Preimplantation Genetic Testing of Embryos

Effective: July 1, 2025

Next Review: March 2026
Last Review: June 2025

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 testing for monogenic conditions (PGT-M) or for structural rearrangements (PGT-SR), are used to detect a specific inherited disorder, and aim to prevent the birth of affected children in people at high risk of transmitting a disorder. 2) Preimplantation genetic testing for aneuploidy (PGT-A) uses similar techniques to screen for potential genetic abnormalities in conjunction with in vitro fertilization for people 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 testing for monogenic conditions (PGT-M) or structural rearrangements (PGT-SR) may be considered **medically necessary** as an adjunct to

in vitro fertilization (IVF) in people 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 when one of the following is met:

1. Both partners are known carriers of a single-gene autosomal recessive disorder; or
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; or
3. One partner is a known carrier of a single-gene autosomal dominant disorder; or
4. One partner is a known carrier of a single X-linked disorder; or

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 testing for monogenic conditions (PGT-M) or structural rearrangements (PGT-SR) as an adjunct to IVF is considered **investigational** in people who are undergoing IVF in all situations other than those specified above.

III. Preimplantation genetic testing for aneuploidy (PGT-A), as an adjunct to IVF is considered **investigational** in people 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 pathogenic gene abnormality prior to implantation of the embryo into the uterus. The ability to identify preimplantation embryos with pathogenic gene variants 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, including (PGT-M, formerly known as preimplantation genetic diagnosis; PGD) and preimplantation genetic testing for structural chromosomal rearrangements (PGT-SR); or screening for aneuploidy (PGT-A, formerly known as preimplantation genetic screening; PGS). PGT-M and PGM-SR are used to detect genetic evidence of a specific inherited disorder in the oocyte or embryo derived from biologic mother or reproductive partner that has a high risk of transmission. PGT-A 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 PGT-M 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 biologic mother is a known carrier of a pathogenic gene variant, and genetic analysis of the polar body is normal, then it is assumed that the variant 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 trophectoderm 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 or other amplification techniques can be used to amplify the harvested DNA with subsequent analysis for single genetic variants. 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 gene variant disorders. However, molecular techniques can be applied with FISH, and thus single-gene variants (eg, microdeletions, duplications) can be recognized with this technique.

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

Three general categories of embryos have undergone PGT:

1. Embryos at risk for a specific inherited single gene abnormality (PGT-M and PGT-SR)

Inherited single-gene pathogenic variants fall into three general categories: autosomal recessive, autosomal dominant, and X-linked. When either or both biologic parents are a known carrier of a pathogenic gene variant, PGT-M testing can be used to deselect embryos harboring the variant. Gender selection of a female embryo is another strategy when the biologic 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, PGT-M is used to deselect male embryos, half of which would be affected. PGT-M could also be used to deselect affected male embryos. While there is a growing list of single gene variants 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 PGT-M is used to deselect affected embryos, the treated reproductive partners are not technically infertile but are undergoing an assisted reproductive procedure for the sole purpose of PGT-M. In this setting, PGT-M may be considered an alternative to selective termination of an established pregnancy after diagnosis by amniocentesis or chorionic villus sampling.

Inherited chromosomal structural rearrangements may be either balanced, with no loss or gain of genetic material, or unbalanced, with some deletion or duplication. The risk of passing such a rearrangement on to offspring varies but can be as high as 50%. PGT-SR is testing to detect these rearrangements.

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, PGT-A of the extruded polar bodies from

the oocyte has been explored as a technique to deselect aneuploid oocytes in older women. In addition to advanced maternal age, PGT-A has been proposed for people with repeated implantation failure.

3. Embryos at a higher risk of translocations

Balanced translocations occur in 0.2% of the neonatal population but at a higher rate in people with infertility or recurrent spontaneous abortions. PGT-SR for structural rearrangements (translocations or inversions) 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[1] 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.

Promotion of greater diversity and inclusion in clinical research of historically marginalized groups (e.g., People of Color [African-American, Asian, Black, Latino and Native American]; LGBTQIA (Lesbian, Gay, Bisexual, Transgender, Queer, Intersex, Asexual); Women; and People with Disabilities [Physical and Invisible]) allows policy populations to be more reflective of and findings more applicable to our diverse members. While we also strive to use inclusive language related to these groups in our policies, use of gender-specific nouns (e.g., women, men, sisters, etc.) will continue when reflective of language used in publications describing study populations.

TECHNICAL FEASIBILITY

Preimplantation genetic diagnosis (PGT-M) has been shown to be a feasible technique to detect pathogenic genetic variants and to deselect affected embryos. Recent reviews continue to state that PGT-M using either polymerase chain reaction (PCR) or FISH can be used to identify numerous single gene disorders and unbalanced chromosomal translocation.[2 3] According to a PGT-M registry initiated by the European Society of Hormone Reproduction and Embryology (ESHRE), the most common indications for PGT-M were thalassemia, sickle cell syndromes, cystic fibrosis (CF), spinal muscular disease, and Huntington’s disease.[4]

In 2007 the ESHRE PGT-M registry reported PGT-M testing on 3,753 oocyte retrievals, resulting in 729 with chromosomal abnormalities, 110 with X-linked diseases, 1,203 with monogenic diseases, and 92 for social sexing.[4] These registry data suggest that PGT-M, 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.[5-7] Other reports focus on other applications of PGT for *predispositions* to late-onset disorders.[8] This contrasts with the initial use of PGT-M in deselecting embryos with genetic variants highly predictive of lethal diseases. PGT-M has also been used for gender selection and "family balancing."[9-11] 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 PGT-M in 24 couples at risk for cystic fibrosis (CF). Thirteen patients became pregnant, and 12 healthy babies were born.[12] In an additional 2013 study on cystic fibrosis, there were 44 PGT-M 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. PGT-M 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.[13] Other anecdotal studies have reported successful PGT-M in patients with osteogenesis imperfecta,[14] Lesch-Nyhan syndrome,[15] bulbar muscular atrophy,[16] and phenylketonuria.[17]

EFFICACY AND SAFETY

An area of clinical concern is the impact of PGT on overall IVF success rates. The available evidence is largely focused on people undergoing IVF due to infertility, and not specifically for PGT-M**.** The Agency for Healthcare Research and Quality (AHRQ) published a comparative effectiveness review on infertility management.[18] The AHRQ reviewed studies compared all types of PGT cycles with non-PGT cycles and found that for women younger than 35 years live birth per embryo transfer was lower for PGT cycles compared to non-PGT cycles.

An important general clinical issue is whether PGT-M 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.[19] All preimplantation genetic diagnoses were confirmed postnatally; there were no diagnostic errors. The incidence of multiple gestations was similar to that seen with IVF. PGT-M 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 variant (e.g., CF, sickle cell disease, and others).

Preimplantation Genetic Testing for Monogenic Conditions

<u>Systematic Reviews</u>

Li (2022) published a systematic review and meta-analysis that included eleven studies to compare pregnancy outcomes in couples with recurrent pregnancy loss (RPL) and abnormal karyotypes to couples with RPL and normal karyotypes.[20] First pregnancy live birth rate (LBR) after RPL was lower in couples with abnormal karyotypes than in couples with normal karyotype (9 studies, OR, 0.55; 95% CI 0.46-0.65; I^2=27%; p<0.00001). Accumulated LBR was not significantly different between couples with abnormal vs. normal karyotype after RPL (4

studies; OR, 0.96; 95% CI, 0.90-1.03; I^2=0; p=0.26) However, miscarriages were more common in couples with an abnormal karyotype (4 studies; OR, 2.21; 95% CI, 1.69-2.89; I^2=0; p<0.00001). A second analysis reported pregnancy outcomes of couples with RPL and abnormal karyotype that had expectant management compared to those that had PGD. While limited by the availability of only two non-randomized studies, the meta-analysis found the difference in accumulated LBR was not significant (2 studies; OR 0.55; 95% CI, 0.11-2.62; I^2=71%; 0=0.45) but PGD was associated with a lower miscarriage rate (2 studies; OR 0.15; 95% CI, 0.04-0.51; I^2=45%; p=0.002). The findings suggest that while miscarriages and unsuccessful first pregnancy are more common in people with chromosomal abnormalities, their overall LBR was the same as for people with normal karyotypes. However, the evidence also suggests repeated attempts are required after unsuccessful first pregnancy to achieve similar outcomes.

A systematic review by Iews (2018) evaluated reproductive outcomes with PGD among patients who had recurrent pregnancy losses due to structural chromosomal rearrangements.[21] 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.[22] 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 PGT-M were identified.

Nonrandomized Studies

A study by Heijligers (2018) evaluated perinatal outcomes following PGD between 1995 and 2014 in the Netherlands.[23] 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.[24] 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.[25] 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.[26] 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).[27] 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.[28] 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.[29] 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 PGT-M for evaluation of embryos in people with a history of aneuploidy in a previous pregnancy.

Section Summary

Studies have shown that PGT-M 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 for Aneuploidy

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 PGT-A for embryo selection in women 35 years or older.[30] 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).[31] About 25% of the embryos biopsied were genetically abnormal; therefore, fewer embryos were transferred in the PGT-A 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.[32] 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. A 2019 comparative review by the Agency for Healthcare Research and Quality (AHRQ) states that available evidence on PGS screening for unexplained fertility is too dated to be applicable to current clinical practice.[18]

Systematic Reviews

Vitagliano (2023) published a systematic review and meta-analysis of seven studies involving 11,335 transfers of euploid embryos that compared maternal age <35 years to maternal age ≥35 years.[33] Maternal age <35 years was associated with a higher ongoing pregnancy rate or live birth rate (OR 1.29; 95% CI, 1.07-1.54; I^2 = 40%), and higher implantation rate (OR 1.22; 95% CI, 1.12-1.32; I^2=0%). The authors concluded that maternal age >35 years is associated with lower success rates for assisted reproductive technology independent of embryo ploidy.

Liang (2023) conducted a systematic review and meta-analysis focused on PGT-A outcomes after recurrent pregnancy failure (RPF).[34] RPF includes recurrent spontaneous abortion (RSA) and recurrent implantation failure (RIF). Thirteen studies were included in the analysis.

The analysis divided the overall outcomes into five groups:

- Six studies of implantation rate showed a significantly higher implantation rate after PGT-A compared to in vitro fertilization/intracytoplasmic sperm injection (IVF/ICSI) (p<0.00001).
- The analysis of clinical pregnancy rate (CPR) involved 12 studies and found PGT-A was associated with higher CPR than IVF/ICSI (p<0.0001).
- Clinical miscarriage rate (CMR) was analyzed in 11 studies that found CMR was significantly lower in the PGT-A group compared to IVF/ICSI (p=0.0047).
- Four studies were included in the analysis of ongoing pregnancy rate (OPR) which found that OPR was higher in the PGT-A group than in the IVF/ICSI group (p<0.0001).
- Nine studies were included in the analysis of live birth rate (LBR) which found LBR was significantly higher in the PGT-A group compared to the IVF/ICSI group (p<0.0001).

Subgroup analysis found that when outcomes were stratified by maternal age, for both women younger than 35 years and women aged 35 and older, CPR and LBR were significantly higher in the PGT-A groups but there was no difference in clinical miscarriage rates (CMR) in either maternal age group when comparing PGT-A to IVF/ICSI.

The authors conclude that for patients with RPF, PGT-A may improve outcomes, but note that PGT-A by itself is inadequate to address RPF. The authors also note the analysis was limited by the small number of studies, and particularly the small number of studies included in sub-group analyses.

Kasaven (2023) published a systematic review and meta-analysis comparing PGT-A to conventional morphologic assessment.[35] The primary outcomes were live birth rate (LBR) and ongoing pregnancy rate (OPR) per embryo transfer. The analysis included 16 studies of which six were randomized controlled trials (RCTs) and 10 were cohort studies. LBR was higher in both the RCTs (p=0.03) and the cohort studies (p<0.001). The OPR per embryo transfer was also higher in the PGT-A group in the RCTs (p=0.04) and in the cohort studies (p<0.001). The authors conclude that PGT-A results in higher rates of LBR and OPR than conventional morphologic assessment but acknowledge that studies comparing PGT-A to other strategies, e.g., FISH and the use of cleavage-stage biopsies, have not found that PGT-A is superior. The authors also note that PGT-A in most of the included studies was not performed for a specific indication and some studies excluded women with risk factors for unsuccessful pregnancy outcomes (e.g., diminished ovarian reserve, history of implantation failure).

Cheng (2022) published a systematic review and meta-analysis to assess whether preimplantation genetic screening for aneuploidy (PGT-A) leads to higher live-birth rates than IVF without PGT-A.[36] Nine RCTs with 3,334 participants were included. The overall live-birth rate was not significantly different (RR 1.13, 95% CI 0.96-1.34, I^2=50%). However, when stratified by maternal age, PGT-A was associated with a higher rate of live births to woman of advanced maternal age (RR 1.34, 95% CI 1.02-1.77, I^2=50), but not women of nonadvanced maternal age (RR 0.94, 95% CI 0,89-0.99, I^2=0%). Miscarriage rates were compared in eight studies. The PGT-A group experienced significantly fewer miscarriages than the control group (RR 0.53%, 95% CI 0.35-0.81, I^2=50). Other secondary outcomes; clinical pregnancy, ongoing pregnancy, multiple pregnancy, and birth weight were not significantly different. Funnel plot showed low risk of publication bias, but four of the nine studies had unclear risk of bias. The authors note the main limitation of the study is high heterogeneity (;<0.001, I^2=79%). The quality of the evidence for live births was deemed moderate.

Chromosomal mosaicism occurs when two or more distinct cell populations are present in the same embryo. Mosaicism is common, occurring in up to 80% of embryos using next generation sequencing (NGS) for PGT.[37] There have been conflicting reports of the impact of mosaicism on pregnancy outcomes, and some people have no embryos without mosaicism available for transfer. Further, healthy babies have been born after mosaic embryo transfer. [37 38] Wang (2023) published a systematic review and meta-analysis of transfer outcomes of aneuploid mosaicism after PGT-A between 2016 and 2021 in China. [37] The authors reported institutional data from 448 women and meta-analysis was performed with data from five other studies. The focus was on the effects of aneuploid mosaicism, especially single chromosome abnormality subtypes, on reproductive outcomes. Outcomes of interest were implantation, ongoing pregnancy, and miscarriage. Implantation and clinical pregnancy rates were lower in single aneuploid embryos compared to euploid embryos for all single aneuploidy subtypes (implantation: whole chromosome loss (WCL), p<0.00001; whole chromosome gain (WCG), p=0.002; chromosome segment gain (CSG), p=0.001; chromosome segment loss (CSL), p=0.002; clinical pregnancy: WCL, p<0.00001**;** WCG, p=0.0007; CSG, p=0.0001; CSL p<0.0001). Miscarriage rates were higher with WCL (p=0.0007) and SCL (p=0.03) compared to euploid embryos, but differences in WSG (p=0.27) and CSG (p=0.22) were not significant. Maternal age >35 years was associated with lower rates of implantation and clinical pregnancy

for every subtype of single aneuploid abnormality compared to euploid. However, for miscarriage, WCL was the only aneuploid subtype associated with maternal age >35 years (p=0.0001). Maternal age ≤35 years was varied in its associations of implantation, clinical pregnancy, and miscarriage rates by single aneuploid subtype. Comparisons of mosaic ratio to euploid embryos found that higher level mosaic ratio (>30% to 60%) was associated with reduced implantation and clinical pregnancy in all aneuploid subtypes (implantation: WCG (p=0.005), WCL (p<0.00001), CSG (p=0.03) and CSL (p=0.002; clinical pregnancy: WCG (p=0.001), WCL (p<0.00001), CSG (p=0.009), and CSL (p<0.0001). WCL was associated with increased miscarriage rates at both lower-level (≤30%) and higher-level mosaic ratios (higher level, p=0.04; lower level, p=0.007). Bias was not addressed in the meta-analysis. The authors did not address limitations of the study.

Using three of the same studies as Wang (2023), Ma (2022) performed a systematic review and meta-analysis focused on pregnancy outcomes after mosaic embryo transfers.[38]. Twelve studies were included in the systematic review and six of those were included in the meta-analysis. The six studies involved 1106 transfer cycles. Three studies used NGS platforms for PGT, two used array comparative genome hybridization (cCGH), and one reported on a combination of NGS and cCGH data. Comparison of mosaicism level <50% to ≥50% found improved rates of implementation and fewer miscarriages at mosaicism levels <50% [Implementation: OR 1.42, 95% CI (1.06, 1.89); Miscarriage: OR 0.45, 95% CI (027, 0.75)]. There was no significant difference between embryos with one mosaic chromosome compared to two, but embryos with three or more mosaic chromosomes had worse outcomes than embryos with single chromosome mosaicism [Implementation rate: OR 1.76, 95% CI (1.23, 2.52) Miscarriage rate: OR 0.78, 95% CI (0.40, 1.54)]. The authors suggest a 50% mosaicism threshold for embryo transfer. Strengths of the study include low heterogeneity (I^2>50%). The authors note limitations of the study include the lack of prospective studies, and variety of genetic screening platforms involved. Importantly, they point out that there is little information on the children that result from mosaic chromosome transfer. Neither Wang (2023) nor Ma (2022) compare universal screening for PGT-A to no screening, or to screening based on risk factors, such as advanced maternal age.

A number of RCTs evaluating PGS (PGT-A) have been published, and these findings have been summarized in a several systematic reviews and meta-analyses.[39-44] One of the most recent and comprehensive meta-analysis was a Cochrane review published by Cornelisse (2020), which included 13 RCTs involving 2,794 women.[39] 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 aCGH to no PGT-A,[45] while another, by Munné (2019, described below) compared PGT-A with the use of NGS–based genome-wide analyses to no PGT-A.[46] 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.

A systematic review and meta-analysis by Shi (2021) evaluated PGS specifically in the setting of advanced maternal age, with a comparison between FISH and newer technologies. The meta-analysis included nine RCTs, six of which had high or unclear risk of bias in at least one domain. These studies had differing definitions of advanced maternal age, which generally ranged from 35 to 44 years of age. The pooled analysis of all nine trials showed no difference

in live birth rate (risk ratio [RR] 1.01, 95% CI 0.75 to 1.35), though an analysis restricted to the three studies that used comprehensive chromosome screening technology, including real-time qPCR, aCGH, and NGS, found a higher birth rate in those randomized to PGS (RR 1.30, 95% CI 1.03 to 1.65).

In meta-analysis limited to PGT-A with comprehensive chromosomal screening conducted on day 3 or day 5, Simopoulou (2021) identified 11 RCTs.[47] 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

A randomized trial by Yan (2021) evaluated the impact of PGT-A on live birth rate in subfertile women between 20 and 37 years of age.[48] The trial included 1,212 patients who were considered to have a “good prognosis for a live birth,” were planning to undergo their first IVF cycle, and had at least three good-quality blastocysts. The patients were randomized 1:1 to receive PGS or standard IVF, and the primary outcome was live births within one year of randomization from up to three embryo transfers. The proportion of patients with the primary outcome was 77.2% (468) in the PGS group and 81.8% (496) in the control group, which met the prespecified noninferiority margin of a 7% difference.

Hu (2024) published a secondary analysis of the Yan (2021) RCT.[49] The study found that when the number of retrieved oocytes was <15, the PGT-A group had a lower cumulative clinical pregnancy loss (CPL) rate than the conventional IVF-embryo transfer (IVF-ET) group (5.9% vs. 13.7%; RR = 0.430; 95% CI, 0.243 – 0.763). However, the PGT-A group also had a lower cumulative live birth rate (CLBR) than the IVF-ET group (75.6% vs.87.1%; RR=0.868; 95% CI, 0.774-0.973). The authors concluded that IVR-ET may be a better choice for patients with a good prognosis, but further research involving larger sample sizes is needed.

Munné (2019) published the results of a multi-center RCT called the Single Embryo Transfer of Euploid Embryo (STAR) study.[46] 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.[45] 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 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).[52] 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 pregnant and multiple gestation rates in in pregnant women under the age of 43 who had blastocysts tested by qPCR-based comprehensive chromosome screening (CCS) versus no screening.[53] 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.[54] 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.[55] 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.[56] 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.

Nonrandomized Studies

There have been many nonrandomized studies of PGS, however, the conclusions that can be drawn from these are limited by study design and they are not discussed in detail.[24 32 57-62]

Section Summary

Most RCTs and meta-analyses of RCTs of initial techniques used for PGT-A found similar or lower ongoing pregnancy and/or live birth rates after IVF with PGT-A compared with IVF without PGT-A. These initial PGT-A tests were not found to improve the net health outcome. Three RCTs evaluating newer PGT-A methods have been published, as well as systematic reviews of these trials. Recent studies of newer methods have found some benefit in subgroups of patients (e.g., advanced maternal age); however, the evidence is limited because the studies tended to include good prognosis patients and study methods had potential biases. Well-conducted RCTs evaluating PGT-A 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 2020, the American College of Obstetricians and Gynecologists (ACOG) issued Committee Opinion #799 on Preimplantation Genetic Testing.[63] 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."

In 2015 (reaffirmed in 2017), 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.[64]

AMERICAN SOCIETY FOR REPRODUCTIVE MEDICINE

In 2024, the American Society for Reproductive Medicine published an updated committee opinion on the use of preimplantation testing for aneuploidy. The opinion states:[65]

> The value of PGT-A as a routine screening test for all patients undergoing in vitro fertilization has not been demonstrated. Although some earlier single-center studies reported higher live-birth rates after PGT-A in favorable-prognosis patients, recent multicenter, randomized control trials in women with available blastocysts concluded that the overall pregnancy outcomes via frozen embryo transfer were similar between

> PGT-A and conventional in vitro fertilization. The value of PGT-A to lower the risk of clinical miscarriage is also unclear, although these studies have important limitations.

In 2023, the American Society for Reproductive Medicine published a joint practice committee opinion with the Genetic Counseling Professional Group on the clinical management of mosaic results from preimplantation genetic testing for aneuploidy of blastocysts, which states:[66]

> The value of preimplantation genetic testing for aneuploidy (PGT-A) as a universal screening test for all patients undergoing in vitro fertilization (IVF) has not been established. Indeed, two randomized controlled trials have shown no benefit of PGT-A in improving live birth rates, particularly in women <38 years of age. Nonetheless, the use of PGT-A has continued to increase in the US. In particular, the significance of suspected chromosomal mosaicism in embryos has been a widely discussed and controversial topic since the first known live births from these embryos were documented in 2015. Although previous interpretations of mosaic results and patient counseling relied heavily on prenatal and pediatric literature about mosaicism, a growing body of evidence suggests that these data may not apply to preimplantation embryos.

The committee opinion also states:

> True embryonic mosaicism has long been recognized as a potential limiting factor in the interpretation of PGT-A and as a contributing factor in misdiagnosis related to biopsy sample size. Suspected mosaicism has typically gone undetected or unreported with prior methods of PGT-A, such as fluorescent in situ hybridization, which tested single cells, and array comparative genomic hybridization, as well as the single nucleotide polymorphism microarray (currently in use). With more recent and sensitive assays, such as NGS, it has become increasingly common to identify and report results consistent with an intermediate copy number. Further, the opinion states, “The frequency and clinical relevance of mosaicism have been the subject of much debate.”

Also in 2023, the American Society of Reproductive Medicine published a committee opinion; The Indications and Management of Preimplantation Genetic Testing for Monogenic Conditions:[67]

- Preimplantation genetic testing for monogenic conditions should be offered if a significant reproductive risk is identified. Acceptance of PGT-M by patients should be optional.
- Preimplantation genetic testing should not be offered for autosomal recessive carrier status without manifestations of symptoms, combination of variants not associated with disease, pseudodeficiency alleles, or somatic-only variants.
- Patients should have genetic counseling about the condition and all reproductive options before PGT-M is performed.
- Patients may also benefit from genetic counseling about PGT-M results, particularly when making embryo transfer decisions.
- Given technical limitations that may result in embryo misdiagnosis, prenatal testing should be offered for pregnancies conceived using PGT-M to confirm the embryo

testing results and screen for other fetal anomalies unrelated to the indication for PGT-M.

- Although PGT laboratory genetic counselors support providers and patients in the PGT-M process, IVF clinics should consider employing genetic counselors to result in smoother case management, more efficient workflows, and improved patient experiences.

SUMMARY

There is enough research to show that preimplantation genetic testing for monogenic disorders (PGT-M) and structural chromosomal rearrangements (PGT-SR) 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, PGT-M and PGT-SR 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 testing for monogenic disorders (PGT-M) or structural rearrangements (PGT-SR) 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 PGT-M and PGT-SR will impact outcomes in these situations. Therefore, PGT-M and PGT-SR are considered investigational when the policy criteria are not met.

There is not enough research to show that preimplantation genetic testing for aneuploidy (PGT-A) improves health outcomes, including pregnancy and live birth rates. Recent studies of newer methods have found some benefit in subgroups of patients (e.g., advanced maternal age); however, the evidence is limited, and larger trials are needed to understand how to use the information on ploidy PGT-A provides to improve patient outcomes. Therefore, preimplantation genetic testing for aneuploidy as a part of the in vitro fertilization process is considered investigational in all situations.

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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
	~~0396U~~	~~Obstetrics (pre-implantation genetic testing), evaluation of 300000 DNA single-nucleotide polymorphisms (SNPs) by microarray, embryonic tissue, algorithm reported as a probability for single-gene germline conditions~~ (Deleted 10/01/2024)
	0552U	Reproductive medicine (preimplantation genetic assessment), analysis for known genetic disorders from trophectoderm biopsy, linkage analysis of disease-causing locus, and when possible, targeted mutation analysis for known familial variant, reported as low-risk or high-risk for familial genetic disorder
	0553U	Reproductive medicine (preimplantation genetic assessment), analysis of 24 chromosomes using DNA genomic sequence analysis from embryonic trophectoderm for structural rearrangements, aneuploidy, and a mitochondrial DNA score, results reported as normal/balanced (euploidy/balanced), unbalanced structural rearrangement, monosomy, trisomy, segmental aneuploidy, or mosaic, per embryo tested
	0554U	Reproductive medicine (preimplantation genetic assessment), analysis of 24 chromosomes using DNA genomic sequence analysis from trophectoderm biopsy for aneuploidy, ploidy, a mitochondrial DNA score, and embryo quality control, results reported as normal (euploidy), monosomy, trisomy, segmental aneuploidy, triploid, haploid, or mosaic, with quality control results reported as contamination detected or inconsistent cohort when applicable, per embryo tested
	0555U	Reproductive medicine (preimplantation genetic assessment), analysis of 24 chromosomes using DNA genomic sequence analysis from embryonic trophectoderm for structural rearrangements, aneuploidy, ploidy, a mitochondrial DNA score, and embryo quality control, results reported as normal/balanced (euploidy/balanced), unbalanced structural rearrangement, monosomy, trisomy, segmental aneuploidy, triploid, haploid, or mosaic, with quality control results reported as contamination detected or inconsistent cohort when applicable, per embryo tested
	81228	Cytogenomic (genome-wide) analysis for constitutional chromosomal abnormalities; interrogation of genomic regions for copy number variants, comparative genomic hybridization [CGH] microarray analysis
	81229	Cytogenomic (genome-wide) analysis for constitutional chromosomal abnormalities; interrogation of genomic regions for copy number and single nucleotide polymorphism (SNP) variants, comparative genomic hybridization (CGH) microarray analysis
	81349	Cytogenomic (genome-wide) analysis for constitutional chromosomal abnormalities
	81479	Unlisted molecular pathology procedure
	88271 – 88275	Molecular cytogenetics (i.e., FISH), code range

Codes	Number	Description
	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	

Date of Origin: *August 2010*