Preimplantation Genetic Testing and Related Services (for Ohio Only)

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Instructions for Use

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Related Policy

- 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 medical necessity 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)
- 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 (e.g., Chromosomal Rearrangements), or chromosomal microarray for the following:
- Alpha-1 Antitrypsin Deficiency (AATD); **or**
- Charcot-Marie-Tooth (CMT) Hereditary Neuropathy; **or**
- Craniofrontonasal Syndrome (EFNB); **or**
- MUTYH-Associated Polyposis (MAP); **or**
- Neurofibromatosis 1 (NF1)

and
- 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:
    - The parents are carriers of an 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 balanced 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)
- 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 chromosome microarray, PCR, or next generation sequencing for the following:
- Aneuploidy screening (PGT-A) due to insufficient evidence of efficacy
- Determining gender when the embryo is not at risk for a sex-inked 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 or embryos for human leukocyte antigen (HLA)-typing or for determining genetic abnormalities. These include:

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

(Zegers-Hochschild et al., 2017)

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/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
81228	Cytogenomic constitutional (genome-wide) microarray analysis; interrogation of genomic regions for copy number variants [e.g., bacterial artificial chromosome (BAC) or oligo-based comparative genomic hybridization (CGH) microarray analysis]
81229	Cytogenomic constitutional (genome-wide) microarray analysis; interrogation of genomic regions for copy number and single nucleotide polymorphism (SNP) variants for chromosomal abnormalities
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)

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

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) in order 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 analysis of single gene or other inherited disorders in an embryo (PGT-M). Use of this technology is hypothesized to increase the success of infertility treatment, especially in women who have worse outcomes due to advanced maternal age, history of recurrent miscarriage, failed in vitro fertilization (IVF) (CDC, 2017) or a balanced chromosome translocation. In addition, it 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.

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. Further studies focused on clinical utility and the development of algorithms to identify populations for which this testing may be beneficial are needed.

In a retrospective cohort study, Kucherov et al. (2023) analyzed the impact of PGT-A on cumulative live birth rate (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 embryo transfer (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 preterm birth, 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. Studies by Yan (2021) and Verpoest (2018), previously discussed in evidence, were included in this systematic review.

The use of PGT-A in individuals with recurrent pregnancy loss (RPL) was the focus of a retrospective study performed by Bhatt et al. (2021) 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 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 next-generation sequencing preimplantation genetic testing

(PGT-A)] in predicting failure of a successful delivery. A secondary outcome measured was the impact of trophectoderm 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 embryo transfers 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 have 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 single nucleotide polymorphism (SNP) testing with array comparative genomic hybridization (aCGH). Interesting findings regarding recombination and aneuploidy origin were revealed. 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 randomized controlled trials involving 2,794 women reporting data on clinical outcomes in patients who underwent IVF with PGT-A versus IVF without PGT-A were included. The quality of evidence ranged from low to moderate. Cumulative live birth (CLBR) was the primary outcome; LBR after first embryo transfer, miscarriage rate, ongoing pregnancy rate, clinical pregnancy rate, multiple pregnancy rate, proportion of women obtaining an embryo transfer and mean number of embryo transfers 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 [odds ratio (OR) 1.05, 95% confidence interval (CI) 0.66 to 1.66, 1 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 embryo transfer improves with PGT-A by polar body biopsy (OR 1.10, 95% CI 0.68 to 1.79, 1 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, 1 RCT, n = 396, low-quality evidence). No data on ongoing pregnancy rate 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, 1 RCT, n = 396, low-quality evidence). Another trial used blastocyst stage biopsy with next-generation sequencing. 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 embryo transfer improves with PGT-A with blastocyst stage biopsy (OR 0.93, 95% CI 0.69 to 1.27, 1 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, 1 RCT, n = 661, low-quality evidence). No data on ongoing pregnancy rate 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 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, 1 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, 10 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 embryo transfer 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; 10 RCTs, n = 1,680, I^2 = 16%; moderate-quality evidence). The addition of PGT-A may reduce ongoing pregnancy rate (OR 0.68, 95% CI 0.51 to 0.90, 5 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, 5 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.

Trophectoderm (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. (2019) 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 trophectoderm 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.

Simon et al. (2018) conducted a retrospective study examining IVF outcomes using single nucleotide polymorphism (SNP) based PGT-A. Outcome data was collected on procedures performed at two U.S. fertility centers from 2010-2013. Women 18-55 years of age who underwent IFV treatment were eligible for inclusion; those who did not elect 24 chromosome SNP-based PGT-A were excluded from analysis. During the study timeframe, 974 women (20-46 years of age) underwent 1,884 IVF cycles (1,621 non-donor, 262 donor) and elected to use SNP-based PGT-A. An implantation rate of 69.9%, clinical pregnancy rate per transfer of 70.6%, and LBR per transfer of 64.5% were observed in the non-donor cycles. Data were stratified by maternal age for analysis, with no significant difference observed in outcome rates per transfer, even for women > 40 years of age. No difference in pregnancy outcome was seen in single embryo transfers (SET) compared with double embryo transfers which supported the authors' recommendation for the utilization of SET when SNP-based PGT-A is used. Larger, prospective studies are recommended to further assess the impact of SNP-based PGT-A on pregnancy outcomes.

Zore et al. (2018) compared the outcomes of frozen single embryo transfer between euploid embryos and those with segmental mosaicism. Three hundred and twenty-seven women had 377 frozen embryo transfers. All embryos underwent biopsy at the blastocyst stage where two or more cells were taken from the trophectoderm. CGH was used to determine if embryos were euploid or had segmental mosaicism. 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.

Munné (2018) reported on the outcomes of the 2018 Preimplantation Genetic Diagnosis International Society (PGDIS) conference regarding PGT-A. Studies and data were reviewed at the conference that demonstrated improved pregnancy rates per transfer in experience centers and in women over the age of 35 who utilize PGT-A, but not in younger women. Studies using cell-free embryo DNA in spent media were promising, showing 80-90% concordance with biopsy. Mosaicism in the trophectoderm was a topic of debate, the outcome of which was PGDIS agreeing to update their guidelines. However, the guidelines will still recommend transferring euploid embryos favorably over mosaic embryos.

Friedenthal et al. (2018) evaluated the difference in pregnancy outcomes using NGS compared to CGH 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 results in better pregnancy outcomes when compared to using CGH.

Gleicher and Orvieto (2017) conducted a comprehensive literature review through January 2017, on research related to current PGS methodologies and outcomes using comparative chromosome screening on 5-6 day TE biopsies, which they call PGS 2.0. This includes aCGH and SNP-based array technologies. Overall, they noted that the literature has a skewed view of clinical utility, and uses embryo transfer as the starting point for measuring success, whereas generally IVF literature uses the initiated IVF cycles as the starting point. When using initiated cycles as a starting point, non-PGS cycles result in a higher LBR over PGS cycles. In addition, they report from their analysis that TE mosaicism may be present in at least half of all embryos, and mathematical models suggest that that the likelihood of false negative and positive results is too high to safely determine which embryos should be transferred or not. Their overall conclusion is that PGS 2.0 does not have clinical utility and may in fact reduce LBRs.

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 embryo transfers 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 trophectoderm mosaicism in a collaboration between The Center for Human Reproduction in New York City and the Center for Studies in Physics and Biology and the Brivanlou Laboratory of Stem Cell Biology and Molecular Embryology using mathematical modeling. As molecular methodologies improve, it has become more apparent that the trophectoderm has more mosaicism than previously appreciated. Recent studies have shown that over a third of embryos considered to be aneuploid were actually mostly euploid-normal on follow up studies. This has raised concerns about the impact on PGT-A results and whether or not mosaic embryos can be transferred. 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 trophectoderm, with the understanding that trophectoderm biopsies often include only one cell. The models assumed that mosaicism was distributed evenly throughout the trophectoderm, 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 trophectoderm 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 patients were included who had indications of advanced maternal age, recurrent miscarriage, or parental carrier of a balanced translocation. 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 their 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.

Kurahashi et al. (2015) conducted a comprehensive review of the literature regarding the analytical validity of CMA for PGS. The authors reported that while oligonucleotide arrays (CMA) are the standard for clinical analysis of individuals with developmental delay and congenital anomalies, the need to use a single cell and then perform WGA when using CMA for PGS may introduce amplification bias. Uneven amplification can occur of various regions of the DNA sampled from the embryo and lead to

inaccuracy in the test results. Newer technologies including bacterial artificial chromosome (BAC) and a multiple displacement method are being explored as ways to mitigate amplification bias. Mosaicism in the embryo is also reported by the authors as a factor to overcome in using CMA for PGS. It has been demonstrated in the oocyte and blastomere that the spindle assembly process that regulates chromosome segregation is transiently deficient, which leads to a high rate of mosaicism during this stage and raises the question of whether or not a single cell biopsied during this stage is representative of the whole embryo. In addition, self-correction of the mosaicism to a euploid embryo has been demonstrated, so low-level mosaicism may not be a concern. Studies have shown that CMA can identify mosaicism in only 25% of embryos and so may miss low levels of mosaicism. This review further describes issues of cell cycle replication as a confounding factor for CMA. DNA replication begins at more than 10,000 sites in a genome, and during S phase, some parts of the genome have finished replicating and have two copies while other regions have not completed replicating and have a single copy of DNA. This variation in copy number could be incorrectly interpreted as abnormal or as high background noise. The risk of cell cycle issues may be mitigated by performing cell sampling just after cell division, or by trophectoderm biopsy in the blastocyst state. Finally, CMA is not optimal for identifying polyploidy which is a significant limitation because triploidy is one of the most common chromosome abnormalities found in miscarriages. Microarrays that are SNP based can be used for detection of polyploidy, but at the time of publication, SNP arrays have not been optimized for WGA. Overall, the authors conclude that CMA for PGS is slowly becoming a clinical standard, but states that the procedure needs to be optimized on an individual basis and tailored protocols are required.

Novik et al. (2014) published a comparison of fluorescence in situ hybridization (FISH) methods used to evaluate chromosomal mosaicism in IVF embryos with CMA to determine the limits of mosaicism detection, accuracy, and mosaicism prevalence. Chromosomal mosaicism is higher in IVF created embryos than in other prenatal specimens and may be found in 71-73% of human embryos. Low levels of mosaicism in prenatal specimens suggest selective pressure against mosaic embryos for ongoing pregnancy. Mosaicism has been reported in embryos evaluated by CMA using trophectoderm (TE) biopsies, but the effect of TE mosaicism on development, implantation and pregnancy outcome is unknown. To determine the limits of mosaicism detection, the authors mixed different ratios of amplified DNA from aneuploid and euploid cells, as well as tested clinical samples. Overall, they were able to identify the limit of mosaicism detection with CMA at 25-37% for gains of DNA, and 37-50% for losses. They used the CMA technique developed to CMA was used to determine if an embryo was euploid, non-mosaic aneuploidy, or mosaic aneuploid. The diagnostic accuracy of the CMA test was assessed by FISH analysis on non-transferred embryos. In 47 embryos, 26 were considered to be non-mosaic aneuploid by CMA, and 100% were confirmed by FISH. In the mosaic category, 95% were confirmed by FISH. The single embryo not confirmed by FISH did have a discordant result with 7% of nuclei with an aneuploid FISH signal that was below the threshold to call the embryo abnormal. Embryos predicted to the euploid by CMA were not tested by FISH. The authors concluded that CMA testing can identify mosaicism in day 5/6 blastocysts and that FISH confirms that the mosaicism is real and not likely a technical artifact.

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.

A search of the FDA website identified an approval (K042279) for the Affymetrix Genechip Microarray Instrumentation System on December 23, 2004. Refer to the following website for more information: http://www.accessdata.fda.gov/cdrh_docs/pdf4/K042279.pdf. (Accessed January 25, 2023)

Additional Products

180K Oligo Array and SNP + CGH Array (Ambry Genetics Corp.); Cytogenomic SNP Microarray (2003414), Cytogenomic SNP Microarray, Prenatal (2002366), and Cytogenomic SNP Microarray, Products of Conception (2005633) (ARUP Laboratories); Chromosomal Microarray Analysis – HR (test #8655), Chromosomal Microarray Analysis HR + SNP Screen (test #8665), Chromosomal Microarray Analysis – CytoScan HD SNP Array – Non-Tumor (test #8650), Targeted Chromosomal Microarray Analysis – Prenatal [test #8656 (amniocentesis) or #8657 (CVS)], and Expanded Chromosomal Microarray Analysis – Prenatal [test #8670 (Amniocentesis) or #8671 (CVS)] (Baylor College of Medicine Medical Genetics Laboratories); Whole-Genome Chromosomal Microarray (GenomeDx), Whole-Genome Chromosomal Microarray, Prenatal, and Whole-Genome Chromosomal Microarray, Products of Conception (GeneDx Inc.); Reveal SNP Microarray – Pediatric; Reveal SNP Microarray – Prenatal, and Reveal SNP Microarray – POC (Integrated Genetics); Chromosomal Microarray, Postnatal, Clarisure Oligo-SNP (test 16478), Chromosomal Microarray, Prenatal, Clarisure Oligo-SNP (test 90927), and Chromosomal Microarray, POC, Clarisure Oligo-SNP (test 90929) (Quest Diagnostics Inc.); Signature ChipOS, Signature ChipOS + SNP, Signature PrenatalChipOS, Signature

PrenatalChipOS + SNP, Signature PrenatalChipTE, and Signature PrenatalChipTE + SNP (Signature Genomic Laboratories LLC), HumanKaryomap-12 DNA Analysis Kit (Illumina), IdentifySGD (Progenity, Inc.), Spectrum PGS (Natera, Inc.), Spectrum-PGD + PGS (Natera, Inc.), NexCCS (Foundation for Embryonic Competence).

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Policy History/Revision Information

Date	Summary of Changes
02/01/2024	**Title Change** • Previously titled *Preimplantation Genetic Testing (for Ohio Only)* **Application** • Added language to indicate any requests for services that are stated as unproven or services for

Date	Summary of Changes
	which there is a coverage or quantity limit will be evaluated for medical necessity using *Ohio Administrative Code 5160-1-01* **Coverage Rationale** • Added language to indicate 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) ○ 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 • Replaced language indicating "PGT *for Monogenic/single gene defects (PGT-M) or inherited structural chromosome rearrangements (PGT-SR)* is proven and medically necessary using polymerase chain reaction (PCR), next generation sequencing (e.g., Chromosomal Rearrangements), or chromosomal microarray for the [listed services]" with "PGT is proven and medically necessary using polymerase chain reaction (PCR), next generation sequencing (e.g., Chromosomal Rearrangements), or chromosomal microarray for the [listed services]" • Added list of indications for which PGT using polymerase chain reaction (PCR), next generation sequencing (e.g., Chromosomal Rearrangements), or chromosomal microarray is proven and medically necessary when criteria [listed in the policy] are met:

Date	Summary of Changes
	○ Alpha-1 Antitrypsin Deficiency (AATD) ○ Charcot-Marie-Tooth (CMT) Hereditary Neuropathy ○ Craniofrontonasal Syndrome (EFNB) ○ MUTYH-Associated Polyposis (MAP) ○ Neurofibromatosis 1 (NF1) **Definitions** • Removed definition of "Significant Health Problems or Severe Disability" **Applicable Codes** • Added CPT/HCPCS codes 0396U, 58970, 58974, 76948, 81349, 89250, 89251, 89253, 89254, 89255, 89257, 89258, 89260, 89261, 89264, 89268, 89272, 89280, 89281, 89290, 89291, 89342, 89352, S4011, S4015, S4016, S4022, and S4037 • Added notation to indicate CPT/HCPCS codes 58970, 58974, 76948, 89250, 89251, 89253, 89254, 89255, 89257, 89258, 89260, 89261, 89264, 89268, 89272, 89280, 89281, 89290, 89291, 89342, 89352, S4011, S4015, S4016, S4022, and S4037 apply to Preimplantation Genetic Testing **Supporting Information** • Updated *Clinical Evidence* and *References* sections to reflect the most current information • Archived previous policy version CS160OH.D – P

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.

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