[8] These registry data suggest that PGD, using either PCR or FISH, can be used to deselect affected embryos.

Several studies have suggested that the role of preimplantation genetic testing (PGT) has expanded to a broader variety of conditions that have not been considered as an indication for genetic testing via amniocentesis or chorionic villus sampling. The report of PGT used to deselect embryos at risk for early-onset Alzheimer’s disease prompted considerable controversy, both in lay and scientific publications.^[9-11] Other reports focus on other applications of PGT for *predispositions* to late-onset disorders.^[12] This contrasts with the initial use of PGD in deselecting embryos with genetic variants highly predictive of lethal diseases. PGD has also been used for gender selection and “family balancing.”^[13-15] A representative

sample of case series and reports on the technical feasibility of PGT to deselect embryos for different indications follows.

Several smaller case series reported on individual diseases. For example, Goossens (2000) reported on 48 cycles of PGD in 24 couples at risk for cystic fibrosis (CF). Thirteen patients became pregnant, and 12 healthy babies were born.^[16] In an additional 2013 study on cystic fibrosis, there were 44 PGD cycles performed for 25 CF-affected homozygous or double-heterozygous CF patients (18 male and seven female partners), which involved testing simultaneously for three variants, resulting in the birth of 13 healthy CF-free children and no misdiagnosis. PGD was also performed for six couples at a combined risk of producing offspring with CF and another genetic disorder. Concomitant testing for CF and other variants resulted in birth of six healthy children, free of both CF and another genetic disorder in all but one cycle.^[17] Other anecdotal studies have reported successful PGD in patients with osteogenesis imperfecta,^[18] Lesch-Nyhan syndrome,^[19] bulbar muscular atrophy,^[20] and phenylketonuria.^[21]

EFFICACY AND SAFETY

Preimplantation Genetic Diagnosis with In Vitro Fertilization

An area of clinical concern is the impact of PGT on overall IVF success rates. For example, is the use of PGT associated with an increased number of IVF cycles required to achieve pregnancy or a live birth? There is a lack of direct evidence comparing IVF success rates with and without PGD. A rough estimate can be obtained by comparing data from the Centers for Disease Control and Prevention (CDC) on IVF success rates overall and ESHRE registry data reporting on success rates after PGD. The most recent CDC data were collected in 2012.^[22] Although this comparison (CDC vs. ESHRE success rates) only provides a very rough estimate, the data suggest that use of PGD lowers the success rate of an in vitro fertilization cycle, potentially due to any of a variety of reasons such as inability to biopsy an embryo, inability to perform genetic analysis, lack of transferable embryos, and effect of PGT itself on rate of clinical pregnancy or live birth. It is important to note that the CDC database presumably represents couples who are predominantly infertile compared to the ESHRE database, which primarily represents couples who are not necessarily infertile but are undergoing IVF strictly for the purposes of PGD.

An important general clinical issue is whether PGD is associated with adverse obstetric outcomes, specifically fetal malformations related to the biopsy procedure. Strom (2000) addressed this issue in an analysis of 102 pregnant women who had undergone PGT with genetic material from the polar body.^[23] 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 to data reported for obstetric outcomes for in vitro fertilization. However, it should be noted that biopsy of the polar body is extra-embryonic material, and thus one might not expect an impact on obstetric outcomes. The patients in this study had undergone PGT for both unspecified chromosomal disorders and various disorders associated with a single gene defect (e.g., CF, sickle cell disease, and others).

Systematic Reviews

A systematic review by lews (2018) evaluated reproductive outcomes with PGD among patients who had recurrent pregnancy losses due to structural chromosomal rearrangements.^[24] There were 20 studies included in the review. There was significant heterogeneity between these studies, precluding meta-analysis. Among the 847 couples who conceived naturally, the live birth rate ranged from 25% to 71%, while among the 526 couples who underwent IVF with PDG the live birth rate ranged from 27% to 87%. The authors noted that the review was limited by the lack of large comparative or randomized studies.

Hasson (2017) published a systematic review of studies comparing obstetric and neonatal outcomes after intracytoplasmic sperm injection (ICSI) without PGD compared with ICSI with PGD.^[25] Studies focused on cases in which there were known parental genetic aberrations. Reviewers identified six studies, including data published by the investigators in the same article. Pooled analysis found no significant differences between the two groups for four of the five reported outcomes, mean gestational age at birth, the rate of preterm delivery, and the rate of malformations. There was a significantly lower rate of low birth weight neonates (<2500 g) in the PGD group compared with the non-PGD group (relative risk [RR] 0.84, 95% confidence interval [CI] 0.72 to 1.00, $p=0.04$).

Randomized Controlled Trials

No randomized controlled trials (RCTs) of PGD were identified.

Nonrandomized Studies

A study by Heijligers (2018) evaluated perinatal outcomes following PGD between 1995 and 2014 in the Netherlands.^[26] The study included 439 pregnancies in 381 women leading to 366 live born children. Of these, two were lost to follow-up. Nine of the remaining 364 children (2.5%) had major congenital malformations, which was consistent with other PGD cohorts, and five had a minor malformation. One misdiagnosis resulted in the spontaneous abortion of a fetus with an unbalanced 47,XX,+der(5)t(X;5)(q13;p14)mat karyotype. Seventy-one (20%) of the children were premature, including eight, all from twin pregnancies, that were very premature (<32 weeks). The authors concluded that there was no evidence that PGD was associated with an increased risk of adverse perinatal outcomes or congenital malformations.

Won (2018) reported clinical outcomes for patients who underwent PGD or PGS at a single center in Korea from January 2014 through December 2015.^[27] This included samples from 116 PGD cycles for 76 couples. Of these PGD cases, there were 24 Robertsonian translocations, 60 reciprocal translocations, 23 with mosaicism, three inversions, four additions, and two deletions. Implantation and clinical pregnancy rates with PGD were higher when testing was performed at the blastocyst stage ($n=26$) as compared with the cleavage stage ($n=90$) (27.5% vs. 17.8% and 38.5% vs. 18.9, respectively).

Maithripala (2017) performed a retrospective chart review of 36 couples with recurrent pregnancy loss due to structural chromosomal rearrangements.^[28] Couples were more likely to choose natural conception than IVF with PGD, and no significant differences in live birth rate were seen between treatment groups.

A study by Kato (2016) included 52 couples with a reciprocal translocation ($n=46$) or Robertsonian translocation ($n=6$) in at least one partner.^[29] All couples had a history of at least two 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 (2015) reported on 124 cycles of PGD in 76 couples with monogenetic diseases (X-linked recessive, autosomal recessive, autosomal dominant).^[30] The most common genetic conditions were α -thalassemia (64 cycles) and β -thalassemia (23 cycles). Patients were not required to have a history of miscarriage. A total of 92 PGD cycles resulted in embryo transfer, with an ongoing pregnancy rate (beyond 8 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 (2013) evaluated PGD for couples carrying reciprocal translocations.^[31] This prospective analysis included the first 59 consecutive couples who completed treatment at a single center. Thirty-two out of the 59 couples (54%) had a history of recurrent miscarriages. The 59 couples underwent a total of 132 cycles. Twenty-eight couples (47%) had at least one pregnancy, 21 couples (36%) had at least one live birth and 10 couples (36%) had at least one pregnancy loss. The estimated live birth rate per couple was 30 of 59 (51%) after three to six 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 did return.

Keymolen (2012) reported clinical outcomes of 312 cycles performed for 142 couples with reciprocal translocations.^[32] Data were collected at one center over 11 years. Seventy-five of 142 couples (53%) had PGD due to infertility, 40 couples (28%) due to a history of miscarriage, and the remainder due to a variety of other reasons. Embryo transfer was feasible in 150 of 312 cycles and 40 women had a successful singleton or twin pregnancy. The live birth rate per cycle was thus 12.8% (40 of 312), and the live birth rate per cycle with embryo transfer was 26.7% (40 of 150).

No studies were identified that specifically addressed PGD for evaluation of embryos when parents have a history of aneuploidy in a previous pregnancy.

Section Summary

Studies have shown that PGD for evaluation of an embryo at identified risk of a genetic disorder or structural chromosomal abnormality is feasible and does not appear to increase the risk of obstetric complications.

Preimplantation Genetic Screening with In Vitro Fertilization

Technology Assessments

A 2008 technology assessment published by the Agency for Healthcare Research and Quality (AHRQ) found two randomized controlled trials that assessed the use of PGS for embryo selection in women 35 years or older.^[33] The first study reported lower pregnancy and live birth rates in the PGS group compared with the control group which did not undergo PGS, though this difference was not statistically significant ($p=0.09$).^[34] About 25% of the embryos biopsied were genetically abnormal; therefore, fewer embryos were transferred in the PGD group. In the second study, which also studied women 35 years or older, Mastenbroek (2007) reported significantly lower pregnancy and live birth rates in the PGS group.^[35] In this study, all women had two embryos transferred; thus, the between-group difference could not be attributed to differences in the number of transferred embryos.

Systematic Reviews

A Cochrane systematic review of PGS for aneuploidy (PGT-A) was published by Cornelisse (2020), which included 13 RCTs involving 2,794 women.^[36] The quality of the included trials ranged from low to moderate, and the main limitations were reported to be imprecision, inconsistency, and risk of publication bias. One study by Verpoest (2018, described below) compared PGT-A with the use of array comparative genomic hybridisation (aCGH) to no PGT-A,^[37] while another, by Munné (2019, described below) compared PGT-A with the use of NGS-based genome-wide analyses to no PGT-A.^[38] The other studies compared PGT-A with FISH to no PGT-A. The review concluded that there was “insufficient good-quality evidence of a difference in cumulative live birth rate, live birth rate after the first embryo transfer, or miscarriage rate between IVF with and IVF without PGT-A as currently performed.” The authors noted that the use of FISH for the PGT-A genetic analysis is outdated and probably harmful.

Natsuaki (2018) published a systematic review and meta-analysis of pregnancy and child development outcomes following PGS.^[39] The review included 26 studies (n=6,192 women) for the clinical pregnancy outcome. Due to heterogeneity, a random-effects model was used in the analysis. Across all effect sizes, the average risk ratio (RR) suggested no statistically significant difference in pregnancy rates between embryos that had preimplantation genetic diagnosis or screening. No significant difference was found between mothers younger than 35 years and those 35 or older who had PGD/S. The screening method used—comprehensive chromosome testing (CCS) versus FISH—also produced no significant differences in reporting a clinical pregnancy. Nineteen studies (n=4,439 women) examined live birth rates and found that undergoing PGD/S made no significant difference in outcome. However, for live births, comprehensive chromosome testing was significantly favorable compared with FISH (RR 0.61, 95% CI 0.38 to 0.98, p=0.03). Evidence from the 18 studies that assessed child development (up to age nine) suggested no significant differences in the areas of anthropometric, psychomotor, cognitive, or behavioral development; neurological functioning; or parent-child relationships between children who were conceived after PGD/S vs no genetic testing.

A meta-analysis published by Dahdouh (2015a) pooled findings of the above three RCTs.^[40] Primary outcomes of the meta-analysis were implantation rates and ongoing pregnancy rates (i.e., beyond 20 weeks). In pooled analyses, rates of both primary outcomes were significantly higher after use of the newer PGS techniques compared to standard care without PGS. For clinical implantation rate, the pooled RR was 1.29 (95% CI 1.15 to 1.45); for sustained implantation rate, the pooled RR was 1.39 (95% CI 1.21 to 1.60). The meta-analysis did not address the live birth rate or adverse obstetric outcomes.

Another meta-analysis on newer PGS methods was published by Chen (2015).^[41] Four RCTs and seven cohort studies were identified. In addition to the three RCTs in the Dahdouh (2015a) systematic review described above, Chen included a 2012 RCT that used single-nucleotide polymorphism microarray analysis. A pooled analysis found a significantly higher implantation rate with PGS than control (RR 1.32, 95% CI 1.18 to 1.47). However, in additional pooled analyses of the RCTs, other outcomes were not significantly better with PGS than with control. For example, for the ongoing pregnancy rate, a pooled analysis of two RCTs had a relative risk of 1.31 (95% CI 0.64 to 2.66). Two RCTs reported a lower miscarriage rate (RR 0.53, 95% CI 0.24 to 1.15). Meta-analyses of the cohort studies found significantly improved ongoing pregnancy rates (RR 1.61, 95% CI 1.30 to 2.00, six studies) and miscarriage rates (RR 0.31,

95% CI 0.21 to 0.46, five studies), but not live birth rate (RR 1.35, 95% CI 0.85 to 2.13, three studies). The cohort studies were subject to limitations such as selection bias.

A different meta-analysis by Dahdouh (2015b) assessed whether PGS with comprehensive chromosome screening (PGS-CCS) improves clinical and sustained implantation rates (>20 weeks) compared with routine care for embryo selection in IVF.^[40] The same three RCTs^[42-44] that met eligibility criteria for the previous systematic reviews by Lee (2015) and Dahdouh (2014) were included in this analysis, and are described in the section below. The meta-analysis (three studies, n=659) showed that PGS-CCS was associated with significantly higher clinical and sustained implantation rates compared to controls, with pooled RRs of 1.29 (95% CI 1.15 to 1.45), and 1.39 (95% CI 1.21 to 1.60), respectively. In the included observational studies clinical and sustained implantation rates were also significantly higher in the PGS-CCS group than the controls, with pooled RRs of 1.78 (95% CI 1.60 to 1.99, seven studies, n=2,993) and 1.75 (95% CI 1.48 to 2.07, four studies, n=1,124), respectively. Statistical heterogeneity (I^2) was minimal for RCTs and substantial among OSs. However, the reviewers acknowledged several limitations of this analysis and their previous review: two of the RCTs came from the same IVF laboratory, and the randomization was carried out in a manner that may have introduced bias.

A systematic review of the literature on PGS-v2 methods was published by Lee (2015).^[45] The authors identified the three RCTs previously described and also considered observational studies. Study findings were not pooled. Sixteen observational studies were included, and they were rated as having poor-to-moderate quality. Thirteen of the observational studies included women of advanced maternal age. Three of the 13 studies had control groups, and all of these found improved implantation rates in the groups undergoing PGS using a newer technique. However, as the authors noted, methodologic limitations in the observational studies make it difficult to draw conclusions about the efficacy of PGS.

An earlier review of RCTs on PGS-v2 was performed by Dahdouh (2014).^[46] RCTs were eligible for inclusion if they compared women undergoing IVF with PGS-v2 techniques on trophoctodermal blastocyst cells with standard IVF care without PGS. The authors did not distinguish between studies using fresh or frozen embryos, or between the various PGS-v2 techniques. Three RCTs met eligibility criteria. Although the reviewers reported that PGS-v2 is associated with higher clinical implantation rates, and higher ongoing pregnancy rates when the same number of embryos is transferred in both PGS and control groups, they conceded that it was unclear if these findings to be extrapolated to other populations of women, including poor-prognosis patients.

A systematic review by Gleicher (2014) considered studies using newer PGS methods that they called PGS#2.^[47] This consists of biopsy on day five to six and aneuploidy assessment of all 24 chromosome pairs (as opposed to PGS#1 that involves biopsy on day three and FISH assessment of limited numbers of chromosomes). The authors did not identify any RCTs that used these newer methods and met the methodologic criterion of using an intention-to-treat analysis with IVF cycle as the denominator. A limitation of the included studies was that they evaluated pregnancy outcomes per the embryo transfer rate rather than per the number of IVF cycles. The authors asserted the data analysis methods used in the available studies misrepresent outcomes and that there are insufficient data that PGS#2 improves health outcomes compared with PGS#1.

A systematic review and meta-analysis was published by Mastenbroek (2011).^[48] This included RCTs that compared the live birth rate in women undergoing IVF with and without PGS for aneuploidies. Fourteen potential trials were identified; five trials were excluded after detailed inspection, leaving nine eligible trials with 1,589 women. All trials used FISH to analyze the aspirated cells. Five trials included women of advanced maternal age, three included “good prognosis” patients, and one trial included women with repeated implantation failure. When data from the five studies with women of advanced maternal age were pooled, the live birth rate was significantly lower in the PGS group (18%) compared to the control group (26%, $p=0.0007$). There was not a significant difference in live birth rates when data from the three studies with good prognosis patients were pooled; rates were 32% in the PGS group and 42% in the control group ($p=0.12$). The authors concluded that there is no evidence of a benefit of PGS as currently applied in practice; they stated that potential reasons for inefficacy include possible damage from the biopsy procedure and the mosaic nature of analyzed embryos.

An additional meta-analysis was published by Checa (2009).^[49] The investigators identified 10 trials with a total of 1,512 women. PGS was performed for advanced maternal age in four studies, for previous failed IVF cycles in one study, and for single embryo transfer in one study; the remaining four studies included the general IVF population. A pooled analysis of data from seven trials (346 events) found a significantly lower rate of live birth in the PGS group compared to the control group. The unweighted live birth rates were 151 of 704 (21%) in the PGS group and 195 of 715 (27%) in the control group ($p=0.003$). Findings were similar in subanalyses including only studies of the general IVF population and only the trials including women in higher-risk situations. The continuing pregnancy rate was also significantly lower in the PGS group compared to the control group in a meta-analysis of eight trials. The unweighted rates were 160 of 707 (23%) in the PGS group and 210 of 691 (30%) in the control group ($p=0.004$). Again, findings were similar in subgroup analyses.

Randomized Controlled Trials

Munné (2019) published the results of a multi-center RCT called the Single Embryo Transfer of Euploid Embryo (STAR) study.^[38] The study reported similar (50.0% versus 45.7%) ongoing pregnancy rates (≥ 20 weeks gestation) for NGS-based PGS versus morphology in good-prognosis patients aged 25 to 40 years. In the subgroup of 267 women aged 35 to 40 years, NGS-based PGS improved ongoing pregnancy rates (50.8% versus 37.2%, $p=0.0349$).

A multi-center trial by Verpoest (2018) evaluated prenatal screening for aneuploidy for women between 36 and 40 years of age.^[37] A total of 396 women undergoing ICSI treatment were randomized to either receive PGS or conventional ICSI without screening. There were no significant differences between groups for clinical pregnancy or live birth rates. However, the PGS group had reduced rates of transfer (RR 0.81, 95% CI 0.74 to 0.89, $p<0.001$) and miscarriage (RR 0.48, 95% CI 0.26 to 0.90, $p=0.02$).

Rubio (2017) published a randomized trial comparing outcomes in women of advanced maternal age who underwent PGS for aneuploidy prior to blastocyst transfer compared with blastocyst transfer without PGS.^[50] The trial included women between 38 and 41 years of age with normal karyotypes who were on their first or second cycle of ICSI. A total of 138 patients were randomized to the PGS group and 140 to the non-PGS control group. Of these, 100 patients in the PGS group and 105 in the non-PGS group completed the intervention. In an intention-to-treat analysis, there was a significantly higher live birth rate in the PGS group (31.9%) than in the control group (18.6%, odds ratio [OR] 2.4, 95% CI 1.3 to 4.2, $p=0.003$). In

the per-protocol analysis, there was a significantly higher rate of live birth in the PGS group than in the control group, both in the per transfer and per patient analyses. Per transfer, there were live births in 65% of the PGS group and 27% of the control group (OR 4.86, 95% CI 2.49 to 9.53, $p < 0.001$). Per patient, there were live births in 44% of the PGS group and 25% of the control group (OR 2.39, 95% CI 1.32 to 4.32, $p = 0.005$). In addition, the implantation was significantly higher in the PGS group (53%) than in the control group (43%, $p < 0.001$) and the miscarriage rate was significantly lower in the PGS group (3%) than in the control group (39%, $p = 0.007$).

Yang (2015) performed a two-phase pilot study that randomly compared next-generation sequencing (NGS) and array comparative genomic hybridization (aCGH) for preimplantation genetic screening.^[51] Phase I retrospectively evaluated the accuracy of NGS for aneuploidy screening in comparison to aCGH from previous IVF-PGS cycles ($n = 38$). Phase II compared clinical pregnancy and implantation outcomes between NGS and aCGH for 172 IVF-PGS patients randomized into two groups: 1) NGS (Group A): patients ($n = 86$) had embryos screened with NGS and 2) aCGH (Group B): patients ($n = 86$) had embryos screened with aCGH. The investigators reported that in phase I, NGS detected all types of aneuploidies of human blastocysts accurately and provided a 100% 24-chromosome diagnosis consistency with the highly validated aCGH method. In phase II, NGS screening resulted in similarly high ongoing pregnancy rates for PGS patients compared to aCGH screening (74.7% vs. 69.2%, respectively, $p = 0.56$). The observed implantation rates were also comparable between the NGS and aCGH groups (70.5% vs. 66.2%, respectively, $p = 0.564$). The investigators acknowledged that the improved pregnancy rates achieved in this study may not be applied to all IVF-PGS patients, especially those at advanced maternal age or with diminished ovarian reserve.

An RCT by Scott (2013) compared sustained implantation and delivery rates in pregnant females between the ages of 21 and 42 years who had blastocysts tested by real-time polymerase chain reaction-based comprehensive chromosome screening (CCS) versus no screening (routine care group).^[42] In the CCS intervention group ($n = 72$ patients) 134 blastocysts were transferred, while in the routine care group ($n = 83$), 163 blastocysts were transferred. Sustained implantation rates (probability that an embryo will implant and progress to delivery) were statistically significantly higher in the CCS group compared with those from the routine care group (89/134, 66.4% vs. 78/163, 47.9%, $p = 0.002$). However, the embryologists were not blinded to the CCS results, potentially inflating the implantation rates in the CCS group. Delivery rates per cycle were also statistically significantly higher in the CCS group (61/72, [84.7%] vs. 56/83 [67.5%], $p = 0.001$).

Forman (2013) performed a randomized trial to compare ongoing pregnancy and multiple gestation rates in pregnant women under the age of 43 who had blastocysts tested by qPCR-based comprehensive chromosome screening (CCS) versus no screening.^[43] The intervention group ($n = 89$) had all viable blastocysts biopsied for CCS and single euploid blastocyst transfer, while the control group ($n = 86$) had their two best-quality, untested blastocysts transferred. Implantation rates were 60.7% in the intervention group and 65.1% in the control group. The rate appeared lower in the intervention group, but this was considered “noninferior.” The authors used a 20% noninferiority margin which may not be the most appropriate approach to evaluating the impact of PGS-v2 on health outcomes. The investigators noted that this study only focused on patients with good prognoses, meaning good responders with normal markers of ovarian reserve and large oocyte yields and an abundance of embryos to evaluate. Further prospective studies will be required to validate the

best way to apply CCS in women who are low responders or who have other abnormal markers of ovarian reserve.

Schendelaar (2013) reported on outcomes when children were four years old. Data were available on 49 children (31 singletons, nine sets of twins) born after IVF with PGS and 64 children (42 singletons, 11 sets of twins) born after IVF without PGS.^[52] The primary outcome of this analysis was the child's neurological condition, as assessed by the fluency of motor behavior. The fluency score ranged from 0 to 15 and is a sub-scale of the neurological optimality score. In the sample as a whole, and among singletons, the fluency score did not differ among children in the PGS and non-PGS groups. However, among twins, the fluency score was significantly lower among those in the PGS group (mean score 10.6, 95% CI 9.8 to 11.3) than those in the non-PGS group (mean score: 12.3, 95% CI 11.5 to 13.1). Cognitive development as measured by IQ score and behavioral development as measured by the total problem score were similar between non-PGS and PGS groups.

Rubio (2013) published findings of two RCTs evaluating PGS.^[53] Studies designs were similar but one included women of advanced maternal age (41 to 44 years old) and the other included couples under 40 years old with repetitive implantation failure (RIF), defined as failing three or more previous attempts at implantation. All couples were infertile and did not have a history of pregnancy or miscarriage with chromosomal abnormality. In all cases, blastocysts were transferred at day five. In the groups receiving PGS, single-cell biopsies were done at the cleavage stage. A total of 91 patients enrolled in the RIF study (48 in the PGS group and 43 in the non-PGS group) and 183 patients in the advanced maternal age study (93 patients in the PGS group and 90 patients in the non-PGS group). Among RIF patients, the live birth rate did not differ significantly between groups. Twenty-three of 48 patients (48%) in the PGS group and 12 of 43 patients (28%) in the non-PGS groups had live births. (The exact p-value was not provided). However, the live birth rate was significantly higher with PGS in the advanced maternal age study. Thirty of 93 patients (32%) in the PGS group and 14 of 90 patients (16%) in the non-PGS group had live births: The difference between groups was statistically significant ($p=0.001$).

Yang (2012) performed a pilot study to assess embryos selected on the basis of morphology and comprehensive chromosomal screening via aCGH compared to embryos selected by morphology only.^[44] Fifty five patients ($n=425$ blastocysts) were biopsied and analyzed via aCGH, and 48 patients ($n=389$ blastocysts) were examined by microscopy only. Clinical pregnancy rate and ongoing pregnancy rate were significantly higher in the aCGH group compared to the morphology-only group (70.9% vs. 45.8%, $p=0.017$) and (69.1% vs. 41.7%, $p=0.009$), respectively. Aneuploidy was detected in 191/425 (44.9%) of blastocysts in the aCGH group, highlighting the imprecision of the morphology-only group. Although the investigators concluded that embryos randomized to the aCGH group implanted with greater efficiency, resulted in clinical pregnancy more often, and yielded a lower miscarriage rate than those selected without aCGH; that additional studies are needed.

Nonrandomized Studies

The retrospective study by Won (2018), described earlier, reported outcomes for 370 PGS cycles for 260 couples.^[27] The most common reason for requesting PGS was recurrent spontaneous abortion ($n=160$), followed by recurrent implantation failure ($n=145$), advanced maternal age ($n=81$), and bad obstetric history ($n=66$). As with PGD testing in this cohort, there were higher implantation and clinical pregnancy rates seen for tests performed at the

blastocysts stage (32.2% and 39.6%, respectively) than for those performed at the cleavage stage (25.5% and 27%, respectively).

Barad (2017) evaluated the impact of PGS on donor oocyte-recipient cycles using data from the Society for Assisted Reproductive Technology Clinic Outcome Reporting System.^[54] Outcomes were compared between 392 PGS cycles and 20,616 control cycles between 2005 and 2013. After adjustment for factors including patient and donor ages, race, infertility diagnosis, and number of embryos transferred, PGS was significantly associated with reduced odds of live birth (OR 0.65, 95% CI 0.53 to 0.80, $p < 0.001$).

Lee (2017) compared outcomes between individuals who underwent PGS for aneuploidy ($n=110$ women) and those who had morphological embryo assessment ($n=1,983$ women) at an institution in Australia.^[55] The authors reported a higher per cycle live birth rate with PGS than morphological assessment only (14.47% vs. 9.12%, $p < 0.01$). However, after three cycles, there was no significant differences between groups for cumulative live-birth rates.

Morphological abnormalities at two years were reported by Beukers (2013).^[56] Data were available on 50 children born after PGS and 72 children born without PGS. Fourteen out of 50 children (28%) in the PGS group and 25 of 72 children (35%) in the group that did not receive PGS had at least one major abnormality; the difference between groups was not statistically significant ($p=0.43$). Skin abnormalities (e.g., capillary hemangioma and hemangioma plana) were the most common, affecting five children after PGS and 10 children in the non-PGS group. In a control group of 66 age-matched children born without assisted reproduction, 20 children (30%) had at least one major abnormality. Developmental outcomes at two and four years have also been reported.

Minasi (2017) evaluated the use of PGS for aneuploidy in a case series of patients that were already undergoing PGD for genetic disorders.^[57] This series included 1122 blastocysts from 304 PGD cycles: 163 for monogenic disease and 141 for chromosomal rearrangements. The authors reported that adding PGS to the testing increased the number of blastocysts identified as not-transferable, however, there was no control group to compare clinical pregnancy outcomes.

In 2011, a follow-up study was published when surviving children were two years-old.^[58] Forty-nine pregnancies in the PGS group and 71 in the control group resulted in live births of at least one child. Forty-five couples with 54 children (36 singletons and 9 twins) in the PGS group and 63 couples with 77 children (49 singletons and 14 twins) in the control group were available for follow-up. The groups of children did not differ significantly in scores on an infant development scale and child development checklist variables. For example, median scores on the total Child Behavior Checklist were 43.0 among children born after PGS and 46.0 in control children ($p=0.44$). However, the neurologic optimality score (NOS) was significantly lower in the PGS group than the control group ($p=0.20$).

Debrock (2010) published a trial that included women of advanced maternal age (at least 35 years) who were undergoing in vitro fertilization.^[59] Randomization was done by cycle; 52 cycles were randomized to a PGS group and 52 to a control group that did not undergo PGS. Cycles were excluded if two or fewer fertilized oocytes were available on day 1 after retrieval or if two or fewer embryos of six or more cells were available on day 3. Individuals could participate more than once, and there was independent randomization for each cycle. More cycles were excluded postrandomization in the control group; outcome data were available for 37 cycles (71%) in the PGS group and 24 cycles (46%) in the control group. Study findings did

not confirm the investigators' hypothesis that the implantation rate would be higher in the group receiving PGS. The implantation rate was 15.1% in the PGS group and 14.9% in the control group ($p=1$). Moreover, the live-birth rate per embryo transferred did not differ significantly between groups; rates were 9.4% in the PGS group and 14.9% in the control group ($p=0.76$). An intention-to-treat analysis of all randomized cycles (included and excluded) did not find any significant differences in outcomes including the implantation rate which was 11 of 76 (14.5%) in the PGS group and 16 of 88 (18.2%) in the control group ($p=0.67$). In the intention-to-treat, the live-birth rate per embryo transferred was 7 of 47 (14.9%) in the PGS group and 10 of 49 (20.4%) in the control group ($p=0.60$).

Mastenbroek (2007) found that PGS reduced the rates of ongoing pregnancies and live births after IVF in women of advanced maternal age (aged 35 through 41 years).^[35] In this study, 408 women (206 assigned to PGS and 202 assigned to the control group) underwent 836 cycles of IVF (434 cycles with and 402 cycles without PGS). The ongoing pregnancy rate was significantly lower in the women assigned to PGS (52 of 206 women [25%]) than in those not assigned to PGS (74 of 202 women [37%], rate ratio, 0.69, 95%CI 0.51 to 0.93). The women assigned to PGS also had a significantly lower live-birth rate (24% vs. 35%, respectively, rate ratio, 0.68, 95% CI 0.50 to 0.92).

Section Summary

Most RCTs and meta-analyses of RCTs of initial techniques used for PGS found similar or lower ongoing pregnancy and/or live birth rates after IVF with PGS compared with IVF without PGS. These initial PGS were not found to improve the net health outcome. Three RCTs evaluating newer PGS methods have been published, as well as systematic reviews of these trials. The RCTs on newer PGS methods tended to include good prognosis patients, and results may not be generalizable to other populations such as older women. Moreover, individual RCTs on newer PGS methods had potential biases. Well-conducted RCTs evaluating PGS in the target population (e.g., women of advanced maternal age) are needed before conclusions can be drawn about the impact on the net health outcome.

PRACTICE GUIDELINE SUMMARY

AMERICAN COLLEGE OF OBSTETRICIANS AND GYNECOLOGISTS

In 2009, American College of Obstetricians and Gynecologists (ACOG) issued an opinion statement, which was reaffirmed in 2014, on preimplantation genetic screening for aneuploidy.^[60] ACOG stated that current data do not support the use of PGS to screen for aneuploidy due solely to maternal age. ACOG also did not recommend PGS for recurrent unexplained miscarriage and recurrent implantation failures in the clinical setting; they recommended that use be limited to research studies.

In 2015 (reaffirmed in 2019), ACOG issued an opinion statement 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.^[61]

AMERICAN SOCIETY FOR REPRODUCTIVE MEDICINE

A 2008 practice committee opinion issued by the American Society for Reproductive Medicine concluded the following:^[62]

- PGD can reduce the risk of conceiving a child with genetic abnormality carried by one or both parents if that abnormality can be identified from a single cell.
- Available evidence does not support the use of PGS as currently performed to improve live birth rates in patients with advanced maternal age, previous implantation failure, recurrent pregnancy loss, or male factor infertility.

SUMMARY

There is enough research to show that preimplantation genetic diagnosis (PGD) leads to improved health outcomes (e.g., birth of unaffected fetuses) when used for evaluation of an embryo that is known to be at elevated risk of a genetic disorder or structural chromosomal abnormality. Therefore, PGD may be considered medically necessary when the evaluation is focused on an elevated risk for a known disease or disorder and the policy criteria are met.

There is not enough research to show that preimplantation genetic diagnosis (PGD) leads to improved health outcomes for the evaluation of an embryo without an elevated risk or in all other situations not outlined in the medically necessary policy criteria. More research is needed to know if or how well PGD will impact outcomes in these situations. Therefore, PGD is considered investigational when the policy criteria are not met.

There is not enough research to show that preimplantation genetic screening (PGS) improves health outcomes, including pregnancy and live birth rates. The research shows that newer PGS methods do not improve health outcomes, particularly in the populations of greatest interest, women of advanced maternal age and women with a history of repeated implantation failure. Therefore, preimplantation genetic screening as a part of the in vitro fertilization process is considered investigational in all situations.

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 60. ACOG Committee Opinion No. 430: preimplantation genetic screening for aneuploidy. *Obstet Gynecol*. 2009;113(3):766-7. PMID: 19300349
 61. Committee Opinion No. 643: Identification and Referral of Maternal Genetic Conditions in Pregnancy. *Obstet Gynecol*. 2015;126:e49-51. PMID: 26393459
 62. Preimplantation genetic testing: a Practice Committee opinion. *Fertil Steril*. 2008;90(5 Suppl):S136-43. PMID: 19007612
 63. BlueCross BlueShield Association Medical Policy Reference Manual "Preimplantation Genetic Testing." Policy No. 4.02.05

CODES

Codes	Number	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/duplications, mosaicism, and segmental aneuploidy, per embryo tested
	81228	Cytogenomic constitutional (genome-wide) microarray analysis; interrogation of genomic regions for copy number variants (eg, bacterial artificial chromosome [BAC] or oligo-based comparative genomic hybridization [CGH] microarray analysis)
	81229	Cytogenomic constitutional (genome-wide) microarray analysis; interrogation of genomic regions for copy number and single nucleotide polymorphism (SNP) variants for chromosomal abnormalities
	81479	Unlisted molecular pathology procedure

Codes	Number	Description
	88271 – 88275	Molecular cytogenetics (i.e., FISH), code range
	89290	Biopsy, oocyte polar body or embryo blastomere, microtechnique (for preimplantation genetic diagnosis), less than or equal to 5 embryo(s)
	89291	;greater than 5 embryo(s)
HCPCS	None	

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