Preimplantation Genetic Testing and Related Services (for Ohio Only)

Policy Number: CS160OH.D
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Instructions for Use

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Related Policies

- Cell-Free Fetal DNA Testing (for Ohio Only)
- Chromosome Microarray Testing (Non-Oncology Conditions) (for Ohio Only)

Application

This Medical Policy only applies to the state of Ohio. Any requests for services that are stated as unproven or services for which there is a coverage or quantity limit will be evaluated for medical necessity using Ohio Administrative Code 5160-1-01.

Coverage Rationale

Preimplantation Genetic Testing (PGT) may be medically necessary in certain circumstances. For medical necessity clinical coverage criteria, refer to the InterQual® CP: Molecular Diagnostics:

- Alpha-1 Antitrypsin Deficiency (AATD)
- Alzheimer's Disease
- Angelman Syndrome (AS)
- Beckwith-Wiedemann Syndrome (BWS)
- Bloom's Syndrome
- Canavan Disease
- Charcot-Marie-Tooth (CMT) Hereditary Neuropathy
- Congenital Factor XIII Deficiency
- Craniofrontonasal Syndrome (EFNB1)
- Duchenne Becker Muscular Dystrophy (DBMD)
- EFEMP2-Related Cutis Laxa
- Familial Dysautonomia (FD)
- Fanconi Anemia (FA)
- FMR1 Related Disorders (Fragile X Syndrome)
- Gaucher Disease
- Genetic Testing for Hereditary Cardiomyopathy
- Glycogen Storage Disease Type I (GSDI)
- Hemophilia A
- Hemophilia B
- Hereditary Hearing Loss
- Huntington Disease (HD)

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- Li-Fraumeni Syndrome (LFS)
- Long QT Syndrome (LQTS)
- Maple Syrup Urine Disease (MSUD)
- Marfan Syndrome
- MUTYH-Associated Polyposis (MAP)
- Neurofibromatosis 1 (NF1)
- Niemann-Pick Disease Type A and B
- Pompe Disease (Glycogen Storage Disease Type II)
- Prader-Willi Syndrome (PWS)
- Retinoblastoma
- Spinal Muscular Atrophy (SMA)
- Tay-Sachs Disease
- Trisomy 13 (Patau syndrome)
- Trisomy 18 (Edwards syndrome)
- Trisomy 21 (Down syndrome)
- Urea Cycle Disorder
- Whole Genome Sequencing (WGS), Whole Exome Sequencing (WES), and Chromosomal Microarray (CMA) for Congenital or Hereditary Disorders

Click here to view the InterQual® criteria.

Preimplantation Genetic Testing (PGT) is proven and medically necessary using polymerase chain reaction (PCR), next generation sequencing (NGS) (e.g., chromosomal rearrangements), or chromosomal microarray (CMA) for the following:

- The embryo is at increased risk of a recognized inherited disorder with both of the following:
  - The increased risk of a recognized inherited disorder is due to one of the following:
    - Each of the intended parents are carriers of the same autosomal recessive disease
    - At least one parent is a carrier of an autosomal dominant, sex-linked, or mitochondrial condition
    - At least one parent is a carrier of a structural chromosome rearrangement
  - The medical condition being prevented must result in Significant Health Problems or Severe Disability and be caused by a single gene (PGT-M) or structural changes of a parents' chromosome (PGT-SR)

PGT is proven and medically necessary for human leukocyte antigen (HLA) typing on an embryo in order for the future child to provide bone marrow or blood to treat an affected sibling.

PGT is unproven and not medically necessary for all other populations and conditions due to insufficient evidence of efficacy. This includes but is not limited to PGT using CMA, PCR, or NGS for the following:

- Aneuploidy screening (PGT-A)
- Determining gender when the embryo is not at risk for a sex-linked disorder
- Predicting risk of polygenic disorders (PGT-P) and/or embryo selection based on polygenic scores (ESPS)

Note: PGT must be ordered after genetic counseling.

Definitions

Preimplantation Genetic Testing (PGT): A test performed to analyze the DNA from oocytes (polar bodies) or embryos (cleavage stage or blastocyst) for human leukocyte antigen (HLA) typing or for determining genetic abnormalities. These include:

- PGT-A: For aneuploidy screening [formerly preimplantation genetic screening (PGS)]
- PGT-M: For monogenic/single gene defects [formerly single-gene preimplantation genetic diagnosis (PGD)]
- PGT-SR: For chromosomal structural rearrangements [formerly chromosomal preimplantation genetic diagnosis (PGD)]

(Zegers-Hochschild et al., 2017)

Significant Health Problems or Severe Disability: A disability or impairment that is physical or mental and substantially limits one or more major life activities. The impairment is expected to last at least 12 months or result in death. (Department of Labor; Office of Disability Employment Policy; Federal Government Definition for Social Security Disability Benefits)

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Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by federal, state, or contractual requirements and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

Coding Clarification: For preimplantation genetic testing related services, refer to the codes identified below with an asterisk (*).

CPT Code	Description
0254U	Reproductive medicine (preimplantation genetic assessment), analysis of 24 chromosomes using embryonic DNA genomic sequence analysis for aneuploidy, and a mitochondrial DNA score in euploid embryos, results reported as normal (euploidy), monosomy, trisomy, or partial deletion/duplication, mosaicism, and segmental aneuploidy, per embryo tested
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; interrogation of genomic regions for copy number and loss-of-heterozygosity variants, low-pass sequencing analysis
81479	Unlisted molecular pathology procedure
*89290	Biopsy, oocyte polar body or embryo blastomere, microtechnique (for pre-implantation genetic diagnosis); less than or equal to 5 embryos
*89291	Biopsy, oocyte polar body or embryo blastomere, microtechnique (for pre-implantation genetic diagnosis); greater than 5 embryos
Related Services	
*58970	Follicle puncture for oocyte retrieval, any method
*58974	Embryo transfer, intrauterine
*76948	Ultrasonic guidance for aspiration of ova, imaging supervision and interpretation
*89250	Culture of oocyte(s)/embryo(s), less than 4 days
*89251	Culture of oocyte(s)/embryo(s), less than 4 days; with co-culture of oocyte(s)/embryos
*89253	Assisted embryo hatching, microtechniques (any method)
*89254	Oocyte identification from follicular fluid
*89255	Preparation of embryo for transfer (any method)
*89257	Sperm Identification from aspiration (other than seminal fluid)
*89258	Cryopreservation; embryo(s)
*89260	Sperm isolation: simple prep (e.g., sperm wash and swim-up) for insemination or diagnosis with semen analysis
*89261	Sperm isolation: complex prep (e.g., Percoll gradient, albumin gradient) for insemination or diagnosis with semen analysis
*89264	Sperm identification from testis tissue, fresh or cryopreserved
*89268	Insemination of oocytes
*89272	Extended culture of oocyte(s)/embryo(s), 4-7 days
*89280	Assisted oocyte fertilization, microtechnique; less than or equal to 10 oocytes
*89281	Assisted oocyte fertilization, microtechnique; greater than 10 oocytes
*89342	Storage (per year); embryo(s)

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CPT Code	Description
Related Services	
*89352	Thawing of cryopreserved; embryo(s)

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HCPCS Code	Description
*S4011	In vitro fertilization; including but not limited to identification and incubation of mature oocytes, fertilization with sperm, incubation of embryo(s), and subsequent visualization for determination of development
*S4015	Complete in vitro fertilization cycle, not otherwise specified, case rate
*S4016	Frozen in vitro fertilization cycle, case rate
*S4022	Assisted oocyte fertilization, case rate
*S4037	Cryopreserved embryo transfer, case rate

Description of Services

Genetic counseling is strongly recommended prior to Preimplantation Genetic Testing (PGT) to inform persons being tested about the advantages and limitations of the test as applied to their unique situation.

PGT is an analysis performed on an embryo, prior to transfer, to screen for aneuploidy (PGT-A), deletions and duplications of genomic material [generally referred to as copy number variations (CNVs)] or structural rearrangements (PGT-SR), and/or analysis of single-gene or other inherited disorders (PGT-M) [American College of Obstetricians and Gynecologists (ACOG), 2020, reaffirmed 2023]. Use of this technology has been theorized to increase the success of infertility treatment (Yan et al., 2021), especially in women who have worse outcomes due to advanced maternal age, history of recurrent miscarriage, failed in vitro fertilization (IVF), or a balanced chromosome translocation. In addition, PGT has been explored as a way to enable single embryo transfer (SET) rather than using multiple embryos to increase the odds of having a successful pregnancy without the risk of a multiple gestation (ACOG, 2020, reaffirmed 2023).

Clinical Evidence

Preimplantation Genetic Testing for Aneuploidy Screening (PGT-A)

There is insufficient evidence to support the use of PGT for aneuploidy screening at this time. Findings from higher quality studies are conflicting. Further studies focused on clinical utility and the development of algorithms to identify populations for which this testing may be beneficial are needed.

Mumusoglu et al. (2025) conducted a systematic review and meta-analysis to assess the utility of PGT-A in managing unexplained RPL. Studies involving individuals with two or more spontaneous pregnancy losses that underwent ART with or without PGT-A were included, and the primary outcome assessed was LBR. Rates of aneuploidy, clinical pregnancy, and clinical pregnancy loss were also evaluated. After exclusion criteria were applied, a total of 18 studies were incorporated in this evaluation. The meta-analysis indicated that the transfer of euploid blastocysts led to comparable pregnancy loss rates and LBRs in individuals with and without unexplained RPL (OR, 1.10; 95% CI 0.57-2.13 and OR, 1.04; 95% CI 0.74-1.44, respectively). Additionally, chromosome analysis of products of conception showed similar rates of aneuploidy among participants with and without RPL. The use of PGT-A reduced the clinical pregnancy loss rate (OR, 0.42; 95% CI 0.27-0.67), while improving the LBR per transfer (OR, 2.17; 95% CI, 1.77-2.65) and per participant (OR, 1.85; 95% CI, 1.18-2.91) in those with unexplained RPL. The authors speculate that individuals with adequate ovarian reserve undergoing ART may find PGT-A beneficial because it potentially increases the number of gametes available for conception, which could reduce the time to live birth. Although this study yielded promising results for individuals with unexplained RPL, further high-quality RCTs comparing ART including PGT-A to standard management for unexplained RPL are needed.

To investigate whether individuals with recurrent pregnancy failure (RPF) who had undergone PGT-A achieved better clinical outcomes than those who did not have PGT-A, Liang et al. (2023) performed a systematic review and meta-analysis of 13 studies including 930 individuals for whom PGT-A had been performed and at least 1434 individuals who did not receive this testing. In the PGT-A group, 1015 ETs were completed. In the group that did not have PGT-A, 1799 embryos were transferred successfully. The analysis yielded evidence of superior clinical outcomes in the PGT-A group with improvements in implantation rate [RR = 2.01, 95% CI, (1.73; 2.34)], clinical pregnancy rate [RR = 1.53, 95% CI, (1.36; 1.71)], OPR [RR = 1.76, 95% CI, (1.35; 2.29)], and LBR [RR = 1.75, 95% CI, (1.51; 2.03)]. The PGT-A group also

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had a significantly lower rate of miscarriage [RR = 0.74, 95% CI, (0.54; 0.99)]. In a subgroup analysis focused on age, PGT-A resulted in better clinical pregnancy rates and LBRs for individuals both under the age of 35 and those 35 years and older, when compared with individuals who did not have PGT-A ($p < 0.01$ and $p < 0.05$, respectively). The researchers assert that their findings strengthen the evidence for the use of PGT-A in individuals with RPF. Several limitations are noted, including the somewhat small number of studies included (especially for subgroup analyses), and the lack of comprehensive raw data. In addition, a high risk of bias related to the blinding of personnel and participants in the included RCTs was noted. Further high-quality controlled trials with larger and more varied populations are needed to support the use of PGT-A in individuals with RPF.

In a retrospective cohort study, Kucherov et al. (2023) analyzed the impact of PGT-A on CLBR when used in IVF cycles. Data from the Society for Assisted Reproductive Technology Clinical Outcome Reporting System (SART CORS), a national registry including over 85% of U.S. programs performing IVF, was used to compare CLBR for individuals using autologous oocytes either with or without PGT-A. Donor oocyte cycles, donor embryo cycles, gestational carrier cycles, cycles where both fresh ET and thawed embryo which had previously been frozen (ET plus FET) or cycles using fresh ET after PGT-A were excluded from the study. In all, 133,494 IVF cycles were evaluated. A decrease in CLBR was found in the PGT-A group across age groups with the exception of individuals over 40 years ($p < 0.01$). The researchers performed a subgroup analysis of only individuals who had undergone FET subsequent to PGT-A (not including those where no embryos were transferrable) and found a very high CLBR (ranging from 71.2% for individuals less than 35 years old to 50.2% for individuals over 42 years old). Of note, rates for PTB, early pregnancy loss, multiple gestations, and LBW were greater in the group that had not undergone PGT-A. The study was limited by its retrospective design, impacting its use for demonstration of causal relationships, and had missing and/or outlier data points. The researchers concluded that overall, for individuals 40 years of age or younger with blastocysts available for ET or PGT-A, there was an association between PGT-A and decreased CLBR which was notably higher for individuals under 35 years of age. They further state that PGT-A may show utility for individuals with advanced maternal age and may be associated with lower rates of miscarriage. For the most accurate individual outcome measure, the authors recommend the use of CLBR per cycle vs. first transfer LBR when determining utility of PGT-A. Lastly, the importance of counseling regarding utility of PGT-A based not only on maternal age, but potential miscarriage benefit is stressed.

In a 2022 systematic review and meta-analysis (Cheng et al.), pregnancy outcomes of individuals undergoing IVF either with or without PGT-A were compared. Nine RCTs including 3,334 individual participants were included in the review. The analysis found that PGT-A was not related to an increase in LBR overall (RR 1.13, 95% CI 0.96-1.34, $I^2 = 79\%$), but it was associated with an increase in the LBR for those with advanced maternal age (RR 1.34, 95% CI 1.02-1.77, $I^2 = 50\%$). In addition, PGT-A was related to a decreased miscarriage rate (RR 0.53, 95% CI 0.35-0.81; $I^2 = 50\%$). The primary limitation of the study is the high level of heterogeneity of the studies included ($p < .001$, $I^2 = 79\%$). Subgroup analysis identified age as the main factor leading to the high heterogeneity. Based on the study results, the authors posit that PGT-A increases LBR for individuals of advanced maternal age. Publications by Yan et al. (2021) and Verpoest et al. (2018), previously discussed in evidence, were included in this systematic review.

The use of PGT-A in individuals with RPL was the focus of a retrospective study performed by Bhatt et al. (2021, included in Mumusoglu 2025 systematic review) using data from SART CORS. The researchers aimed to discern whether PGT-A was associated with improved LBRs in couples with RPL who were undergoing IVF with frozen embryo transfer (IVF-FET). RPL was defined as a history of at least 3 pregnancy losses. In total, 12,631 FET cycles for 10,060 couples were analyzed, including 4,287 cycles in couples with history of a tubal disease, who formed a control group. Couples with RPL undergoing FET either with or without PGT-A made up the experimental group. The primary outcome of this study was LBR. Rates of clinical pregnancy, spontaneous abortion and biochemical pregnancy loss were secondary outcomes. Results indicated that in this large study, PGT-A was associated with an increase in LBR and clinical pregnancy for individuals with RPL. The greatest difference was seen in individuals older than 42 years. However, because this retrospective study included only individuals with RPL undergoing FET, the results may not be generalizable to all those with RPL. In addition, the data regarding clinical evaluation and treatments received for RPL for the individuals included in the study was not obtainable. The authors encourage counseling on all options for management of RPL which may include IVF with PGT-A for embryo selection to increase the chance of live birth, especially for those individuals with advanced maternal age.

Simopoulou et al. (2021) published a systematic review and meta-analysis of RCTs focusing on identification of age group(s) that may benefit from PGT-A and the best day to perform biopsy for the testing. A systematic literature search identified 11 RCTs using PGT-A with comprehensive chromosomal screening (CCS) on either day three or day five that met eligibility criteria. After analysis, the researchers found that PGT-A was not related to improved LBRs per individual in the overall population (RR: 1.11; 95% CI: 0.87-1.42; n = 1,513; $I^2 = 75\%$), but it was associated with lower miscarriage rates (RR: 0.45; 95% CI: 0.25-0.80; n = 912; $I^2 = 49\%$). Notably, however, PGT-A was associated with improved cumulative LBR per individual (RR: 1.36; 95% CI: 1.13-1.64; n = 580; $I^2 = 12\%$). In subgroup analysis, PGT-A was

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associated with a higher LBR for individuals older than 35 years (RR: 1.29; 95% CI: 1.05-1.60; n = 692; I^2 = 0%) but did not have this association for younger individuals (RR: 0.92; 95% CI: 0.62-1.39; n = 666; I^2 = 75%). In terms of timing, day five biopsies showed an improved LBR per ET (RR: 1.37; 95% CI: 1.03-1.82; I^2 = 72%). The authors concluded that while PGT-A did not appear to improve outcomes for the overall population, it was associated with improved LBRs when performed on blastocyst stage embryos in individuals over the age of 35 years. However, the number of studies included in the meta-analysis was relatively small and the ages of most of the individuals included were not necessarily representative of individuals who commonly undergo PGT-A testing. The researchers encourage further study to evaluate characteristics of individuals that may benefit from PGT-A and focus on developing an algorithm to assist with decision making regarding the appropriate population for PGT-A use.

In a 2021 publication, Tiegs et al. reported the outcome of their prospective, multicenter, blinded, non-selection study to evaluate the value of a diagnosis of aneuploidy [made via targeted NGS PGT-A] in predicting failure of a successful delivery. A secondary outcome measured was the impact of TE biopsy on lasting implantation. A total of 402 individuals with infertility received 484 single, frozen blastocyst transfers. Unblinded PGT-A results performed using NextSeq 500/550 NGS-based PGT-A were compared to clinical outcomes of ETs and a calculation of predictive values was made. Significant difference in outcome by PGT-A diagnosis was found: 64.7% (202/312) of euploid embryos progressed to either sustained implantation or delivery while none of the 102 embryos diagnosed as whole chromosome aneuploid progressed to either sustained implantation or delivery. Thus, the clinical error rate in aneuploid diagnoses was 0%. There was no difference in sustained implantation between the control group, which was aged matched and had not undergone biopsy, and the PGT-A testing group. The authors assert that the PGT-A assay evaluated was found to be prognostic of failure to deliver when such testing revealed an aneuploid result and did not result in the discard of embryos that had significant reproductive potential. They do, however, note limitations, including the inability to analyze predictive values associated with segmental PGT-A or whole chromosome mosaic diagnoses due to the low incidence of those results. Additionally, the retrospective identification of a control group to evaluate impact of cell biopsy on sustained implantation limits the study's strength. Lastly, about half of the study subjects were less than 35 years of age; however, the false positive rates of aneuploidy are typically higher in this group compared with older subjects, so this may have further challenged the accuracy of the assay used in this study. The researchers recommend non-selection studies be performed for every new PGT-A assay as additional technologies emerge.

Konstantinidis et al. (2020) studied the incidence and patterns of trisomies and recombination separately and in conjunction with each other at the blastocyst stage by SNP testing with aCGH. SNP microarrays were performed on 1,442 blastocyst embryos from 268 couples who underwent PGT for known single gene disorders; 24-chromosome aneuploidy screening by aCGH was done concurrently. One hundred percent of meiotic trisomies were maternal in origin and incidence increased significantly with maternal age ($p < 0.0001$). Meiosis I trisomies and meiosis II trisomies were 55.8% and 44.2%, respectively. Recombination studies were performed for 11, 476 chromosomes and 17,763 recombination events were reported. The average number of recombination sites was 24.0 ±0.3 for male meiosis and 41.2 ±0.6 for autosomal female meiosis. One hundred ninety euploid embryos and 69 embryos with maternal meiotic trisomies were compared which revealed similar recombination rates ($p = 0.425$) and non-recombinant chromatid rates ($p = 0.435$). Although the study provided unique data regarding recombination and aneuploidies in embryos, further research and data is needed to establish clinical validity and clinical utility.

The effectiveness and safety of PGT-A was evaluated by Cornelisse et al. (2020), who performed a systematic review of six databases and two trial registries in September 2019. Thirteen RCTs involving 2,794 women reporting data on clinical outcomes in individuals who underwent IVF with PGT-A versus IVF without PGT-A were included. The quality of evidence ranged from low to moderate. CLBR was the primary outcome; LBR after first ET, miscarriage rate, OPR, clinical pregnancy rate, multiple pregnancy rate, proportion of women obtaining an ET and mean number of ETs represented the secondary outcomes. The authors' reported results were as follows: One trial used polar body biopsy with aCGH. It is uncertain whether the addition of PGT-A by polar body biopsy increases the CLBR compared to IVF without PGT-A (OR 1.05, 95% CI, 0.66 to 1.66, one RCT, n = 396, low-quality evidence). The evidence suggests that for the observed CLBR of 24% in the control group, the chance of live birth following the results of one IVF cycle with PGT-A is between 17% and 34%. It is uncertain whether the LBR after the first ET improves with PGT-A by polar body biopsy (OR 1.10, 95% CI, 0.68 to 1.79, one RCT, n = 396, low-quality evidence). PGT-A with polar body biopsy may reduce miscarriage rate (OR 0.45, 95% CI, 0.23 to 0.88, one RCT, n = 396, low-quality evidence). No data on OPR were available. The effect of PGT-A by polar body biopsy on improving clinical pregnancy rate is uncertain (OR 0.77, 95% CI, 0.50 to 1.16, one RCT, n = 396, low-quality evidence). Another trial used blastocyst stage biopsy with NGS. It is uncertain whether IVF with the addition of PGT-A by blastocyst stage biopsy increases CLBR compared to IVF without PGT-A, since no data were available. It is uncertain if LBR after the first ET improves with PGT-A with blastocyst stage biopsy (OR 0.93, 95% CI, 0.69 to 1.27, one RCT, n = 661, low-quality evidence). It is uncertain whether PGT-A with blastocyst stage biopsy reduces miscarriage rate (OR 0.89, 95% CI, 0.52 to 1.54, one RCT, n = 661, low-quality evidence). No data on OPR or clinical pregnancy rate were available. IVF with PGT-A versus IVF without PGT-A with the use of FISH for the genetic analysis: eleven trials were

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included in this comparison. It is uncertain whether IVF with addition of PGT-A increases CLBR (OR 0.59, 95% CI, 0.35 to 1.01, one RCT, n = 408, low-quality evidence). The evidence suggests that for the observed average CLBR of 29% in the control group, the chance of live birth following the results of one IVF cycle with PGT-A is between 12% and 29%. PGT-A performed with FISH probably reduces live births after the first transfer compared to the control group (OR 0.62, 95% CI, 0.43 to 0.91, ten RCTs, n = 1,680, I^2 = 54%, moderate-quality evidence). The evidence suggests that for the observed average LBR per first transfer of 31% in the control group, the chance of live birth after the first ET with PGT-A is between 16% and 29%. There is probably little or no difference in miscarriage rate between PGT-A and the control group (OR 1.03, 95%, CI, 0.75 to 1.41; ten RCTs, n = 1,680, I^2 = 16%; moderate-quality evidence). The addition of PGT-A may reduce OPR (OR 0.68, 95% CI 0.51 to 0.90, five RCTs, n = 1,121, I^2 = 60%, low-quality evidence) and probably reduces clinical pregnancies (OR 0.60, 95% CI 0.45 to 0.81, five RCTs, n = 1,131; I^2 = 0%, moderate-quality evidence). The authors concluded that due to the poor quality of evidence regarding CLBR, LBR after transfer or miscarriage rate between IVF with and IVF without PGT-A, routine clinical practice of PGT-A is not supported.

TE biopsy, a technique to assess aneuploidy for PGT, can result in false positive and false negative test results because the chromosome number in TE cells is not always concordant with the chromosome number of the inner cell mass, which develops into the fetus. Huang et al. (2019b) conducted an investigational study to determine the effectiveness of noninvasive preimplantation genetic testing for aneuploidy (niPGT-A) as compared to the standard TE biopsy method. Fifty-two frozen donated blastocysts were analyzed by next-generation sequencing to serve as a gold standard. TE biopsy PGT-A and niPGT-A results were generated for all samples and compared with sequencing results from corresponding embryos. The false negative rate for niPGT-A was zero. The positive predictive value and specificity were higher for niPGT-A than for TE biopsy PGT-A. In addition, the authors stated that the concordance rates for embryo ploidy and chromosome copy number were also higher for niPGT-A than seen in TE biopsy PGT-A. Based on this study, the authors concluded that niPGT-A by DNA sequencing of DNA released in culture media from both TE and ICM provides a non-invasive method which is less prone to errors linked to embryo mosaicism, though future studies with larger sample sizes are necessary.

Munné et al. (2019) conducted a multicenter RCT (the Single Embryo Transfer of Euploid Embryo [STAR] study) to assess the benefit of PGT-A when used to select embryos for frozen-thawed ET. A total of 661 individuals 25–40 years (average age 33.7 ±3.6 years) undergoing IVF using autologous oocytes with at least two blastocysts of adequate quality for biopsy and vitrification by day six were enrolled in the study; participants were enrolled from 34 clinics and tested in nine laboratories across the U.S., Canada, the U.K., and Australia. Three hundred thirty participants were randomized to the arm of the trial using PGT-A for selection of embryos and 331 were randomized to the control arm using morphology alone for embryo selection. Participants, physicians, and IVF clinical staff (not the embryologists) were blinded to the participant's randomization status. The primary outcome was OPR at 20 weeks' gestation per ET. In the PGT-A group, 274 participants (83.0%) received the planned treatment, and in the control group 313 (94.6%) received the planned treatment. Some randomized participants did not receive their planned treatment for various reasons including lack of euploid embryos, withdrawal from the study, thaw failure, or deviation from protocol. Noted was that the frequency of lack of euploid embryos increased with maternal age. After analysis, the OPR was found to be comparable between the PGT-A group and the control group, with no significant difference found per ET (50% [137/274] vs 46% [143/313]) or per intention to treat (ITT) at time of randomization (41.8% [138/330] vs 43.5% [144/331]). In addition, the rates of negative b-hCG, biochemical pregnancy, miscarriage, and elective termination per ET did not demonstrate significant differences between study arms. A post hoc subgroup analysis showed a higher OPR in women aged 35–40 years after PGT-A (51% [62/122] vs. 37% [54/145]) per ET but not per ITT. Ultimately, the authors concluded that PGT-A did not lead to improved overall pregnancy outcomes across all women in the study, whether evaluated per ET or ITT, but did support use of PGT-A for individuals 35-40 years of age to improve outcomes per frozen-thawed ET (though the improvement was not significant when analyzed per ITT). They expressed surprise that in spite of detecting a relatively high rate of aneuploidy in both the control and PGT-A arms of the study, PGT-A did not appear to improve the rate of implantation or OPG per ET in the younger participants. Since the IVF laboratory staff was not blinded to study participation or assigned group, it is possible that more embryos of lesser quality were biopsied and vitrified because of study participation that otherwise may have been discarded. This could have contributed to the failure to achieve a greater benefit of PGT-A and represents a potential limitation of the study. In addition, the targeted sample size of 300 transfers/study arm was not reached, primarily due to lack of sufficient euploid embryos in the PGT-A arm, and there was no control of participant demographics; more than half of participants were younger than 35 years, which is considerably younger than is experienced in most fertility clinics. This trial highlighted the difficulties of large, multicenter RCTs in complex medical treatments such as IVF and underscored the importance of fully vetting novel diagnostics and laboratory procedures prior to implementation in standard clinical practice.

Zore et al. (2019) compared the outcomes of frozen SET between euploid embryos and those with segmental mosaicism. Three hundred and twenty-seven women had 377 FETs. All embryos underwent biopsy at the blastocyst stage where two or more cells were taken from the TE. CGH was used to determine if embryos were euploid or had segmental mosaicism.

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Three hundred and fifty-seven were euploid, and 20 had segmental mosaicism. The spontaneous miscarriage rate was 18.2% in euploid embryos, compared to 40% in segmental mosaic embryos. Furthermore, the LBR for euploid embryos was 53.8%, whereas for segmental mosaics the LBR was 30%. The authors concluded that reporting segmental mosaicism was important to help with selection of embryos for transfer, and noted that although reduced, segmental mosaics still had the potential to result in a live birth.

Friedenthal et al. (2018) evaluated the difference in pregnancy outcomes using NGS compared to CGH for PGT-A in single frozen thawed transferred embryos (STEET) in a retrospective review. A total of 916 STEET cycles from 2014 to 2016 were reviewed, and included 548 NGS cases, and 368 cases using CGH. The outcomes analyzed included implantation rate, LBR, and miscarriage rate. The NGS group had a higher implantation rate (72% vs. 65%) than CGH, and a higher LBR compared to CGH (62% vs. 54%). The miscarriage rate was similar between the two groups. The authors concluded that NGS was better at detecting reduced viability embryos caused by mosaicism and using NGS may result in better pregnancy outcomes when compared to using CGH.

Barad et al. (2017) conducted a retrospective analysis of the impact of PGT-A on pregnancy outcomes in donor oocyte-recipient cycles. The authors utilized the data obtained between 2005 and 2013, from the Society for Assisted Reproductive Technology Clinic Outcome Reporting System. This database relies on voluntary reporting, and 90% of the US IVF centers participate. In this cohort, first ETs with day 5/6 embryos were reviewed, for a total of 20,616 control cycles and 392 PGT-A cycles. The data showed that the pregnancy and LBRs were lower in the PGT-A group by 35% when compared to the control group. The authors concluded that PGT-A was not associated with improved odds of pregnancy, live birth, or miscarriage rate.

Gleicher et al. (2017) addressed the issue of TE mosaicism . The authors developed two models to assess the likelihood of false positive and false negative results on an average six cell biopsy from a 300 cell TE, with the understanding that TE biopsies often include only one cell. The models assumed that mosaicism was distributed evenly throughout the TE, even though in reality it is often clonal. In their first model that examined the probability of a false negative with results from one or more euploid cells, they determined that there is a high probability of selecting a euploid cell, even when the ratio of euploid cells is low. In the second model, the probability of a false positive from an aneuploid result was examined. The authors found that even with 1-2 cells being aneuploidy, the embryo could theoretically still be mostly euploid. When three cells were found to be aneuploid, it is mathematically more likely consistent with embryo aneuploidy. The author's goal was to examine, through mathematical modeling the likely reliability of being able to choose or discard an embryo based on ploidy results of a single cell TE biopsy. They concluded that mathematically, one cannot use the results of a single cell to determine the ploidy of an embryo, and therefore cannot reliably predict which embryos should be used or discarded.

Capalbo et al. (2015) compared SNP based microarray screening, aCGH, and qPCR techniques for screening embryos. The authors conducted a prospective double-blind observational study from Oct. 2012-Dec. 2013. TE biopsies were done on day 5-6. Forty-five participants with indications of advanced maternal age, recurrent miscarriage, or parental carrier of a balanced translocation were included. A total of 124 blastocysts underwent aCGH. Of these, 122 survived warming and re-expansion and underwent TE biopsy and qPCR analysis. Two samples failed qPCR and were excluded. Eighty-two percent of embryos showed the same diagnosis between aCGH and qPCR and 18% were discordant for at least one chromosome. Discordant blastocysts were warmed and TE was biopsied again on 21 embryos that survived another rewarming and underwent a blinded SNP array analysis. A conclusive result was obtained in 18 of the 21. In four of these, the qPCR, aCGH, and SNP array did not match and were considered mosaic aneuploid. Overall, when the data is viewed per chromosome, the aCGH and qPCR results were consistent in 99.9% of cases where both methods were performed on TE biopsy from the same embryo. The SNP based reanalysis, however, showed a higher discordant rate between aCGH and qPCR. The authors concluded that TE biopsies can be a highly reliable and effective approach for PGS, and that until aCGH is studied for clinical negative predictive value, this comparative study can only demonstrate that aCGH results in a higher aneuploidy rate than other contemporary and better validated methods of chromosome screening.

U.S. Food and Drug Administration (FDA)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

Laboratories that perform preimplantation genetic testing are regulated by the FDA under the Clinical Laboratory Improvement Amendments. Refer to the following website for more information: https://www.fda.gov/medical-devices/ivd-regulatory-assistance/clinical-laboratory-improvement-amendments-clia. (Accessed December 27, 2024)

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A list of nucleic acid-based tests that have been cleared or approved by the FDA Center for Devices and Radiological Health is available at: https://www.fda.gov/medical-devices/in-vitro-diagnostics/nucleic-acid-based-tests. (Accessed January 28, 2025)

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Policy History/Revision Information

Date	Summary of Changes

06/01/2025	**Related Policies**
	• Added reference link to the Medical Policy titled *Cell-Free Fetal DNA Testing (for Ohio Only)*
	Coverage Rationale
	• Revised list of indications for which Preimplantation Genetic Testing (PGT) is proven and medically necessary using polymerase chain reaction (PCR), next generation sequencing (NGS) (e.g., chromosomal rearrangements), or chromosomal microarray (CMA):
	  ○ Removed:
	  ▪ Alpha-1 Antitrypsin Deficiency (AATD)
	  ▪ Charcot-Marie-Tooth (CMT) Hereditary Neuropathy
	  ▪ Craniofrontonasal Syndrome (EFNB)
	  ▪ MUTYH-Associated Polyposis (MAP)
	  ▪ Neurofibromatosis 1 (NF1)
	  ○ Replaced:
	  ▪ "When the embryo is at increased risk of a recognized inherited disorder due to the parents are carriers of *an* autosomal recessive disease" with "when the embryo is at increased risk of a recognized inherited disorder due to *each of the intended* parents are carriers of *the same* autosomal recessive disease"
	  ▪ "When the embryo is at increased risk of a recognized inherited disorder due to at least one parent is a carrier of a *balanced* structural chromosome rearrangement" with "when the embryo is at increased risk of a recognized inherited disorder due to at least one parent is a carrier of a structural chromosome rearrangement"
	Definitions
	• Added definition of "Significant Health Problems or Severe Disability"
	Applicable Codes
	• Revised description for CPT codes 81228 and 81229
	Supporting Information
	• Updated *Description of Services*, *Clinical Evidence*, *FDA*, and *References* sections to reflect the most current information
	• Archived previous policy version CS160OH.C

Instructions for Use

This Medical Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the federal, state (Ohio Administrative Code [OAC]) or contractual requirements for benefit plan coverage must be referenced as the terms of the federal, state (OAC) or contractual requirements for benefit plan coverage may differ from the standard benefit plan. In the event of a conflict, the federal, state (OAC) or contractual requirements for benefit plan coverage govern. Before using this policy, please check the federal, state (OAC) or contractual requirements for benefit plan coverage. UnitedHealthcare reserves the right to modify its Policies and Guidelines as necessary. This Medical Policy is provided for informational purposes. It does not constitute medical advice.

UnitedHealthcare uses InterQual® for the primary medical/surgical criteria, and the American Society of Addiction Medicine (ASAM) for substance use, in administering health benefits. If InterQual® does not have applicable criteria, UnitedHealthcare may also use UnitedHealthcare Medical Policies, Coverage Determination Guidelines, and/or Utilization Review Guidelines that have been approved by the Ohio Department for Medicaid Services. The UnitedHealthcare Medical Policies, Coverage Determination Guidelines, and Utilization Review Guidelines are intended to be used in

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connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

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