

Preimplantation Genetic Testing and Related Services

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[➔ Instructions for Use](#)

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- | Related Policies |
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| <ul style="list-style-type: none"> • Cell-Free Fetal DNA Testing • Chromosome Microarray Testing (Non-Oncology Conditions) • Infertility Diagnosis, Treatment, and Fertility Preservation |
| Related Clinical Guideline |
| <ul style="list-style-type: none"> • Fertility Solutions Medical Necessity Clinical Guideline: Infertility |

Coverage Rationale

[➔ See Benefit Considerations](#)

Preimplantation Genetic Testing (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 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 chromosome microarray, PCR, or next generation sequencing 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.

Medical Records Documentation Used for Reviews

Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. Medical records documentation may be required to assess whether the

member meets the clinical criteria for coverage but does not guarantee coverage of the service requested; refer to the protocol titled [Medical Records Documentation Used for Reviews](#).

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)

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 the member specific benefit plan document 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 Clarifications:

- For the Preimplantation Genetic Testing (PGT) benefit, refer to the codes identified below with an asterisk (*).
- Benefit limits do not include Preimplantation Genetic Testing (PGT) for the specific genetic disorder (CPT codes 81228, 81229, 81349, and 81479).

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

CPT Code	Description
*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)
Related Services	
*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)
*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) 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/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).

Benefit Considerations

Indications for Coverage

Certain plans may include coverage for:

- Preimplantation genetic testing
- PGT-M or PGT-SR as it may be considered a covered expense if the fetus is at risk for a genetic disorder

Refer to the member specific benefit plan document to determine if the coverage applies.

Preimplantation Genetic Testing (PGT) and Related Services

Preimplantation Genetic Testing (PGT) performed to identify and to prevent genetic medical conditions from being passed onto offspring. To be eligible for benefits the following must be met:

- PGT must be ordered by a physician after genetic counseling
- The genetic medical condition, if passed onto offspring, would result in Significant Health Problems or Severe Disability, and be caused by a single gene (detectable by PGT-M) or structural changes of a parents' chromosome (detectable by PGT-SR)
- Benefits are limited to PGT for the specific genetic disorder and the following related services when provided by or under the supervision of a Physician:
 - Ovulation induction (or controlled ovarian stimulation)
 - Egg retrieval, fertilization, and embryo culture
 - Embryo biopsy
 - Embryo transfer
 - Cryo-preservation and short-term embryo storage (less than one year)

Coverage Limitations and Exclusions

- Benefits are not available for long-term storage costs (greater than one year).
- Benefits are not available for Preimplantation Genetic Testing – Aneuploidy (PGT-A).

Clinical Evidence

Preimplantation Genetic Testing (PGT)

Ginström Ernstad et al. (2023) published the results of a Swedish registry-based study which compared perinatal outcomes and early childhood health of children born specifically after PGT (n = 390) with children who were born after in-vitro fertilization (IVF)/intracytoplasmic sperm injection (ICSI) (n = 61,060), along with a matched group born after spontaneous conception (n = 42,034). Only singleton pregnancies were included in the analysis, which incorporated births occurring between January 1996 and September 2019. The primary outcomes assessed were preterm birth (PTB) and low birthweight (LBW). Childhood morbidity was a secondary outcome. Data from individuals who had undergone PGT and IVF/ICSI were cross-linked to national health registries including the Medical Birth Register, the Patient Register, and the Cause of Death Register. Mean follow up time for children born after PGT was 4.6 years; for children born after IVF/ICSI, it was 9.0 years and for births after spontaneous conception, 5.1 years. The analysis revealed that PTB took place in 7.7% of infants born after PGT and 7.3% of infants born after IVF/ICSI. LWB rates were 4.9% for PGT and 5.2% for IVF/ICSI. The researchers found no difference between these two groups with regard to birth defects. Compared to spontaneous conception, however, infants born after PGT had a higher risk of PTB (AOR 1.73, 95% CI 1.17–2.58). In addition, the rate of LBW was 4.9% in the PGT group and 3.2% in the spontaneous conception group (AOR 1.52, 95% CI 0.93–2.49). With regard to health in early childhood, no significant differences were found between the PGT group and the all-IVF/ICSI or spontaneous conception group for risk of asthma or allergic disorders. Other health issues including sepsis, hypothyroidism, attention deficit hyperactivity disorder, autism spectrum disorders, mental retardation, cerebral palsy and epilepsy were very rare in the PGT group, occurring in a maximum of only three children. Rates of placenta previa and caesarean delivery were not significantly different between the PGT and IVF/ICSI group, however, rates of these maternal complications were significantly higher after PGT when compared to spontaneous conception (AOR 6.46, 95% CI 3.38–12.37 and AOR 1.52, 95% CI 1.20–1.92, respectively). The authors contend that their results indicate that alone, the biopsy performed for PGT does not negatively impact maternal, perinatal, or early childhood health outcomes; outcomes for PGT an IVF/ICSI were similar. They advise, however, that results should be interpreted with caution since the sample size of children born after PGT was small, follow up time was generally short and there were a limited number of children with established diagnoses. Additional long-term follow up studies on children born after PGT are recommended.

In a 2021 systematic review and meta-analysis, Hou et al. evaluated the risk of obstetric and neonatal adverse outcomes related to PGT. Participants included 785,445 individuals from 19 studies who were separated into an IVF/ ICSI group (n = 731,151) and a PGT group (n = 54,924). Outcomes included mean birth weight, LBW, very low birth weight, mean gestational age at birth, PTB, very preterm birth, intrauterine growth retardation (IUGR), birth defects, sex ratio, hypertensive disorders of pregnancy, cesarean section, gestational diabetes, disorders of the placenta and preterm premature rupture of membranes. The analysis showed that pregnancies following PGT had reduced rates of LBW (risk ratio [RR] 0.85, 95% confidence interval [CI] 0.75 to 0.98), very low birth rates (RR 0.52, 95% CI 0.33 to 0.81), and very preterm births (RR 0.55, 95%CI 0.42 to 0.70) compared to these rates in the pregnancies following IVF/ICSI, but higher rates of hypertensive disorders of pregnancy (RR 1.30, 95% CI 1.08 to 1.57). PGT was not associated with a higher risk

of any of the other adverse outcomes. In a subgroup analysis of blastocyte biopsies only, PGT using blastocyte biopsy yielded a lower rate of very low birth weight (RR 0.55, 95% CI 0.31 to 0.95) and was not associated with increased risk of other obstetric/neonatal outcomes. Subgroup analysis was also undertaken for frozen-thawed embryo transfer cycles and indicated that pregnancies with PGT were associated with a lower rate of very low birth weight and cesarean birth but a higher rate of IUGR and preterm birth than in the IVF/ICSI group; no other elevated risk was identified for frozen-thawed embryo transfers. The authors concluded that based on the pooled analysis, PGT did not lead to an increase in the risk of adverse obstetric and neonatal outcomes, however the association between PGT and elevated risk of IUGR will require further investigation. The analysis was limited by differences in the stage of embryo biopsy (cleavage stage vs. blastocyst stage) and lack of studies including obstetric indicators, such as placental disorders. In addition, none of the studies included were randomized controlled trials (RCTs), reducing the value of the meta-analysis. The researchers suggest ongoing analysis with potential inclusion of spontaneously conceived pregnancies as a control group to help further determine the safety and efficacy of PGT/embryo biopsy. Study by Li et al. (2021), previously discussed in this policy, was included in this systematic review.

Zheng et al. (2021) published a systematic review and meta-analysis evaluating outcomes of pregnancies in which an embryonic biopsy with PGT was performed in comparison to spontaneously conceived (SC) pregnancies or pregnancies conceived after IVF/ICSI. A total of 15 studies including 3682 babies born from pregnancies following PGT, 127,719 babies born from pregnancies following IVF/ICSI and 915,222 babies born from SC pregnancies were analyzed. Primary outcomes for the study included LBW and congenital malformations (CMs). Secondary outcomes included preterm delivery, very preterm delivery, gestational age, birth weight, very low birth weight, neonatal intensive care unit (NICU) admission, hypertensive disorders of pregnancy, gestational diabetes, placenta previa and preterm rupture of membranes. Subgroups undergoing analyses included preimplantation genetic diagnosis (PGD), preimplantation genetic screening (PGS), cleavage stage biopsy in conjunction with fresh embryo transfer and blastocyst biopsy in conjunction with frozen-thawed embryo transfer. Study findings indicated that RR for LBW was higher in pregnancies following PGT when compared to SC pregnancies (RR = 3.95, 95% CI: 2.32–6.72), however there was no difference in the risk of CMs. LBW and CM pooled results showed similar risk in pregnancies following PGT and IVF/ICSI. For preterm delivery and hypertensive disorders of pregnancy, risks were significantly higher in pregnancies following PGT when compared with SC pregnancies (RR = 3.12, 95% CI: 2.67–3.64 and RR = 3.12, 95% CI: 2.18–4.47, respectively). In addition, lower gestational age (mean difference [MD] = -0.76 weeks, 95% CI -1.17 to -0.34) and birthweight (MD = -163.80 g, 95% CI: -299.35 to -28.24) were found for pregnancies following PGT vs. SC pregnancies. Compared with pregnancies following IVF/ICSI, however, the risk of very preterm delivery and very low birth weight were significantly decreased in pregnancies following PGT (41% and 30%, respectively). Lastly, risk of hypertensive disorders of pregnancy were 50% higher in pregnancies following PGT when compared with pregnancies following IVF/ICSI. The additional subgroup analyses found that both pregnancies following PGD and PGS were associated with a higher risk of preterm delivery and a lower gestational age than SC pregnancies. The authors concluded that overall, their meta-analysis indicates that pregnancies following PGT may be related to increased risk of LBW, preterm delivery and hypertensive disorders of pregnancy when compared to SC pregnancies. When compared with pregnancies following IVF/ICSI, obstetric and neonatal outcomes appear to be favorable, though pregnancies following PGT were associated with higher risk of hypertensive disorders of pregnancy. Limitations include potential for bias related to merging data from RCTs and non-RCTs, limited available data, and variations in the populations studied. The authors recommend further studies including RCTs and prospective cohorts to confirm these findings.

In 2016, Chang and colleagues published a review of the outcomes of in vitro fertilization utilizing PGT from 2011-2012 from the United States Assisted Reproductive Technology Surveillance Data. Overall, they included 97,069 non-PGT cycles and 9,833 cycles that used PGT in their analysis. Most were for aneuploidy screening (55.6%), 29% were for “other reasons,” and 15% were for preventing genetic disease. In the “other reasons” category, only 2% of clinics provided information on the reason for PGT, and it was primarily for gender selection. In 2011, 98% of clinics reporting doing at least one PGT cycle, and in 2012, 100% of reporting clinics had performed PGT cycles. The clinical characteristics between the three groups differed. The aneuploidy screening group tended to be older (> 37 years) and had a higher rate of prior miscarriages. As a group, they had fewer miscarriages than other age matched groups in the study and had a higher chance of a live birth compared to the age matched non-PGT group. They were more likely to have multiple births compared to the non-PGT group. This group was also more likely to have low birth weight babies. The genetic disease group was younger and did not have a history of prior miscarriages. In this group, in women ages 35-37, the adjusted odds of achieving a pregnancy and live birth were lower than the non-PGT group. In all categories, women using PGT who were < 35 years old and transferred one embryo, the odds of clinical pregnancy and live birth were lower than compared to the non-PGT group. Information was not available on the PGT techniques used by the different clinics, on biopsy type, protocol to select chromosome abnormalities, number of embryos, embryo morphology, and number of embryos discarded. The authors concluded that PGT might improve outcomes in populations at risk of a genetically affected child, including aneuploidy, on the basis of family history, but additional data collection and outcome data is necessary to better understand the overall value and effectiveness of PGT. Prospective, randomized studies are needed.

Preimplantation Genetic Testing for Monogenic/Single Gene Defects (PGT-M)

In a Cochrane systematic review, Vlajkovic et al. (2022) sought to investigate the benefits and/or harms of biopsies performed on day three of embryo development compared to those performed on day five in individuals undergoing PGT-M with IVF or ICSI cycles. Only one small RCT was found, including 20 participants and there was risk of bias due to low level of precision and lack of blinding of study personnel. Based on the limited data available, there is uncertainty regarding whether there is a difference in live births and miscarriages, ectopic pregnancies, stillbirths, termination of pregnancy and viable intrauterine pregnancies between embryos biopsied on day three and day five for PGT-M. Further studies are needed to confirm what impacts may exist for biopsies performed on either day three or five of embryo development.

Ben-Nagi et al. (2019) conducted an observational study to determine if LBR is affected by oocyte yield as well as number of blastocysts biopsied, and/or the number of acceptable blastocysts to transfer post PGT-M or PGT-SR. Participants were 175 couples referred to an IVF center from 2014 to 2017 that chose to undergo either PGT-M or PGT-SR. One hundred forty-five (83%) of couples had PGT-M, while 30 (17%) had PGT-SR. Forty-four (25%) couples had second or third cycles of IVF, for a total of 249 oocyte retrievals and 230 frozen embryo transfers (FET); 196 (79%) due to single-gene disorders and 53 (21%) for chromosomal rearrangement. One hundred twenty-two (53%) of the FETs resulted in live birth, 16 (7%) resulted in ongoing pregnancy, 21 (9%) resulted in miscarriage, and 69 (30%) resulted in failed implantation. The authors found that the number of oocytes collected ($p = 0.007$; OR 1.06), the number of blastocysts biopsied ($p = 0.001$; OR 1.14), and the number of suitable embryos to transfer ($p = 0.00$; OR 1.38) were all significantly positively associated achieving a live birth. The likelihood of live birth increased by 14% per additional blastocyst biopsied and by 38% per suitable embryo to transfer. Stratified analysis determined that the odds of live birth per acceptable embryo for transfer was 1.28 for single-gene disorders and 3.23 for chromosomal rearrangement.

Kubikova et al. (2018) reported on the development of a multiplex polymerase chain reaction (PCR) test for PGT-M of the beta-globin gene (HBB), responsible for beta-thalassemia and sickle cell anemia. The analysis utilized the amplification of overlapping small HBB segments to cover the entire gene, with analysis using next generation sequencing. In addition, 17 closely linked SNPs were tested simultaneously to aid in defining haplotypes in combination with HBB sequencing. A validation study on five family trios representing 14 different mutations was conducted, and results were consistent with previously obtained genetic results. Three of the families continued on to using this protocol for PGT-M. One couple had a single cell embryo biopsy at an early cleavage stage, and the other two families had about five cells extracted from the trophectoderm from blastocyst stage embryos. A total of 21 embryos were tested and had successful whole genome amplification, and NGS analysis was successful. Typical karyotyping and linkage analysis was performed simultaneously as a comparison for standard PGT methods. All but one embryo had an average read depth of 1000x for HBB. The single embryo that failed was found to have nullisomy for chromosome 11 where the HBB gene is located. In one couple, there were low call rates and a high allele dropout rate in the standard karyotype method, likely associated with suboptimal amplification after blastocyst biopsy. Results were resolved using linkage analysis of parental SNPs to confirm mutations and haplotypes found in the embryos. The allele drop out was not found in the NGS analysis. The authors concluded that the use of a trophectoderm biopsy with next generation sequencing provided better accuracy than traditional PGT testing. Pregnancy rates, outcomes, and confirmation of PGT results postnatally were not reported in this study.

Volozonoka et al. (2018) examined the difference between multiple displacement amplification (MDA) and OmniPlex whole genome amplification when used for comparative genomic hybridization (CGH), Sanger sequencing, SNaPshot (single-base extension sequencing) and fragment size analysis. Nine couples at risk for single gene disorders consented to participate in the study. Disease genes involved included ACTA2, HTT, KRT14, ALOX12B, TPP1, GLB1, MTM1, and DMD. A total of 62 embryos were tested, and 1-8 trophectodermal cells were taken from the outer layer. All embryos survived the extraction. Thirty-nine embryos underwent whole genome amplification using MDA and the remaining went through OmniPlex linear amplification. Amplification detection was determined by capillary electrophoresis. Direct mutation analysis used Sanger sequencing or SNaPshot, and chromosomes were analyzed using CGH. Whole genome amplification, regardless of method, and testing was successful and provided a conclusive result in all embryos. Five unaffected and euploid embryos were transferred, resulting in four clinical pregnancies and the live birth of two healthy children. Key differences were noted, however. The MDA approach to whole genome amplification resulted in heavier DNA strings and resulting electrograms were clearer, and the base error rate was lower compared to other PCR based approaches. MDA had significant amplification bias that caused high CGH noise. The authors concluded that methodology choice should depend on which downstream analysis is most needed, and both amplification techniques could be used if there are enough embryonic cells available.

Sallevelt et al. (2017) reported on the use of PGT-M using a single blastomere for mitochondrial disorders. Mitochondrial diseases are transmitted only from the mother, and the expression of disease is dependent on the mutation load, meaning the number of mitochondria carrying the mutation compared to the number of wildtype mitochondria present. Prenatal diagnosis has a potential problem in that the mutational load across all tissues may not be able to be identified

completely, and therefore the future phenotype of the fetus cannot be predicted easily. PGT-M is the preferred choice for female carriers, as only mutation free embryos can be transferred. If no mutation free embryos are available, embryos with a low mutation load can be transferred, which reduces the risk of an affected child, but cannot eliminate it. At the time of the study, two blastomeres had been used in PGT-M for mitochondrial disease to better predict the mutation load. This has a negative impact on the LBR. The authors studied the value of using only one blastomere in a cohort of nine women carrying a m.3243A > G mutation that causes mitochondrial encephalopathy with lactic acidosis and stroke-like episodes (MELAS). These women produced 73 embryos that had two or more blastomeres removed from which 294 single blastomeres were analyzed. Only one blastomere was concluded to have a false negative result. This was based on this cell having a mutation load of about 5%, within the range where an embryo transfer might have been considered, but surrounding blastomeres from the same embryo had a higher mutational load of 22-30%. The authors concluded that as the false negative rate was 0.34%, a single blastomere would be sufficient for PGT-M. Pregnancy rates and outcomes were not highlighted by the authors because their goal was to determine first if a single cell would provide the correct diagnosis. Single cells were analyzed but excluded from the data reporting, as well as multi-cells, and used for embryo transfer which they feel would confound the data.

Preimplantation Genetic Testing for Chromosomal Structural Rearrangements (PGT-SR)

In a 2022 retrospective analysis, Nakano et al. sought to assess the effectiveness of PGT-SR using array comparative genomic hybridization (aCGH) or NGS in the prevention of recurrent miscarriage. The evaluation included 31 couples with balanced translocations who had undergone a total of 68 PGT-SR cycles between 2012 and 2020. In all, 242 blastocytes underwent biopsy for aCGH or NGS and the blastocysts identified as genetically transferrable were transferred in the subsequent frozen-thawed single embryo transfer cycle. The study found a genetically transferable rate of 21.2% with 35 blastocysts transferred to the uterus. Rate of clinical pregnancy was 57.1% and ongoing pregnancy rate was 100%. The authors concluded that their results supported the use of PGT-SR using aCGH or NGS to evaluate chromosomes and ultimately help prevent recurrent miscarriages. In addition, the results may be helpful in genetic counseling for carriers of balanced translocations.

Huang et al. (2019a) performed a retrospective cohort study of 194 reciprocal translocation carrier couples who had experienced two or more adverse pregnancy histories. Two hundred sixty-five PGT-SR cycles were examined to assess the impact of PGT-SR on normal live birth, birth defect, and miscarriage rates in reciprocal translocation carrier couples. Prior to PGT-SR, the reproductive history of the couples consisted of 592 pregnancies; 83.6% resulted in miscarriages, 6.1% live birth with defects, 4.9% were terminated due to unwanted pregnancy, and 2.9% resulted in normal live births. Post PGT-SR, 118 clinical pregnancies resulted in 85.6% normal live births, 11% miscarriage, 3.4% with birth defects. The authors concluded that reciprocal translocation carriers in this study had a low risk of miscarriage and birth defects and a higher frequency of normal live births following PGT-SR.

Zhou et al. (2018a) examined the validity of using massive parallel sequencing (MPS) on trophectoderm samples for PGT for chromosome translocation carriers. Twelve couples with chromosome translocations participated in a study. Nine had balanced translocations, and three were carriers of a numerical chromosome abnormality. A total of 105 embryos were biopsied on day three and had one cell removed. The cells underwent whole genome amplification and were then tested for genomic imbalances using MPS and CGH and confirmed using routine karyotyping. Results were obtained for MPS and CGH for 101 embryos, and there was concordance between MPS and CGH for 19 euploid and 82 unbalanced or aneuploidy embryos. There were four discrepancies, however. In one blastomere, MPS found a deletion of an X chromosome not found by CGH. This may be caused by a low density of SNPs on the CGH platform in that region. In another case, MPS identified a 186 Mbp duplication on chromosome 1, and a 15.6 Mbp duplication on chromosome 5, whereas CGH identified the duplications but of a different size. This could be related to amplification bias impacting CGH that would have been corrected in the MPS bioinformatics process. In the third embryo, karyotyping and MPS identified an unbalanced translocation between chromosome 3 and 6, and CGH only identified the imbalance in chromosome 3. In the final discrepant embryo, karyotype and MPS identified an unbalanced translocation between chromosomes 13 and 22, and CGH only identified the imbalance in chromosome 13. Twelve of the nineteen embryos that were found to be free of genomic imbalances were used for frozen-thaw embryo transfer, resulting in 1 live birth and 5 ongoing pregnancies.

Brunet et al. (2018) examined the use of next generation sequencing to identify complex chromosome rearrangements in the embryos of chromosomal translocation carriers. Six couples with complex rearrangements underwent PGT-SR. Biopsies were done on day 5 or 6 blastocysts. A total of 84 oocytes were retrieved, resulting in 25 embryos that had trophectoderm biopsy and NGS analysis. Vitrified warm single embryo transfers were done with six euploid embryos resulting in four healthy live births for four couples. One couple chose to confirm the PGT-SR results with prenatal diagnosis, and the other three did not. Two couples did not have any transferable embryos after two cycles.

Segmental mosaicism is a concern for both PGT-A and PGT-SR. Zhou et al. (2018b) examined the frequency of de-novo segmental aneuploidy identified by next generation sequencing (NGS). The study took place over a three-year time period and involved 5,735 blastocysts from 1,854 couples who underwent PGT-A (n = 770) and PGT-SR (n = 1084) on trophectoderm biopsies. Biopsied cells underwent whole genome amplification using GenomePlex amplification, and low coverage massively parallel sequencing (MPS) on the Proton platform. Overall, 581 blastocysts were found to have 782 de novo segmental aneuploidies. Most carried only one, but 115 had two, and 38 had three or more. There was no association with advanced maternal age or a specific chromosome. In 1,377 cycles, 1,686 blastocysts were transferred resulting in clinical pregnancies in 49% of the PGT-SR group and 47% of the PGT-A group. The miscarriage rate was about 9% in both groups. At the time of publication, there were 84 prenatal diagnostic tests and 645 delivered babies that were considered normal and healthy. Forty blastocysts with de novo segmental aneuploidy were donated for further research and were additionally analyzed by FISH as a comparison analysis. Of the donated blastocysts, 39 were successfully analyzed and FISH confirmed the segmental aneuploidy identified by NGS. Because de novo segmental aneuploidy can be caused by either meiosis during gamete formation or during mitosis during embryo development, the trophectoderm and inner cell mass were evaluated for 26 blastocysts. Five showed pure segmental mosaicism in both the trophectoderm and inner cell mass, but fourteen showed different levels of mosaicism between the two tissue types. The authors concluded that this analysis showed that segmental de novo aneuploidy is a real issue and is not an artifact of whole genome amplification. Further studies are needed to understand de novo segmental mosaicism and its impact on embryo development.

Maithripala et al. (2018) reviewed the reproductive choices of 36 couples who experienced recurrent miscarriage as a result of one member of the couple carrying a balanced chromosome translocation. The couples were identified through a retrospective chart review of 2,321 couples seen in a highly specialized reproductive assistance clinic between 2005 and 2013. The pre-diagnosis obstetrical history was obtained, and it was similar for all couples. The date of parental diagnosis was identified for each couple and used in determining the time from diagnosis to live birth as a point of comparison between couples that chose natural conception and those that picked PGD as their reproductive choice. Twenty-three couples chose to pursue natural conception, and thirteen chose PGT-SR. In the natural conception group, there were 24 live births with a live birth incidence of 1 birth per 4.09 years, and 74% of women had at least one live birth in the follow up period. In the PGT-SR group, six live births were recorded, reflecting a live birth incidence of 1 birth per 5.63 years, and 38% of women had at least one live birth in the follow up period. There was no significant difference between the groups in post-parental diagnosis miscarriage or LBRs. It should be noted that in the PGT-SR group, the miscarriage rate did not take into consideration PGT-SR specific variables. There were 8 failed PGT-SR cycles, which included four euploid embryo transfers that did not result in pregnancy. While failed PGT-SR and miscarriage cannot be equated, the authors felt it was meaningful to report as cycle failure represents a significant effort resulting in failure to achieve live birth.

Jewels et al. (2018) conducted a systematic review of the literature to examine the evidence supporting the use of PGT-SR in couples who have experienced recurrent miscarriages due to an inherited structural chromosome rearrangement. Meta-analysis was not possible because of significant differences between the studies. The authors identified 20 studies after a comprehensive review of the literature. Live birth was the primary outcome that was analyzed, and secondary outcomes reviewed included miscarriage rate and time to successful pregnancy. A pooled total of 847 couples that conceived naturally had an LBR of 25-71%. A pooled total of 562 couples had PGT-SR and had a similar LBR of 26-87%. There were no large comparative or randomized studies found. The studies also had different inclusion criteria and some evaluated participants for additional causes of miscarriage, such as auto-immune disease, whereas others did not. Some studies found a lower miscarriage rate in the PGT-SR group, and others did not. Two studies were identified as the best comparative analysis for examining the miscarriage rate and time to live birth post-parental diagnosis, and the studies had conflicting results. One found a lower miscarriage rate in the PGD group, and the other did not. Both found a similar time to LBR for PGT-SR and natural conception.

The ability of NGS to detect complex chromosome rearrangements as compared with CGH was the focus of a study by Chow et al. (2018). The authors used archived whole genome amplified DNA from 342 embryos at risk of genomic imbalance because of translocation or inversion carrier parents. All embryos had been previously analyzed by CGH. There were 287 blastomere biopsies and 55 trophectoderm biopsies. Overall, the concordance rate on abnormal results was 100% between NGS and CGH, regardless of the biopsy type. The concordance in normal embryos was 98% in the blastomere biopsy group, and 79% on trophectoderm biopsies. NGS detected de novo segmental aneuploidy and low-level mosaicisms that were not identified by CGH. The authors concluded that NGS was an acceptable technology to use in PGT-SR.

Zhang et al. (2017) examined the utility of using SNP-microarray in families with balanced translocations to accurately identify euploid embryos for transfer. In 68 blastocysts from 11 translocation families, SNP-microarray identified 42 unbalanced or aneuploidy embryos, and 26 balanced or normal chromosomes. Ten families became pregnant on the first cycle; one family was successful on cycle three. Amniocentesis on the resulting pregnancies matched the embryo

microarray analysis, resulting in a 100% sensitivity and sensitivity in this cohort, but the authors caution that a larger sample size is needed to further validate sensitivity and sensitivity.

Preimplantation Genetic Testing for HLA Typing (PGT-HLA)

A collaborative multi-center study by Kakourou et al. (2018), with the support of the European Society of Human Reproduction and Embryology (ESHRE), focused on the diagnostic and clinical efficacy of PGT for human leukocyte antigen (HLA) potential positive outcomes. A total of 14 centers submitted data through a custom database from 716 HLA-PGD cycles; of these 704 cycles from 364 couples met inclusion criteria. The mean maternal age was 33.5 years and 81.3% of the couples tested had requested HLA-typing without concurrent exclusion of single monogenic disease (58.63% beta-thalassemia). Overall 9,751 oocytes were obtained and 5,532 embryos underwent analysis. Cycles predominantly used fresh oocytes (94.9%) with day three biopsy (85.3%). A diagnosis was made in 4,343 embryos (78.5%); of these 677 were found to be genetically suitable. Subsequently, 56.6% of the 364 couples underwent embryo transfer and 598 total embryos were transferred (382 cycles). Ultimately, HCG-positive pregnancies were obtained in 164 couples and 136 babies were born to 113 couples. Limitations to overall success of the procedure included maternal age, number of oocytes collected per cycle and genetic chance. In 57 cases, hematopoietic stem cell transplantation (HSCT) was reported; 64.9% utilized combined umbilical cord-blood and bone marrow transplantation and 77% of transplants identified no complications. In this study, the diagnostic efficacy (78.5%) was noted to be lower than the data previously reported for general PGD by ESHRE (92.6%). Pregnancy rate was 23.3% compared to the previously reported 25%. However, when embryo transfer was complete, the LBR and embryo transfer data were comparable between this study (34.3%) and existing ESHRE PGD data (34%). Diagnostic efficacy was also lower in this study than reported in other PGD-HLA sources (78.5% vs.89.5%-94.1%). The study was limited by the use of retrospective data collection from facilities with varying practices and strategies for assistive reproductive technology (ART) as well as potential reporting bias when using the online database. As the first multi-center study that analyzed the clinical utility of PGD-HLA over 15 years, important parameters for more positive endpoints were brought to light. The authors indicate that the study reinforces the need for high-level collaboration of all specialists involved in ART including PGD/HLA testing and the need for ongoing data collection. They note that published systematic data on methodology, clinical and diagnostic results, and the success rates of ART and HSCT remain limited at this time.

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.

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 embryo transfers 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]), ongoing pregnancy rate (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 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 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 US 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 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 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; $n = 1513$; $I^2 = 75\%$), 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, multi-center, blinded, nonselection study to evaluate the value of a diagnosis of aneuploidy (made via targeted next-generation sequencing 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 SNP testing with 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 RCTs 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, $n = 1680$, $I^2 = 54\%$, 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, $n = 1680$, $I^2 = 16\%$; 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, $n = 1121$, $I^2 = 60\%$, low-quality evidence) and probably reduces clinical pregnancies (OR 0.60, 95% CI 0.45 to 0.81, 5 RCTs, $n = 1131$; $I^2 = 0\%$, 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. (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 trophoctoderm 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.

Zore et al. (2019) 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 trophoctoderm. 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.

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 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 trophoctoderm 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 trophoctoderm 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 trophoctoderm, with the understanding that trophoctoderm biopsies often include only one cell. The models assumed that mosaicism was distributed evenly throughout the trophoctoderm, 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 trophoctoderm 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.

Preimplantation Genetic Testing for Polygenic Disorders (PGT-P)

PGT-P is genetic testing that screens an embryo for disorders that involve multiple genes and provides a statistical prediction of increased clinical risk. Evidence for the utility of PGT-P for the selection of embryos is currently lacking and ethical concerns exist related to use of this technology.

In a recent systematic review of guidelines for PGT-M, Siermann et al. (2022) sought to leverage PGT-M guidelines to better understand current issues and practice on the ethical acceptability of PGT-M and make comparisons with PGT-P. A total of 38 documents were reviewed including national, European, and global guidelines. The researchers identified two main themes, including 1) what PGT is considered appropriate for and 2) who should make decisions regarding the use of PGT. They felt that many topics addressed in the PGT-M documents may apply to PGT-P as well, however, PGT-P screens for risks involving multiple polygenic conditions which compounds the ethical challenges for this type of testing. There is a lack of regulatory guidance, guidelines or position papers that address the ethical use of PGT-P. Ultimately, the authors concluded that based on the PGT-M documents reviewed, the ethical acceptability for PGT-P is limited at this time.

In a 2022 Precision Medicine Insight, Hayes addressed the use of PGT-P for selection of embryos for implantation. Evidence was limited and focused mostly on models for validation of polygenic risk scoring that could be used for embryo screening. No studies that could inform utility of PGT-P for embryo selection were identified. Per Hayes, professional guidelines addressing the use of PGT-P for embryo selection were also limited and provided weak support against using PGT-P in this manner.

Clinical Practice Guidelines

American College of Medical Genetics and Genomics (ACMG)

The ACMG published in 2023 a “points to consider” statement addressing the clinical application of polygenic risk scores (PRS) (Abu-El-Hajja et al.). This document states that the ACMG does not consider preimplantation PRS appropriate for clinical use at this time, noting the potential legal, social, and ethical considerations related to PRS in embryos.

In a 2021 position statement, the ACMG addressed direct-to-consumer prenatal testing for multigenic or polygenic disorders indicating that issues surrounding testing for such disorders are very complex. These disorders have been shown to be controlled, at least in part, by multiple genetic loci and the potential influence of unknown environmental factors. The ACMG ultimately recommends that prenatal testing for diseases or disorders that exhibit polygenic or multigenic heritability is not appropriate for clinical use at this time and should not be offered direct-to-consumer.

American College of Obstetricians and Gynecologists (ACOG)

Committee Opinion Number 799 (ACOG, 2020, reaffirmed 2023) indicates that the clinical utility of PGT-M and PGT-SR is firmly established, but the utility of PGT-A has not yet been fully determined. ACOG further recommends:

- Confirmation of PGT-M results by chorionic villus sampling (CVS) or amniocentesis should be offered to all patients
- Confirmation of PGT-SR results by CVS or amniocentesis should be offered to all patients
- Traditional diagnostic testing or screening for aneuploidy should be offered to all patients who have had PGT-A, in accordance with recommendations for all pregnant patients

In Committee Opinion Number 410 (2008, reaffirmed 2020) ACOG addressed ethical issues related to genetic testing for pregnant individuals and those considering pregnancy. ACOG urges providers to maximize their knowledge of available genetic tests along with the limitations of those tests and recognize the potential consequences to individuals who have undergone such testing if/when a genetic diagnosis is uncovered. The importance of integrating geneticists and genetic counselors into the care of individuals for whom genetic testing is being considered is also stressed. ACOG encourages clinicians to discuss with their patients the importance of sharing pertinent genetic information with potentially impacted family members as well. Lastly, because it may be possible for genetic information to lead to discrimination (e.g., in the

workplace, related to insurability), ACOG encourages clinicians to work to prevent such consequences when possible and advocate against genetic discrimination.

American Society for Reproductive Medicine (ASRM)

A committee opinion intended to update and expand the previous ASRM PGT opinion was published by ASRM Practice Committee and Genetic Counseling Professional Group in 2023. The document asserts that the initial application of PGT-M was for prevention of severe, untreatable, or life-threatening diseases with onset in childhood; currently this technology is being proposed for use across a wide range of genetic conditions for which there is more limited and/or controversial evidence. The 2023 opinion is summarized as follows:

- PGT-M should be offered if there is an identified significant reproductive risk
- PGT is not recommended in cases of:
 - Autosomal recessive carrier status with no manifestation of symptoms
 - A combination of variants that are not associated with disease
 - Pseudodeficiency alleles
 - Somatic-only variants
- Comprehensive genetic counseling including education regarding the condition in question and all reproductive options is recommended for individuals considering PGT-M
- Counseling may also be beneficial after results of PGT-M are obtained, particularly if embryo transfer decisions are being made
- Considering technical limitations that have the potential to result in misdiagnosis of an embryo, pregnancies that were conceived after use of PGT-M should be offered prenatal testing to confirm embryo results and screen for other fetal anomalies
- IVF clinics are encouraged to employ genetic counselors for workflow efficiency, smoother case management and better experiences for individuals considering PGT-M

In 2022, the ASRM Ethics Committee addressed the use of reproductive technology for the selection of sex for nonmedical reasons in an Ethics Committee Opinion. The opinion indicates that the use of PGT-A with IVF for sex selection only, with no medical indications, is ethically controversial and should not be encouraged. Discussion of knowledge of embryo sex at the time of transfer and the impact this may have on embryo selection should take place at the time of informed consent for PGT-A, as PGT-A may be performed for indications unrelated to sex selection with fetal sex as an incidental finding. The opinion asserts that providers that offer assisted reproduction services are not ethically obligated to either provide, or refuse to provide, methods of sex selection that are not medically indicated.

A revised committee opinion addressing the clinical management of mosaic results from PGT-A was published by the ASRM Practice Committee in 2023. The updated opinion integrates additional studies focused on mosaic embryo transfer and offers up-to-date recommendations for management of embryos with mosaic results from PGT-A based on the most current evidence. The document indicates that the value of PGT-A for universal screening for individuals undergoing IVF has not been established and in fact, has been shown to have no benefit for improvement of LBR in 2 RCTs (Yan et al., 2021; Munné et al, 2019). Still, the use of PGT-A is increasing in the United States; with this increase, the importance of suspected chromosomal mosaicism in embryos has become a topic of much discussion and controversy. The ASRM recommends comprehensive genetic counseling for all individuals considering embryo transfer with PGT-A results indicating mosaicism and for those that conceive after mosaic embryo transfer. The counselor should have specialty training in the realm of PGT and mosaic results. Referral to a pediatric geneticist is recommended for individuals whose results indicate abnormal physical or developmental phenotypes.

An opinion regarding the disclosure of fetal sex when incidentally revealed as part of PGT was published by the ASRM in 2018. The committee recommends that clinics should have policies in place regarding the determination and disclosure of fetal sex when performing PGT. Patients should give consent as to whether they wish to know available information on sex of embryo(s). Nondiscrimination policies should be developed by clinics performing PGT and patients should be made aware of such policies. In addition, clinics should have policies for using randomized selection of embryos in cases where more embryos are available than can be transferred. Finally, clinics should also develop policies that prohibit consideration of sex of embryo as a factor for transfer and prioritize embryo quality for selection instead. (Ethics Committee of the ASRM, 2018)

The Ethics committee of ASRM published a comprehensive review of the use of PGT-M for adult-onset conditions in 2018. The committee concluded that PGT-M for monogenic adult-onset conditions is ethical when the condition is serious and no safe, effective interventions are available. Genetic counselors experienced with PGT-M should provide comprehensive counseling to couples considering PGT-M for adult-onset diseases.

American Society for Reproductive Medicine (ASRM)/Society for Assisted Reproductive Technology (SART)

In this joint Practice Committee Opinion from 2018, ASRM and SART state that while some studies have demonstrated higher birth rates after the use of PGT-A and single-embryo transfer, the studies have important limitations. They conclude that the value of PGT-A as a screening test for in vitro fertilization patients has yet to be determined. Large, prospective studies evaluating a variety of approaches to embryo selection are needed to determine the safety and risks of various technologies.

European Society for Human Reproduction and Embryology (ESHRE)

A 2022 position statement from ESHRE supports the ESHG position regarding PRS in PGT, acknowledging that PRSs can yield helpful data for populations by identifying at-risk groups, but asserting that making predictions for individuals is not reliable. In addition, ESHRE agrees with ESHG that significant ethical and scientific concerns exist around this technology. In summary, ESHRE states that the clinical utility of PRS is low to absent for selection of embryos and does not support its use in clinical practice.

In 2020, ESHRE published a series of four papers promoting best practices in PGT; however, the authors note that the papers should not be interpreted as standard of care or inclusive/exclusive of other methods of care. ESHRE recommends that PGT should only be applied when the reliability of the diagnosis is high and potential contraindications (such as age, ability to retrieve gametes, signs/symptoms of autosomal dominant or x-linked disorder which could cause medical complications during the IVF/pregnancy process) have been considered. Physical and psychological problems should be addressed as well. PGT testing is inappropriate in case of uncertain genetic diagnosis (for example genetic/molecular heterogeneity), or in case of uncertain mode of inheritance. For identifying chromosome structural rearrangements, PGT-SR is a routine procedure in most IVF/PGT centers for patients unable to achieve a pregnancy or at high risk of pregnancy loss and/or abnormal live born births resulting from inheritance of unbalanced products of the rearrangement. However, PGT-SR is only recommended if the technique applied can detect all expected unbalanced forms of the chromosomal rearrangement. PGT-M testing is carried out to confirm pathogenic germline genetic variant(s) that may have serious health effects potentially manifesting at birth, in childhood or in adulthood. Exclusion or non-disclosure testing may be appropriate for late-onset disease, such as Huntington's disease, to avoid pre-symptomatic testing of the individual with a family history of the disease. Exclusion testing is preferred over PGT with non-disclosure of test results to the couple. Cited indications for PGT-A have included advanced maternal age, recurrent implantation failure, severe male factor (SMF) and recurrent miscarriage in couples with normal karyotypes, however the value of PGT-A for all or a subset of individuals undergoing IVF remains heavily debated and is the subject of ongoing discussions and research.

European Society of Human Genetics (ESHG)

In a 2022 publication, Forzano et al. (on behalf of the Executive Committee and the Public and Professional Policy Committee of the ESHG) states the utility for embryo selection using PRS analysis is "severely limited" with no clinical research assessing its diagnostic effectiveness in embryos performed to date. The ESHG recommends education regarding the use of PRS and its limitations and indicates that societal debate focused on what could be considered acceptable regarding individual trait selection must take place before any further implementation of this technology.

European Society of Human Genetics (ESHG)/European Society for Human Reproduction and Embryology (ESHRE)

In a 2017 consensus paper, ESHG and ESHRE (Harper et al., 2017) reviewed the pros and cons PGT-M and PGT-A. The authors noted that RCTs for PGT-A are lacking, and that what constitutes success in the literature has been defined differently by different authors, creating a situation where it is not possible to conduct a meta-analysis of available literature. The data to date suggests that PGT-A may improve the clinical outcome for patients with normal ovarian reserve, but more data is needed to determine the validity of PGT-A in other patient populations and at which stage of embryo biopsy.

Preimplantation Genetic Diagnosis International Society (PGDIS)

The PGDIS updated their position statement regarding the transfer of mosaic embryos to include new evidence in 2021 (Leigh et al.). The position statement indicates that embryos with higher-level mosaicism appear to be associated with less favorable outcomes when compared to lower-level mosaicism, and relative percentage of mosaicism seems to better predict outcome than the involvement of specific chromosomes. As such, relative percentage of mosaicism should be included in patient discussions and in reporting. The PGDIS further states that decision to transfer a mosaic embryo can be prioritized based either on the level or type of mosaicism, and if there is a choice between similar levels of mosaicism, preference may be considered based on morphology of embryo or the nature of the variation. Comprehensive patient

education and support regarding potential mosaic embryos and prioritization of euploid blastocysts continue to be part of the recommendations for clinicians.

In a 2019 position statement (Cram et al.), the PGDIS states that “chromosome testing strategies, such as PGT-A, improve initial IVF outcomes by avoiding unwitting transfer of aneuploid embryos in morphology-based selection practices.” The statement goes on to address the transfer of mosaic embryos, stating that transfer of an euploid embryo is preferred, but if that is not feasible, priority for transfer of a mosaic embryo should be based on the level of mosaicism over the specific chromosome involved, with preference given to embryos with a mosaicism of less than forty percent. In the event where there must be a choice between the transfer of two unequivocal mosaic embryos, mosaicism involving uniparental disomy, intra-uterine growth retardation, or live-born syndromes should be given lower priority. Patients should be educated on the risks associated with the transfer of mosaic embryos, and it is recommended that an additional cycle of PGT-A be considered to increase the likelihood of obtaining an euploid embryo for transfer.

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 January 10, 2024)

Refer to the following website for a list of nucleic acid-based tests that have been cleared or approved by the Center for Devices and Radiological Health: <https://www.fda.gov/medical-devices/in-vitro-diagnostics/nucleic-acid-based-tests>. (Accessed January 10, 2024)

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