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Invasive Prenatal Diagnosis of Genetic Diseases

Clinical Policy Bulletins | Medical Clinical Policy Bulletins

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Policy History

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Definitions

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Policy

Scope of Policy

This Clinical Policy Bulletin addresses invasive prenatal diagnosis of genetic diseases.

I. Medical Necessity

A. Aetna considers the following medically necessary:

1. Invasive prenatal diagnosis by chorionic villus sampling (CVS), genetic amniocentesis, and percutaneous umbilical blood sampling (PUBS) (cordocentesis) for diagnosis of fetal chromosomal abnormalities.
2. Preimplantation genetic testing for monogenic disorders (PGT-M) (formerly called preimplantation genetic diagnosis [PGD]) which detects specific genetic diseases (usually autosomal recessive conditions) by using molecular analysis techniques on single cells removed from the embryo. PGT-M / PGD on single cells is considered medically necessary when all of the following criteria are met:

   a. Technical and clinical performance of the genetic test is supported by published peer-reviewed medical literature; and
   b. PGT-M / PGD is performed for any of the following indications:

      i. To diagnose an autosomal dominant condition when at least one parent is a known carrier; or
      ii. To diagnose an autosomal recessive condition when both parents are known carriers (e.g., cystic fibrosis when parents are known mutation carriers); or
      iii. To diagnose an X-linked condition when at least one parent is a known carrier (e.g., hemophilia) (Note: If PGT-M / PGD is requested for evaluation of Fragile X syndrome, medical necessity criteria are met if one parent is a known carrier of more than 55 triplet repeats of the Fragile X gene, which is associated with risk for disease in the offspring); or

iv. To diagnose an embryo at risk for a disease-causing chromosome rearrangement when one parent is a known carrier of a balanced (e.g. Robertsonian translocation, inversion) or unbalanced chromosomal rearrangement (e.g. insertion, deletion) translocation; and

c. Results of genetic testing will directly impact and change management of the individual being tested who is a covered member; and
d. The PGT-M / PGD procedure will eliminate the need for subsequent invasive prenatal diagnosis by genetic amniocentesis or CVS; and
e. A specific mutation, or set of mutations, has been identified, that specifically identifies the genetic disease with a high degree of reliability; and
f. The genetic disease is associated with clinically significant morbidity or disability.

Aetna considers PGT-M / PGD not medically necessary for sex selection for non-medical purposes.

Note: PGT-M (formerly called PGD) and Preimplantation genetic testing for aneuploidy (PGT-A) (formerly called preimplantation genetic screening [PGS]) are performed on embryos produced after IVF cycles. The methods used to retrieve PGT-M (PGD) material from embryos are the same, irrespective of the type of genetic analysis required. The biopsy procedure entails micro-manipulation and special techniques are used to avoid contamination from exogenous DNA (e.g., cellular DNA from non-fertilizing sperm) in the IVF laboratory. However, for carriers of single gene disorders (e.g., cystic fibrosis, spinal muscular atrophy) where polymerase chain reaction [PCR] will be applied on PGT-M (PGD) material from embryos, ICSI is considered medically necessary to avoid contamination from non-fertilizing sperm for members with the ART benefit. ICSI is considered not medically necessary for creation of embryos that will undergo aneuploidy (PGT-A) screening. The procedure to obtain the cell sample for PGT-M / PGD (i.e., the embryo biopsy) is considered medically necessary when criteria for PGT-M / PGD are met. However, the IVF procedure (i.e., the procedures and services required to create the embryos to be tested and the transfer of the appropriate embryos back to the uterus after testing) is covered only for persons with ART benefits who meet medical necessity criteria for IVF outlined in CPB 0327 - Infertility (0327.html). Please check benefit plan descriptions.

B. Aetna considers conventional cytogenetic analysis and quantitative fluorescent polymerase chain reaction (QF-PCR) a medically necessary method to detect trisomies whenever prenatal testing is performed solely because of an increased risk of aneuploidy in chromosomes 13, 18, 21, X or Y.

1. Both conventional cytogenetics and QF-PCR are considered medically necessary in all cases of prenatal diagnosis referred for a fetal ultrasound abnormality (including an increased nuchal translucency measurement greater than 3.5 mm) or a familial chromosomal rearrangement.
2. Cytogenetic follow-up of QF-PCR findings of trisomy 13 and 21 is considered medically necessary to rule out inherited Robertsonian translocations.

Note: Established nongenetic indications for amniocentesis include assessment of fetal lung maturity, and evaluation of the fetus for infection, degree of hemolytic anemia, blood or platelet type, hemoglobinopathy, and neural tube defects. Amniocentesis is also performed as a therapeutic procedure to remove excess amniotic fluid. See CPB 0449 - Fetal Surgery in Utero (../400_499/0449.html).

II. **Experimental, Investigational, or Unproven**

Aetna considers the following experimental, investigational, or unproven:

- Preimplantation genetic testing for aneuploidy (PGT-A) (formerly called preimplantation genetic screening [PGS]) (either too many or too few chromosomes in an embryo), including but not limited to optimization of IVF outcomes, history of failed IVF cycles, or recurrent miscarriages;

  Note: There are multiple ways to perform PGT-A / PGS. Two modalities commonly used are microarray analysis, with single nucleotide polymorphism (SNP) or comparative genomic hybridization (CGH) analysis. Another way is the Igenomix SMART PGT-A (Preimplantation Genetic Testing - Aneuploidy) Test, which entails the analysis of 24 chromosomes using embryonic DNA genomic sequence analysis for aneuploidy, and a mitochondrial DNA score in euploid embryos.

- Invasive prenatal screening and preimplantation genetic testing for a VUS (also known as unclassified variant or variant of uncertain significance);
- IriSight Prenatal Analysis;
- Multigene panels at time of PGT-M / PGD testing;
- PGT-M / PGD for fetal chromosomal abnormalities because the procedure is not as accurate as cytogenetic analysis performed on prenatal diagnosis specimens obtained by CVS or amniocentesis;
- PGT-M / PGD to determine the human leukocyte antigen (HLA) or other marker status of an embryo as a potential donor for future stem cell transplant because PGT-M / PGD has not been established as the standard of care for assessing the suitability of embryos for stem cell transplantation;
- Natera Spectrum PGT-M (preimplantation genetic testing for monogenic disorders) due to insufficient evidence of technical and clinical performance in published peer-reviewed medical literature.

III. Related Policies

- CPB 0282 - Noninvasive Down Syndrome Screening (../200_299/0282.html)
- CPB 0327 - Infertility (0327.html)
- CPB 0449 - Fetal Surgery in Utero (../400_499/0449.html)
- CPB 0464 - Serum and Urine Marker Screening for Fetal Aneuploidy (../400_499/0464.html)

Applicable CPT / HCPCS / ICD-10 Codes

CPT codes covered if selection criteria are met:

Code	Code Description
59000	Amniocentesis; diagnostic
59012	Cordocentesis (intrauterine), any method
59015	Chorionic villus sampling, any method
81171	AFF2 (AF4/FMR2 family, member 2 [FMR2]) (eg, fragile X mental retardation 2 [FRAXE]) gene analysis; evaluation to detect abnormal (eg, expanded) alleles
81172	AFF2 (AF4/FMR2 family, member 2 [FMR2]) (eg, fragile X mental retardation 2 [FRAXE]) gene analysis; characterization of alleles (eg, expanded size and methylation status)
81243	FMR1 (Fragile X mental retardation 1) (eg, fragile X mental retardation) gene analysis; evaluation to detect abnormal (eg, expanded) alleles
81244	FMR1 (fragile X mental retardation 1) (eg, fragile X mental retardation) gene analysis; characterization of alleles (eg, expanded size and promoter methylation status)

	promoter methylation status)
88248	Chromosome analysis for breakage syndromes; baseline breakage, score 50-100 cells, count 20 cells, 2 karyotypes (eg, for ataxia telangiectasia, Fanconi anemia, fragile X)
88271 - 88299	Molecular cytogenetics
89290 - 89291	Biopsy, oocyte polar body or embryo blastomere, microtechnique (for pre-implantation genetic diagnosis); less than, equal, or greater than 5 embryos [not covered to enhance delivery rates in advanced reproductive technologies]
CPT codes not covered for indications listed in the CPB:	
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
0335U	Rare diseases (constitutional/heritable disorders), whole genome sequence analysis, including small sequence changes, copy number variants, deletions, duplications, mobile element insertions, uniparental disomy (UPD), inversions, aneuploidy, mitochondrial genome sequence analysis with heteroplasmy and large deletions, short tandem repeat (STR) gene expansions, fetal sample, identification and categorization of genetic variants
0336U	Rare diseases (constitutional/heritable disorders), whole genome sequence analysis, including small sequence changes, copy number variants, deletions, duplications, mobile element insertions, uniparental disomy (UPD), inversions, aneuploidy, mitochondrial genome sequence analysis with heteroplasmy and large deletions, short tandem repeat (STR) gene expansions, blood or saliva, identification and categorization of genetic variants, each comparator genome (eg, parent)
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
86828 - 86829	Antibody to human leukocyte antigens (HLA), solid phase assays (eg, microspheres or beads, ELISA, flow cytometry); qualitative assessment of the presence or absence of antibody(ies) to HLA Class I and/or Class II HLA antigens
86830 - 86831	Antibody to human leukocyte antigens (HLA), solid phase assays (eg, microspheres or beads, ELISA, Flow cytometry); antibody identification by qualitative panel using complete HLA phenotypes, HLA Class I or HLA Class II
86832 - 86833	Antibody to human leukocyte antigens (HLA), solid phase assays (eg, microspheres or beads, ELISA, Flow cytometry); high definition qualitative panel for identification of antibody specificities (eg, individual antigen per bead methodology), HLA Class I or HLA Class II
86834 - 86835	Antibody to human leukocyte antigens (HLA), solid phase assays (eg, microspheres or beads, ELISA, Flow cytometry); semi-quantitative panel (eg, titer), HLA Class I or HLA Class II
89280	Assisted oocyte fertilization, microtechnique; less than or equal to 10 oocytes [ICSI (Intracytoplasmic sperm injection)]
89281	Assisted oocyte fertilization, microtechnique; greater than 10 oocytes [ICSI (Intracytoplasmic sperm injection)]
Other CPT codes related to the CPB:	

Other CPT codes related to the CPB:	
58321 - 58322	Artificial insemination
81228 - 81229	Cytogenomic constitutional (genome-hyphenwide) microarray analysis
Other HCPCS codes related to the CPB:	
S3840	DNA analysis for germline mutations of the RET proto-oncogene for susceptibility to multiple endocrine neoplasia type 2
S3841 - S3853	Genetic testing
S4011 - S4022	In vitro fertilization
ICD-10 codes covered for indications listed in the CPB (not all-inclusive):	
E70.310	X-linked ocular albinism
E71.520 - E71.529	X-linked adrenoleukodystrophy
Q80.1	X-linked ichthyosis
Q90.0 - Q90.9	Down syndrome
Q91.0 - Q91.3	Trisomy 18 [Edward's syndrome]
Q91.4 - Q91.7	Trisomy 13 [Patau's syndrome]
Q95.0 - Q95.9	Balanced rearrangements and structural markers, not elsewhere classified
Q96.0 - Q96.9	Turner's syndrome
Q98.0 - Q98.4	Klinefelter syndrome
Q98.6	Male with structurally abnormal sex chromosome
Q98.7	Male with sex chromosome mosaicism
Q98.8	Other specified sex chromosome abnormalities, male phenotype
Q99.2	Fragile X chromosome
Z14.01 - Z14.02	Asymptomatic and symptomatic hemophilia A carrier
Z14.1	Cystic fibrosis carrier
Z14.8	Genetic carrier of other disease
ICD-10 codes not covered for indications listed in the CPB:	
N96	Recurrent pregnancy loss
Q99.8	Other specified chromosome abnormalities [not covered for VUS (unclassified variant or variant of uncertain significance)]
Q99.9	Chromosomal abnormality, unspecified [not covered for VUS (unclassified variant or variant of uncertain significance)]
Z13.79	Encounter for other screening for genetic and chromosomal anomalies
Z31.441	Encounter for testing of male partner of patient with recurrent pregnancy loss

Background

Preimplantation genetic testing (PGT) includes two categories: preimplantation genetic testing for monogenic/single gene disorders (formerly known as preimplantation genetic diagnosis) and preimplantation genetic testing for aneuploidies (formerly known as preimplantation genetic screening). According to the American Society for Reproductive Medicine, the term 'preimplantation genetic diagnosis' (PGD) applies when one or more genetic parents carry a gene mutation or a balanced chromosomal rearrangement and testing is performed to determine whether that specific mutation or an unbalanced chromosomal complement has been transmitted to the oocyte or embryo. PGD, which is now referred to as 'preimplantation genetic testing for monogenic disorders' (PGT-M), is performed on embryos following in vitro fertilization (IVF) to detect genetic disorders prior to implantation into the uterus. With PGT-M, cell(s) are removed from embryos under microscopic guidance, analyzed for the presence of genetic disorders and only the unaffected embryos are implanted into the uterus. PGT-M is used when one or both parents carry a gene mutation and are at high risk of conceiving a child with a particular genetic disease.

The term 'preimplantation genetic screening' (PGS) is now referred to as 'preimplantation genetic testing for aneuploidy' (PGT-A). PGT-A applies when the genetic parents are known or presumed to be chromosomally normal and their embryos are screened for aneuploidy. PGT-A is performed on embryos following IVF to screen for aneuploidy in parents who have no known chromosomal anomaly, mutation or other genetic abnormality. PGT-A has been proposed for individuals at risk for having an increased occurrence of aneuploid embryos, such as women of advanced maternal age and those with a history of recurrent early pregnancy loss or repeated IVF failure.

PGT-M can detect specific genetic diseases (usually autosomal recessive conditions) by using molecular analysis techniques on single cells removed from the embryo. For many conditions, the usual type of prenatal diagnosis (i.e., chromosomal analysis/karyotyping) is accomplished on multiple cells obtained by chorionic villus sampling (CVS) or genetic amniocentesis. PGT-M on single cells is considered medically necessary only when there is a need to diagnose specific, detectable single gene mutations (e.g., molecular diagnosis of hereditary disease such as cystic fibrosis when parents are known mutation carriers or fragile X syndrome when the mother is a known carrier) in persons with genetic disorders for whom the PGT-M (PGD) procedure will eliminate the need for subsequent invasive prenatal diagnosis by genetic amniocentesis or CVS. PGT-M for fetal chromosomal abnormalities is currently not as accurate as cytogenetic analysis performed on prenatal diagnosis specimens obtained by CVS or amniocentesis; therefore PGT-M is considered experimental and investigational for that indication.

The diagnosis of fragile X syndrome and other FMR1 disorders is established through the use of specialized molecular genetic testing to detect CGG trinucleotide repeat expansion in the 5' UTR of FMR1 with abnormal gene methylation for most alleles with >200 repeats. Typically, a definite diagnosis of FXS requires the presence of a full-mutation repeat size (>200 CGG repeats) while the diagnosis of FXTAS or FXPOI is associated with a premutation-sized repeat (55-200 CGG repeats).

According to the literature, the accuracy of single gene testing conducted on single cells is thought to be as accurate using PGT-A procedures as it would be on cell samples obtained by conventional CVS or amniocentesis. However, PGT-A procedures have not been shown to be as accurate as conventional techniques for diagnosing chromosomal errors. Because preimplantation genetic diagnostic procedures are less accurate in detecting chromosomal abnormalities (detecting up to 95 % of chromosomal errors using fluorescent in-situ hybridization (FISH) techniques, versus 100 % detection with analysis of full karyotype), CVS or amniocentesis is usually necessary to confirm the results of FISH-based PGT-M cytogenetic procedures.

PGT-A, formerly known as 'preimplantation genetic diagnosis-aneuploidy screening' (PGD-AS) and PGS for fetal aneuploidy, involves in-vitro genetic testing of embryos to detect numerical chromosomal abnormalities (aneuploidies). PGD-AS has been investigated as a method of increasing the effectiveness of in-vitro fertilization (IVF) by increasing the live birth rate and reducing the risk of complications from IVF. Miscarried fetuses are often found to have an aneuploidy, as most aneuploides are not compatible with life. Aneuploides have also be found in aborted embryos created by means of IVF. Clinical research is currently being conducted to find out whether PGD-AS can increase the likelihood of live birth from each implanted embryo in IVF. By increasing the likelihood of a live birth from each implanted embryo, PGD-AS has the potential to decrease the need to implant 2 embryos instead of 1, thus reducing the risk of multiple pregnancy from IVF and its attendant complications. PGD-AS is also being investigated for use in women undergoing IVF as an alternative to standard methods of prenatal diagnosis of Down syndrome and other aneuploides.

A systematic evidence review of PGD-AS by the Health Council of the Netherlands (GR, 2007) found "little useful research data" on the effect, reliability and safety of PGD-AS. The assessment reported that small-scale studies of PGD-AS have been conducted in women with repeated implantation failure, with recurrent miscarriage, and in women of advanced maternal age; the assessment found that these studies "do not point to any marked improvement in the likelihood of pregnancy." The assessment also found that it "remains unclear" whether PGD-AS is an effective alternative to prenatal diagnosis. The assessment concluded that "[m]ore data is needed before [PGD-AS] can be carried out or offered as a matter of routine." The assessment noted that, if further research established that PGD-AS increases the success rate of IVF, it will be important to clearly establish the indications for PGD-AS and to assure its quality and safety.

In a literature review, Shulman (2003) stated that fetal cells in maternal blood represent the future of prenatal screening and diagnosis. The possibility of analyzing fetal cells recovered from maternal blood could provide screening and diagnostic protocols characterized by high sensitivity and specificity with no direct risk to the developing fetus. However, years of research have thus far not led to the development of reliable and consistent protocols.

In a review, Sierra and Stephenson (2006) stated that research has generated interest in genetic markers for recurrent pregnancy loss such as skewed X-chromosome inactivation and human leukocyte antigen-G polymorphisms. Assisted reproductive technologies, in particular, PGD have been offered to couples with recurrent pregnancy loss; however, more research is need before their routine use can be advocated. This is in agreement with the observation of Shahine and Cedars (2006) who noted that although analysis with PGD confirms a high rate of aneuploidy in patients with advanced maternal age, recurrent pregnancy loss, and recurrent IVF failure, its use in these patient populations has not been consistently demonstrated to increase pregnancy rates. They stated that randomized controlled studies with large patient populations, performed in programs with expertise in PGD technology, are needed before PGD can routinely be recommended as a means for increasing pregnancy rates in patients with advanced maternal age, recurrent pregnancy loss, and recurrent IVF failure.

Staessen and colleagues (2004) evaluated the possible benefit of PGD for aneuploidy screening (PGD-AS) on the outcome following assisted reproductive technology (ART). A prospective randomized controlled clinical trial was performed comparing the outcome after blastocyst transfer combined with PGD-AS by means of FISH for the chromosomes X, Y, 13, 16, 18, 21 and 22 in advanced maternal age couples (aged greater than or equal to 37 years) with a control group without PGD-AS. From the 400 (200 for PGD-AS and 200 controls) couples that were enrolled in the trial, an oocyte pick-up was carried out effectively in 289 cycles (148 PGD-AS cycles and 141 control cycles). Positive serum human chorionic gonadotropin rates per transfer and per cycle were the same for PGD-AS and controls: 35.8 % (19.6 %) [%/per embryo transfer (per cycle)] and 32.2 % (27.7 %), respectively (not statistically significant). Significantly fewer embryos were transferred in the PGD-AS group than in the control group ($p < 0.001$). The implantation rate (with fetal heart beat) was 17.1 % in the PGD-AS group versus 11.5 % in the control group (not significant; $p = 0.09$). These researchers observed a normal diploid status in 36.8 % of the embryos. They concluded that this randomized controlled study provided no arguments in favor of PGD-AS for improving clinical outcome per initiated cycle in patients with advanced maternal age when there are no restrictions in the number of embryos to be transferred.

Urman et al (2005) stated that the success of ART, although gradually increasing over the years, is still less than satisfactory. Even though many couples have benefited from this approach, many have also been frustrated following multiple failed attempts. Couples who fail to conceive after multiple IVF/ICSI treatments often seek treatment options that are new and that have not been offered before. Some of these include immunological testing and treatment, allogeneic lymphocyte therapy, intra-tubal transfer of zygotes and embryos, blastocyst transfer, sequential embryo transfer, assisted hatching, co-cultures, and PGD-AS. Although the evidence behind some of these new approaches is more robust, most suffer from lack of well-designed randomized studies comparing them with other treatment options. Randomized controlled trials are extremely difficult to conduct, as couples will resist being randomized into a treatment group where previously failed procedures will be repeated. In the mean time, ART programs should resist offering treatment options that are not evidence-based, or at least they should share with the couple the information that is available and should stress that none of these is a panacea for their problem.

In a Cochrane review, Twisk and co-workers (2006) concluded that to date there is inadequate data to determine if PGS is an effective intervention in IVF and ICSI for improving live birth rates. These investigators noted that available data on PGS for advanced maternal age showed no difference in live birth rate and ongoing pregnancy rate. Furthermore, only 2 randomized trials were found, of which one included only 39 patients. They noted that for both studies comments on their methodological quality can be made. Therefore more properly conducted randomized controlled trials are needed. Until such trials have been performed, PGS should not be used in routine patient care.

Ogilvie et al (2001) stated that reciprocal translocations are found in about 1 in 500 people, whereas Robertsonian translocations occur with a prevalence of 1 in 1,000. Balanced carriers of these rearrangements, although phenotypically normal, may present with infertility, recurrent miscarriage, or offspring with an abnormal phenotype after segregation of the translocation at meiosis. Once the translocation has been identified, prenatal diagnosis can be offered, followed by termination of pregnancies with chromosome imbalance. Couples who have suffered repeated miscarriage or those who have undergone termination of pregnancy as a result of the translocation carrier status of one partner are looking increasingly to PGD as a way of achieving a normal pregnancy. Similarly, infertile couples in which one partner is a translocation carrier may request PGD to ensure transfer of normal embryos after in-vitro fertilization. Translocation PGD has been applied successfully in several centers worldwide and should now be considered as a realistic treatment option for translocation carriers who do not wish to trust to luck for a successful natural outcome.

Sermon (2002) noted that the first clinically applied PGD was reported more than a decade ago and since then PGD has known an exponential growth. This report described the use of polymerase chain reaction (PCR) to sex embryos from couples at risk for X-linked diseases. Not surprisingly, in the first years, the development of PCR-based tests led to PGD for well-known monogenic diseases such as cystic fibrosis and thalassaemia. When FISH was introduced it quickly replaced PCR-based methods, which had led to misdiagnoses, for sexing of embryos. FISH was also quickly introduced for aneuploidy screening, which has as its main aim the improvement of IVF results in patients with poor reproductive outcome, and later for PGD in translocation carriers.

Pehlivan et al (2003) noted that PGD using FISH is being used widely to prevent the transmission of sex-linked diseases, to screen for translocations, and for aneuploidy screening in specific IVF patient groups, along with FISH analysis of spermatozoa in infertile men. These investigators analyzed their clinical results in patients at risk of transmitting sex-linked diseases (n = 55), in carriers of translocations (n = 43), in women who have recurrent miscarriage (2 or more miscarriages) (n = 128), recurrent IVF failure (3 or more failed IVF attempts) (n = 47), and patients of advanced maternal age (37 years old or older) (n = 79). The use of the FISH technique in carriers of sex-linked diseases and translocation patients prevents transmission of these conditions and provides good IVF outcome. In patients with recurrent miscarriage, implantation failure, and advanced maternal age, a high incidence of embryos with abnormal chromosomes 13, 16, 18, 21, 22, X, and Y was observed (range 69 to 75 %), as expected. In those 3 groups of patients, the selection of euploid embryos for transfer resulted in good pregnancy rates with a low incidence of miscarriage.

Munne (2005) stated that individuals carrying translocations suffer from reduced fertility or spontaneous abortions and seek help in form of ART and PGD. While most translocations are relatively easy to detect in metaphase cells, the majority of embryonic cells biopsied in the course of IVF procedures are in interphase. These nuclei are thus unsuitable for analysis by chromosome banding or painting using FISH. Thus several methods have been devised to detect translocation imbalance through FISH in single cells for purpose of PGD, among them polar body chromosome painting, interphase FISH with combination of subtelomeric and centromeric probes, breakpoint spanning probes, and cell conversion. Results with PGD indicate a significant decrease in spontaneous abortions, from 81 % before PGD to 13 % after PGD. They also indicate very high rates of chromosome abnormalities in embryos from translocation carriers, 72 % for Robertsonian translocations and 82 % for reciprocal translocations. Sperm analysis was found to be a good predictor of IVF and PGD outcome, with samples with more than 60 % abnormal forms indicating poor prognosis. Similarly, the predictability from first PGD cycle results for future cycles was 90 %. The authors concluded that PGD can help translocation carriers to achieve viable pregnancies, but the success of the process is conversely related to the baseline of unbalanced gametes.

Donoso and Devroey (2007) stated that PGD diagnosis for aneuploidy screening (PGD-AS) constitutes a technique developed to improve embryo selection in patients with a poor outcome after IVF treatment due to an increased frequency of numerical chromosome abnormalities in the embryos. Although multiple studies have evaluated the performance of PGD-AS in different groups of patients, inconsistencies in the evidence available have not enabled definitive conclusions to be drawn. According to randomized trials, PGD-AS does not improve the outcome of women of advanced age when there is no limitation on the number of embryos to be transferred. In patients who have experienced recurrent implantation failure or recurrent miscarriage, PGD-AS only seems to provide diagnostic information, especially when aneuploid embryos alone are found. The authors concluded that additional evidence is needed before PGD-AS is implemented as part of routine clinical practice.

The American Society for Reproductive Medicine (2007) reached the following conclusions regarding preimplantation genetic screening (PGS):

- Available evidence does not support the use of PGS as currently performed to improve live-birth rates in patients with advanced maternal age;
- Available evidence does not support the use of PGS as currently performed to improve live-birth rates in patients with previous implantation failure;
- Available evidence does not support the use of PGS as currently performed to improve live-birth rates in patients with recurrent pregnancy loss;
- Available evidence does not support the use of PGS as currently performed to reduce

miscarriage rates in patients with recurrent pregnancy loss related to aneuploidy
- Because the prevalence of aneuploidy is high in the embryos of patients with recurrent implantation failure, decisions concerning future treatment should not be based on the results of PGS in one or more cycles.

According to the Preimplantation Genetic Diagnosis International Society (PGDIS) program and laboratory quality assurance guidelines for the performance of PGD (2008), there are no restrictions on the technique of insemination in PGD performed for aneuploidy and translocations using FISH; however, for carriers of single gene disorders where PCR will be applied, or for molecular (comparative genomic hybridization [CGH], DNA microarrays) assessment of chromosome status, ICSI is recommended to avoid cellular DNA from non-fertilizing sperm. This is in agreement with the *European Society of Human Reproduction and Embryology (ESHRE) PGD Consortium Best Practice Guidelines for Clinical Preimplantation Genetic Diagnosis (PGD) and Preimplantation Genetic Screening (PGS)* (2005) that stated, "[t]hese guidelines recommend ICSI as the method for insemination when performing a PCR-based diagnostic test on single embryonic cells since the risk of contamination from extraneous cells or DNA has greater consequences for the accuracy of the test when using PCR compared with fluorescence in situ hybridization (FISH)." Furthermore, the guidelines stated, "ICSI or conventional insemination is acceptable for FISH cases."

The American College of Obstetricians and Gynecologists (ACOG) (2009) stated "Current data does not support a recommendation for preimplantation genetic screening for aneuploidy using fluorescence in situ hybridization solely because of maternal age. Also, preimplantation genetic screening for aneuploidy does not improve in vitro fertilization success rates and may be detrimental. At this time there are no data to support preimplantation genetic screening for recurrent unexplained miscarriage and recurrent implantation failures; its use for these indications should be restricted to research stuides with appropriate informed consent."

In a randomized, controlled, prospective clinical study, Meyer et al (2009) examined if the routine use of PGS in "good prognosis" women improves IVF cycle outcome. Infertile women predicted to have a good prognosis as defined by: age less than 39 years, normal ovarian reserve, body mass index less than 30 kg/m(2), presence of ejaculated sperm, normal uterus, less than or equal to 2 previous failed IVF cycles were included in thisstudy. Patients were randomized to the PGS group or the control group on day 3 after oocyte retrieval; 23 women underwent blastomere biopsy on day 3 after fertilization (PGS group), and 24 women underwent routine IVF (control group). All embryos were transferred on day 5 or 6 after fertilization. Main outcome measures were pregnancy, implantation, multiple gestation, and live birth rates. No statistically significant differences were found between the PGS and control groups with respect to clinical pregnancy rate (52.4 % versus 72.7 %). However, the embryo implantation rate was statistically significantly lower for the PGS group (31.7 % versus 62.3 %) as were the live birth rate (28.6 % versus 68.2 %) and the multiple birth rate (9.1 % versus 46.7 %). The authors concluded that in a "good prognosis" population of women, PGS does not appear to improve pregnancy, implantation, or live birth rates.

In a systematic review and meta-analysis, Checa and colleagues (2009) evaluated the effectiveness of PGS in raising pregnancy rates in couples without known genetic disorders. Systematic review and meta-analysis of randomized controlled trials were carried out. Two reviewers independently determined study eligibility and extracted data. A total of 10 randomized trials (1,512 women) were included. The quality of evidence was moderate. Meta-analyses using a random-effects model suggest that PGS has a lower rate of ongoing pregnancies (risk ratio [RR] = 0.73, 95 % confidence interval [CI]: 0.62 to 0.87) and a lower rate of live births (RR = 0.76, 95 % CI: 0.64 to 0.91) than standard IVF/ICSI. The authors concluded that in women with poor prognosis or in general IVF program, IVF/ICSI with PGS for aneuploidy does not increase but instead was associated with lower rates of ongoing pregnancies and live births. The use of PGS in daily practice does not appear to be justified.

In a prospective randomized controlled trial (RCT), Debrock et al (2010) tested the hypothesis that patients with advanced maternal age (AMA; greater than or equal to 35 years of age) have a higher implantation rate (IR) after embryo transfer of embryos with a normal chromosomal pattern for the chromosomes studied with PGS compared with patients who had an embryo transfer without PGS. The clinical IR per embryo transferred was compared after embryo transfer on day 5 or 6 between the PGS group (analysis of chromosomes 13, 16, 18, 21, 22, X, and Y) and the control group without PGS. No differences were observed between the PGS group and the control group for the clinical IR (15.1 %; 14.9 %; RR = 1.01; exact CI: 0.25 to 5.27), the ongoing IR (at 12 weeks) (9.4 %; 14.9 %), and the live born rate per embryo transferred (9.4 %; 14.9 %; RR = 0.63; exact CI: 0.08 to 3.37). Fewer embryos were transferred in the PGS group (1.6 +/- 0.6) than in the control group (2.0 +/- 0.6). A normal diploid status was observed in 30.3 % of the embryos screened by PGS. The authors concluded that in this RCT, the results did not confirm the hypothesis that PGS results in improved reproductive outcome in patients with AMA.

Harper and Harton (2010) stated that in PGD, PCR has been used to detect monogenic disorders, and in PGD/PGS, FISH has been used to analyze chromosomes. A total of 10 RCTs using FISH-based PGS on cleavage-stage embryos and 1 on blastocyst-stage embryos have shown that PGS does not increase delivery rates. Is the failure of PGS due to a fundamental flaw in the idea, or are the techniques that are being used unable to overcome their own, inherent flaws? Array-based technology allows for analysis of all of the chromosomes. Two types of arrays are being developed for use in PGD: (i) array CGH (aCGH) and (ii) single nucleotide polymorphism (SNP)-based arrays. Each array can determine the number of chromosomes, however, SNP-based arrays can also be used to haplotype the sample. The authors described aCGH and SNP array technology and made suggestions for the future use of arrays in PGD and PGS. They concluded that if array-based testing is going to prove useful, 3 steps need to be taken: (i) validation of the array platform on appropriate cell and tissue samples to allow for reliable testing, even at the single-cell level; (ii) deciding which embryo stage is the best for biopsy: polar body, cleavage, or blastocyst stage; and (iii) performing RCTs to show improvement in delivery rates. If RCTs are able to show that array-based testing at the optimal stage for embryo biopsy increases delivery rates, this will be a major step forward for assisted reproductive technology patients around the world.

In a clinical research study, Fragouli and colleagues (2010) identified and transferred cytogenetically normal embryos after screening all chromosomes of first and second polar bodies (PBs) or trophectoderm samples with the use of CGH. Zygotes from 32 couples with repeated implantation failure and poor response to ovarian stimulation underwent PB biopsy. Patients with repeated implantation failure who were candidates for blastocyst transfer received trophectoderm biopsy. Zygotes or blastocysts were vitrified while chromosome analysis took place. Euploid embryos were transferred during a subsequent cycle. Main outcome measures were cytogenetic status and implantation and pregnancy rates. The oocyte and blastocyst aneuploidy rates were 65.5 % and 45.2 %, respectively. Abnormalities affecting all chromosomes were detected. Implantation and pregnancy rates for the patients with PB biopsy were 11.5 % and 21.4 %, respectively, whereas for patients receiving blastocyst analysis they were 58.3 % and 69.2 %. The authors concluded that initial results for patients of AMA (39.8 years) with repeated implantation failure and poor ovarian response were encouraging. However, they stated that further study is needed to confirm whether or not screening is beneficial. Blastocyst analysis was associated with high pregnancy rates, suggesting that comprehensive chromosome screening may assist patients with repeated implantation failure capable of producing blastocysts in achieving pregnancies.

Geraedts and associates (2010) noted that screening of human preimplantation embryos for numerical chromosome abnormalities has been conducted mostly at the preimplantation stage using FISH. However, it is clear that PGS as it is currently practiced does not improve live birth rates. Thus, the ESHRE PGS Task Force has decided to start a proof of principle study with the aim of determining whether biopsy of the first and second polar body followed by subsequent analysis of the complete chromosome complement of these polar bodies using an array-based technique enables a timely identification of the chromosomal status of an oocyte. If the principle of this approach can be proven, it is obvious that a multi-center RCT should then be started to determine the clinical value of this technique. In this way, the ESHRE PGS Task Force hopes to redirect preimplantation screening from the blind alley to the main road of assisted reproduction.

Wells (2010) stated that chromosome abnormalities are common among human oocytes and are usually lethal to any embryos they produce. Thus, it seems logical that a reliable technique for distinguishing between normal and aneuploid embryos would be a useful tool for physicians and embryologists, assisting the choice of which embryo(s) to prioritize for uterine transfer. This concept has led to the development of a variety of methods for the detection of chromosome abnormalities in oocytes and embryos, most often referred to as PGS. However, several well-controlled studies have been unable to show an advantage of chromosome screening in terms of pregnancy and birth rates. Some investigators have suggested that damage to embryos, sustained during cleavage-stage biopsy, might explain why PGS has not always provided the anticipated benefits.

Mastenbroek et al (2011) performed a a systematic review and meta-analysis of RCTs on the effect of PGS on the probability of live birth after IVF. PubMed and trial registers were searched for RCTs on PGS. Trials were assessed following pre-determined quality criteria. The primary outcome was live birth rate per woman, secondary outcomes were ongoing pregnancy rate, miscarriage rate, multiple pregnancy rate and pregnancy outcome. A total of 9 RCTs comparing IVF with and without PGS were included in this meta-analysis. Fluorescence in situ hybridization was used in all trials and cleavage stage biopsy was used in all but 1 trial. Preimplantation genetic screening significantly lowered live birth rate after IVF for women of advanced maternal age (risk difference: -0.08; 95 % CI: -0. 13 to -0.03). For a live birth rate of 26 % after IVF without PGS, the rate would be between 13 and 23 % using PGS. Trials where PGS was offered to women with a good prognosis and to women with repeated implantation failure suggested similar outcomes. The authors concluded that there is no evidence of a beneficial effect of PGS as currently applied on the live birth rate after IVF. On the contrary, for women of advanced maternal age, PGS significantly lowers the live birth rate. Technical drawbacks and chromosomal mosaicism underlie this inefficacy of PGS. They stated that new approaches in the application of PGS should be evaluated carefully before their introduction into clinical practice.

Harper and Sengupta (2012) stated that for the last 20 years, PGD has been mostly performed on cleavage stage embryos after the biopsy of 1-2 cells and PCR and FISH have been used for the diagnosis. The main indications have been single-gene disorders and inherited chromosome abnormalities. Preimplantation genetic screening for aneuploidy is a technique that has used PGD technology to examine chromosomes in embryos from couples undergoing IVF with the aim of helping select the chromosomally "best" embryo for transfer. It has been applied to patients of advanced maternal age, repeated implantation failure, repeated miscarriages and severe male factor infertility. Recent RCTs have shown that PGS performed on cleavage stage embryos for a variety of indications does not improve delivery rates. At the cleavage stage, the cells biopsied from the embryo are often not representative of the rest of the embryo due to chromosomal mosaicism. There has therefore been a move towards blastocyst and polar body biopsy, depending on the indication and regulations in specific countries (in some countries, biopsy of embryos is not allowed). Blastocyst biopsy has an added advantage as vitrification of blastocysts, even post-biopsy, has been shown to be a very successful method of cryo-preserving embryos. However, mosaicism is also observed in blastocysts. There have been dramatic changes in the method of diagnosing small numbers of cells for PGD. Both array-CGH and SNP arrays have been introduced clinically for PGD and PGS. The authors concluded that for PGD, the use of SNP arrays brings with it ethical concerns as a large amount of genetic information will be available from each embryo. For PGS, RCTs need to be conducted using both array-CGH and SNP arrays to determine if either will result in an increase in delivery rates.

Fiorentino (2012) noted that embryo assessment is a crucial component to the success of IVF. A high rate of embryos produced in-vitro present chromosomal abnormalities and have reduced potential for achieving a viable pregnancy. The author reviewed the use of PGD by array-CGH, for comprehensive aneuploidy screening of embryos, to improve IVF outcomes. Data from comprehensive aneuploidy screening of embryos showed that aneuploidies may occur in any of the 24 chromosomes, indicating that aneuploidy screening of all chromosomes is necessary to determine whether an embryo is chromosomally normal. Initial studies on clinical application of this technology have documented improved pregnancy outcomes following transfer of screened embryos. However, the optimal stage of pre-implantation development at which PGS should be performed still remains to be determined. The author concluded that although clinical results have been promising, further evidence is needed to establish whether PGS results in enhanced live birth rate, and if this is the case, to identify which patients may benefit from the procedure. They stated that the results from several ongoing RCTs, performed at different cell biopsy stage and categories of patients, will provide the data needed to accept or reject the clinical effectiveness of PGS.

Brezina et al (2013) stated that the past several decades have seen tremendous advances in the field of medical genetics. The application of genetic technologies to the field of reproductive medicine has ushered in a new era of medicine that is likely to greatly expand in the coming years. Concurrent with an IVF cycle, it is now possible to obtain a cellular biopsy from a developing embryo and genetically evaluate this sample with increasing sophistication and detail. Preimplantation genetic screening is the practice of determining the presence of aneuploidy (either too many or too few chromosomes) in a developing embryo. However, how and in whom PGS should be offered is a topic of much debate.

An UpToDate review on "Preimplantation genetic screening (PGS) for aneuploidy" (Schattman, 2014) states that "Because of the limitations of testing a single cell from a heterogeneous multi-cell embryo, an abnormal result from analysis of a single blastomere by any method does not necessarily indicate that the embryo will be abnormal. Since there are false positives, embryos initially considered abnormal may be re-analyzed at the blastocyst stage and transferred if subsequent testing is normal. PGS using day 3 blastomere biopsy and FISH decreases the chances of live birth. For women of advanced maternal age or a history of IVF implantation failure, we recommend not undergoing PGS (Grade 1A). In couples with recurrent pregnancy loss, PGS is unlikely to benefit those with proven karyotypically normal miscarriages. In patients with karyotypically abnormal miscarriages, PGS may decrease the risk of subsequent miscarriage, although there is no evidence that it will increase the probability of having a child. In young, good prognosis couples, PGS using blastocyst biopsy and 23 chromosome analysis may improve the chance of conception with single embryo transfer; however, the chance of live birth after frozen embryo transfers is not increased".

Schmutzler et al (2014) examined if embryos derived from oocytes detected euploid for 5 chromosomes implant better than those that were biopsied but where the genetic detection failed. They were nevertheless transferred, thus serving as a sham control. From 2004 to 2008, these researchers performed 104 cycles of PGS with laser biopsy of the first polar body and FISH with 5 chromosomes. It was offered to all patients with 8 or more oocytes, free of charge. The average female age was 36 years. If no euploid oocytes were available, not detected oocytes were transferred. In 104 cycles, 99 embryo transfers (95 %) were performed, resulting in 28 pregnancies (27 %), 20 births (71 %) and 8 miscarriages (29 %). The implantation rate in the euploid group was 19 versus 13 % in the not detected group (non-significant). This trend was the same independent of age and embryo morphology. The authors concluded that the pregnancy rate does not differ significantly from the national average. Moreover, they stated that the trend in better implantation rates of euploid oocytes justifies a continuation of studies in this matter.

Gleicher et al (2014) stated that only a few years ago the American Society of Assisted Reproductive Medicine (ASRM), the European Society for Human Reproduction and Embryology (ESHRE) and the British Fertility Society declared preimplantation genetic screening (PGS#1) ineffective in improving IVF pregnancy rates and in reducing miscarriage rates. A presumably upgraded form of the procedure (PGS#2) has recently been re-introduced, and was assessed in a systematic review. PGS#2 in comparison to PGS#1 is characterized by: (i) trophectoderm biopsy on day 5/6 embryos in place of day-3 embryo biopsy; and (ii) FISH of limited chromosome numbers is replaced by techniques, allowing aneuploidy assessments of all 24 chromosome pairs. Reviewing the literature, these investigators were unable to identify properly conducted prospective clinical trials in which IVF outcomes were assessed based on "intent-to-treat". Thus, whether PGS#2 improves IVF outcomes cannot be determined. Re-assessments of data, alleged to support the effectiveness of PGS#2, indeed, suggested the opposite. Like with PGS#1, the introduction of PGS#2 into unrestricted IVF practice again appeared premature, and threatens to repeat the PGS#1 experience, when thousands of women experienced reductions in IVF pregnancy chances, while expecting improvements. The authors concluded that PGS#2 is an unproven and still experimental procedure, which, until evidence suggests otherwise, should only be offered under study conditions, and with appropriate informed consents.

Deng and Wang (2015) evaluated the aneuploidy formation in the blastocysts derived from frozen donor eggs and also evaluated the efficiency of egg vitrification as an ART for egg cryopreservation. In this study, donated human eggs from young women were cryopreserved by vitrification and PGS was performed in the resulted blastocysts by DNA microarray. A total of 764 frozen eggs from 75 egg thawing cycles were warmed and 38 blastocysts were biopsied for PGS before embryo transfer. A 97.1 % of egg survival rate was obtained and 59.1 % of embryos developed to blastocyst stage. After biopsy and PGS, it was found that 84.2 % of blastocysts were euploid and 15.8 % were aneuploid. Aneuploidy rates varied among donors. Transfers of blastocysts without PGS resulted in higher clinical pregnancy and implantation rates as compared with transfer of blastocysts with PGS. The authors concluded that although the overall aneuploidy rate was low in the blastocysts derived from frozen donor eggs, high aneuploidy rates were observed in the embryos resulting from some donated eggs. They noted that clinical pregnancy rate was not improved by PGS of embryos resulting from donor eggs, indicating that PGS may not be necessary for embryos derived from donor eggs in most cases.

Lee and colleagues (2015) noted that the majority of published studies comparing a strategy of preimplantation genetic diagnosis for aneuploidy (PGD-A) with morphologically assessed embryos have reported a higher implantation rate per embryo using PGD-A, but insufficient data has been presented to evaluate the clinical and cost-effectiveness of PGD-A in the clinical setting. Aneuploidy is a leading cause of implantation failure, miscarriage and congenital abnormalities in humans, and a significant cause of ART failure. Pre-clinical evidence of PGD-A indicates that the selection and transfer of euploid embryos during ART should improve clinical outcomes. These investigators examined if PGD-A with analysis of all chromosomes during ART is clinically and cost effective? These researchers performed a systematic review of the literature for full text English language articles using MEDLINE, EMBASE, SCOPUS, Cochrane Library databases, NHS Economic Evaluation Database and EconLit. The Downs and Black scoring check-list was used to assess the quality of studies. Clinical effectiveness was measured in terms of pregnancy, live-birth and miscarriage rates. A total of 19 articles meeting the inclusion criteria, comprising 3 RCTs in young and good prognosis patients and 16 observation studies were identified. Five of the observational studies included a control group of patients where embryos were selected based on morphological criteria (matched cohort studies). Of the 5 studies that included a control group and reported implantation rates, 4 studies (including 2 RCTs) demonstrated improved implantation rates in the PGD-A group. Of the 8 studies that included a control group, 6 studies (including 2 RCTs) reported significantly higher pregnancy rates in the PGD-A group, and in the remaining 2 studies, equivalent pregnancies rates were reported despite fewer embryos being transferred in the PGD-A group. The 3 RCTs demonstrated benefit in young and good prognosis patients in terms of clinical pregnancy rates and the use of single embryo transfer. However, studies relating to patients of advanced maternal age, recurrent miscarriage and implantation failure were restricted to matched cohort studies, limiting the ability to draw meaningful conclusions. The authors concluded that given the uncertain role of PGD-A techniques, high-quality experimental studies using intention-to-treat analysis and cumulative live-birth rates including the comparative outcomes from remaining cryopreserved embryos are needed to evaluate the overall role of PGD-A in the clinical setting. It is only in this way that the true contribution of PGD-A to ART can be understood.

Invasive Prenatal Diagnosis

Prenatal invasive diagnostic genetic tests are laboratory studies that are performed during pregnancy when a developing fetus is at risk for or is suspected of having a chromosomal or congenital abnormality. Testing may be performed on a variety of specimens including amniotic fluid, chorionic villi or percutaneous umbilical blood samples.

Chromosome analysis (karyotype) of chorionic villus samples (CVS) or amniotic fluid cells is a laboratory method used to detect aneuploidy such as Down syndrome, trisomy 18 and other chromosome abnormalities in a developing fetus. Other laboratory methods used to detect prenatal chromosome abnormalities via CVS and amniotic fluid include fluorescence in situ hybridization (FISH).

Molecular genetic testing is used to analyze deoxyribonucleic acid (DNA) extracted from fetal cells by CVS and amniocentesis to detect gene mutations prenatally in fetuses that may be at risk for genetic disorders such as cystic fibrosis (CF) or Tay-Sachs disease.

Preimplantation Genetic Screening

Gleicher and colleagues (2016) stated that to preclude transfer of aneuploid embryos, current PGS usually involves 1 trophectoderm biopsy at blastocyst stage, assumed to represent embryo ploidy. Whether one such biopsy can correctly assess embryo ploidy has recently, however, been questioned. This descriptive study investigated accuracy of PGS in 2 ways: (i) 2 infertile couples donated 11 embryos, previously diagnosed as aneuploid and, therefore, destined to be discarded. They were dissected into 37 anonymized specimens, and sent to another national laboratory for repeat analyses to assess (a) inter-laboratory congruity and (b) intra-embryo congruity of multiple embryo biopsies in a single laboratory; and (ii) reports on human IVF cycle outcomes after transfer of allegedly aneuploid embryos into 8 infertile patients. Only 2/11 (18.2 %) embryos were identically assessed at 2 PGS laboratories; 4/11 (36.4 %), on repeat analysis were chromosomally normal, 2 mosaic normal/abnormal, and 5/11 (45.5 %) completely differed in reported aneuploidies. In intra-embryo analyses, 5/10 (50 %) differed between biopsy sites; 8 transfers of previously reported aneuploid embryos resulted in 5 chromosomally normal pregnancies, 4 delivered and 1 ongoing; 3 patients did not conceive, though 1 among them experienced a chemical pregnancy. The authors concluded that although populations of both study parts were too small to draw statistically adequately powered conclusions on specific degrees of inaccuracy of PGS, the presented results did raise concerns especially about false-positive diagnoses. While inter-laboratory variations may at least partially be explained by different diagnostic platforms utilized, they could not explain observed intra-embryo variations, suggesting more frequent trophectoderm mosiaicsm than previously reported. The authors conclude that together with recently published mouse studies of lineages-specific degrees of survival of aneuploid cells in early stage embryos, these results called into question the biological basis of PGS, based on the assumption that a single trophectoderm biopsy can reliably determine embryo ploidy. They stated that prudence has to be exercised by practitioners in IVF across all patients when offering PGS under the hypothesis that the procedure improves IVF outcomes.

Majumdar and associates (2016) noted that a majority of human embryos produced in-vitro are aneuploid, especially in couples undergoing IVF with poor prognosis; PGS for all 24 chromosomes has the potential to select the most euploid embryos for transfer in such cases. In a retrospective, case-control study, these researchers examined the effectiveness of PGS for all 24 chromosomes by microarray CGH (array CGH) in Indian couples undergoing IVF cycles with poor prognosis. This study was undertaken in an institution-based tertiary care IVF center to compare the clinical outcomes of 20 patients, who underwent 21 PGS cycles with poor prognosis, with 128 non-PGS patients in the control group, with the same inclusion criterion as for the PGS group. Single cells were obtained by laser-assisted embryo biopsy from day 3 embryos and subsequently analyzed by array CGH for all 24 chromosomes. Once the array CGH results were available on the morning of day 5, only chromosomally normal embryos that had progressed to blastocyst stage were transferred. The implantation rate and clinical pregnancy rate (PR) per transfer were found to be significantly higher in the PGS group than in the control group (63.2 % versus 26.2 %, p = 0.001 and 73.3 % versus 36.7 %, p = 0.006, respectively), while the multiple PRs sharply declined from 31.9 % to 9.1 % in the PGS group. The authors concluded that the findings of this pilot study showed that PGS by array CGH can improve the clinical outcome in patients undergoing IVF with poor prognosis. Moreover, they stated that further prospective, randomized clinical studies with a larger sample size are needed to validate these preliminary findings.

One of the major drawbacks of the study was the considerably smaller number of patients in the PGS group as compared to the control group. The high cost associated with genetic analysis proved to be a major deterrent for patients to undertake PGS, since opting for PGS resulted in doubling the cost of the IVF cycle. Another reason for the low recruitment was probably the nature of the patient population being investigated, since a high percentage of patients tend to drop-out after the first few IVF failures or miscarriages. Moreover, many patients who did give consent to undergo PGS failed to fulfill the minimum criterion required to undergo biopsy. The retrospective design was another drawback of the study.

Preimplantation Genetic Testing for Aneuploidy as a Screening Test for In-Vitro Fertilization

In a retrospective study, Simon and colleagues (2018) measured in-vitro fertilization (IVF) outcomes following 24-chromosome SNP-based preimplantation genetic testing for aneuploidy (PGT-A) and euploid embryo transfer. Subjects were women aged 20 to 46 years undergoing IVF treatment. Intervention entailed 24-chromosome SNP-based PGT-A of day 5/6 embryo biopsies. Main outcome measures included maternal age-stratified implantation, clinical pregnancy, and live-birth rates (LBRs) per embryo transfer; miscarriage rates; and number of embryo transfers per patient needed to achieve a live-birth. An implantation rate of 69.9 %, clinical pregnancy rate per transfer of 70.6 %, and LBR per transfer of 64.5 % were observed in 1,621 non-donor frozen cycles with the use of SNP-based PGT-A. In addition, SNP-based PGT-A outcomes, when measured per cycle with transfer, remained relatively constant across all maternal ages; when measured per cycle initiated, they decreased as maternal age increased. Miscarriage rates were approximately 5 % in women less than or equal to 40 years old. No statistically significant differences in pregnancy outcomes were found for single-embryo transfers (SET) versus double-embryo transfers with SNP-based PGT-A. On average, 1.38 embryo transfers per patient were needed to achieve a live-birth in non-donor cycles. These researchers stated that the findings that SNP-based PGT-A could mitigate the negative effects of maternal age on IVF outcomes in cycles with transfer, and that pregnancy outcomes from SET cycles were not significantly different from those of double-embryo transfer cycles, supported the use of SET when transfers were combined with SNP-based PGT-A. The authors concluded that these results showed that IVF with the use of 24-chromosome SNP-based PGT-A and subsequent euploid embryo transfer led to high implantation, clinical pregnancy, and LBRs, and low miscarriage rates, primarily with SET. They hoped that these findings would facilitate discussion and improvement of IVF best practices, including PGT-A-based IVF and SET, and help clinicians to set appropriate expectations for patients undergoing IVF.

The authors stated that this study had 2 drawbacks. First, owing to the retrospective nature of the study, not all variables could be controlled. For example, the administration of PGT-A was elective and not randomized, so it was possible that PGT-A was preferentially used in certain cases; the cohort at the Conceptions Reproductive Associates of Colorado (CRA; Littleton), with the higher (81 %) rate of performing PGT-A, was more likely to be representative of an unselected cohort. Better outcomes were observed at CRA than at the Pacific Fertility Center (PFC; San Francisco); however, with a lower rate (40 % versus 81 %) of patients performing PGT-A, it was possible that the CRA cohort was biased toward patients with better prognosis. Second, the data presented in this study were not sufficient to demonstrate the absolute impact of SNP-based PGT-A on IVF outcomes, because there was no suitable control cohort available. These researchers stated that larger prospective randomized studies are needed to overcome these drawbacks.

In a cross-sectional survey at an academic medical center, Quinn and associates (2018) examined how patients make decisions regarding use of PGT-A for IVF. A total of 300 subjects initiating an IVF cycle over 8 weeks were asked to complete a validated survey to determine how they decided whether or not to pursue PGT-A. All patients were previously counseled that the primary goal of PGT-A is to maximize pregnancy rates per embryo transfer. Survey responses were compared between those who elected PGT-A and those who did not with a Chi-squared or t test. Of 191 subjects who completed the survey, 117 (61 %) planned PGT-A, while 74 (39 %) did not. Among those who decided to undergo PGT-A, 56 % stated their primary reason was to have a healthy baby, while 18 % chose PGT-A to reduce the incidence of birth defects, and 16 % aimed to decrease the risk of miscarriage. Patients who decided not to pursue PGT-A stated they prioritized avoiding the scenario in which they might have no embryos to transfer (36 %) or reducing cost (31 %). Both groups rated physicians as the single most important source of information in their decision-making (56 % versus 68 %, p = NS). The authors concluded that patients who chose to undergo PGT-A had different priorities from those who do not. Many patients planning PGT-A did so for reasons that were not evidence-based. While patients cited physicians as their primary source of information in the decision-making process, rationales for selecting PGT-A were inconsistent with physician counseling.

Lews and co-workers (2018) noted that recurrent pregnancy loss (RPL) is a common, yet elusive, complication of pregnancy. Among couples at high risk of RPL, such as those carrying a structural chromosomal re-arrangement, PGD has been proposed as a tool to improve LBRs and reduce the incidence of miscarriage; however, no clear consensus has been reached on its benefits in this population. In a systematic review, these investigators summarized existing published research on the effect of PGD on pregnancy outcomes among carriers of chromosomal abnormalities with RPL. A comprehensive search of common databases was conducted, which yielded 20 studies. Meta-analysis was precluded due to significant heterogeneity between studies. The primary outcome of interest was LBR, and a pooled total of 847 couples who conceived naturally had a LBR ranging from 25 to 71 % compared with 26.7 to 87 % among 562 couples who underwent IVF and PGD. The authors stated that limitations of the study included the lack of large comparative or randomized control studies. They stated that patients experiencing RPL with structural chromosomal re-arrangement should be counselled that good reproductive outcomes could be achieved through natural conception, and that IVF-PGD should not be offered first-line, given the unproven benefits, additional cost and potential complications associated with ART.

Benard and colleagues (2019) stated that PGT avoids the transmission of monogenic diseases or structural chromosome abnormality to the offspring in fertile couples. Furthermore, it allows screening for aneuploidies (PGT-A), with the aim of selecting 1 euploid embryo before transfer in infertile couples undergoing IVF. Indeed, aneuploidies are frequent and explain most IVF failures and early miscarriages. The authors concluded that the indications for PGT-A remain controversial, due to the lack of clear evidence of improved outcomes after IVF. They stated that cost-effectiveness studies and follow-up of neonatal outcomes are needed.

Furthermore, the Practice Committees of the American Society for Reproductive Medicine and the Society for Assisted Reproductive Technology’s opinion on "The use of preimplantation genetic testing for aneuploidy"(ASRM, 2018) stated that" The value of preimplantation genetic testing for aneuploidy (PGT-A) as a screening test for in-vitro fertilization (IVF) patients has yet to be determined. Several studies demonstrate higher birth rates after aneuploidy testing and elective single-embryo transfer (eSET), suggesting the potential for this testing to decrease the risk of multiple gestations, though these studies have important limitations".

Cornelisse and colleagues (2020) noted that in in-vitro fertilization (IVF) with or without intracytoplasmic sperm injection (ICSI), selection of the most competent embryo(s) for transfer is based on morphological criteria. However, many women do not achieve a pregnancy even after "good quality" embryo transfer. One of the presumed causes is that such morphologically normal embryos have an abnormal number of chromosomes (aneuploidies). Preimplantation genetic testing for aneuploidies (PGT-A), formerly known as preimplantation genetic screening (PGS), was therefore developed as an alternative method to select embryos for transfer in IVF. In PGT-A, the polar body or one or a few cells of the embryo are obtained by biopsy and tested. Only polar bodies and embryos that show a normal number of chromosomes are transferred. The first generation of PGT-A, using cleavage-stage biopsy and FISH for the genetic analysis, was demonstrated to be ineffective in improving live-birth rates. Since then, new PGT-A methodologies have been developed that perform the biopsy procedure at other stages of development and use different methods for genetic analysis. Whether or not PGT-A improves IVF outcomes and is beneficial to patients has remained controversial. Ina Cochrane review , these investigators examined the safety and effectiveness of PGT-A in women undergoing an IVF treatment. They searched the Cochrane Gynecology and Fertility (CGF) Group Trials Register, CENTRAL, Medline, Embase, PsycINFO, CINAHL, and 2 trials registers in September 2019 and checked the references of appropriate papers. All RCTs reporting data on clinical outcomes in subjects undergoing IVF with PGT-A versus IVF without PGT-A were eligible for inclusion. Two review authors independently selected studies for inclusion, assessed risk of bias, and extracted study data. The primary outcome was the cumulative live-birth rate (cLBR). Secondary outcomes were live-birth rate (LBR) after the first embryo transfer, miscarriage rate, ongoing pregnancy rate, clinical pregnancy rate, multiple pregnancy rate, proportion of women reaching an embryo transfer, and mean number of embryos per transfer.

These researchers included 13 trials involving 2,794 women. The quality of the evidence ranged from low-to-moderate. The main drawbacks were imprecision, inconsistency, and risk of publication bias. IVF with PGT-A versus IVF without PGT-A with the use of genome-wide analyses. Polar body biopsy: One trial used polar body biopsy with aCGH. It is unclear if the addition of PGT-A by polar body biopsy increased the cLBR compared to IVF without PGT-A (odds ratio [OR] 1.05, 95 % CI: 0.66 to 1.66, 1 RCT, n = 396, low-quality evidence). The evidence suggested that for the observed cLBR of 24 % in the control group, the chance of live-birth following the results of 1 IVF cycle with PGT-A was between 17 % and 34 %. It was unclear if the LBR after the first embryo transfer improved 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 was uncertain (OR 0.77, 95 % CI: 0.50 to 1.16, 1 RCT, n = 396, low-quality evidence). Blastocyst stage biopsy: One trial used blastocyst stage biopsy with next-generation sequencing (MGS). It was unclear if IVF with the addition of PGT-A by blastocyst stage biopsy increased cLBR compared to IVF without PGT-A, since no data were available. It was unclear if LBR after the first embryo transfer improved 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 was unclear if PGT-A with blastocyst stage biopsy reduced 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: A total of 11 trials were included in this comparison. It was unclear if IVF with addition of PGT-A increased cLBR (OR 0.59, 95 % CI: 0.35 to 1.01, 1 RCT, n = 408, low-quality evidence). The evidence suggested that for the observed average cLBR of 29 % in the control group, the chance of live-birth following the results of 1 IVF cycle with PGT-A was between 12 % and 29 %. PGT-A performed with FISH probably reduced 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 suggested 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 was between 16 % and 29 %. There was 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 = 1121, I^2 = 60 %, low-quality evidence) and probably reduced 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 there is insufficient good-quality evidence of a difference in cumulative live-birth rate, live-birth rate after the first embryo transfer, or miscarriage rate between IVF with and IVF without PGT-A as currently performed. No data were available on ongoing pregnancy rates. The effect of PGT-A on clinical pregnancy rate is uncertain. These researchers stated that women need to be aware that it is unclear if PGT-A with the use of genome-wide analyses is an effective addition to IVF, especially in view of the invasiveness and costs involved in PGT-A. Moreover, PGT-A using FISH for the genetic analysis is probably harmful. The currently available evidence is insufficient to support PGT-A in routine clinical practice.

Igenomix SMART PGT-A (Preimplantation Genetic Testing - Aneuploidy) Test

The SMART PGT-A (Preimplantation Genetic Testing - Aneuploidy) Test entails the analysis of 24 chromosomes using embryonic DNA genomic sequence analysis for aneuploidy, and a mitochondrial DNA score in euploid embryos. Results are reported as normal (euploidy), monosomy, trisomy, or partial deletion/duplications, mosaicism, and segmental aneuploidy, per embryo tested.

The ASRM and the Society for Assisted Reproductive Technology’s Committee Opinion on “The use of preimplantation genetic testing for aneuploidy (PGT-A)” (2018) stated that the value of PGT-A as a screening test for in-vitro fertilization (IVF) patients has yet to be determined. Several studies demonstrated higher birth rates after aneuploidy testing and elective single-embryo transfer (eSET), suggesting the potential for this testing to decrease the risk of multiple gestations, although these studies had important limitations.

Cornelisse and colleagues (2020) noted that in IVF with or without ICSI, selection of the most competent embryo(s) for transfer is based on morphological criteria; however, many women do not achieve a pregnancy even after “good quality'” ET. One of the presumed causes is that such morphologically normal embryos have an abnormal number of chromosomes (aneuploidies); PGT-A, formerly known as PGS, was therefore developed as an alternative method to select embryos for transfer in IVF. In PGT-A, the polar body or 1 or a few cells of the embryo are obtained by biopsy and tested. Only polar bodies and embryos that showed a normal number of chromosomes are transferred. The 1st generation of PGT-A, using cleavage-stage biopsy and FISH for the genetic analysis, was shown to be ineffective in improving livebirth rates. Since then, new PGT-A methodologies have been developed that carry out the biopsy procedure at other stages of development and use different methods for genetic analysis. Whether or not PGT-A improves IVF outcomes and is beneficial to patients has remained controversial. In a Cochrane review, these researchers examined the safety and effectiveness of PGT-A in women undergoing an IVF treatment. They searched the Cochrane Gynecology and Fertility (CGF) Group Trials Register, CENTRAL, Medline, Embase, PsycINFO, CINAHL, and 2 trials registers in September 2019 and checked the references of appropriate papers. All RCTs reporting data on clinical outcomes in subjects undergoing IVF with PGT-A versus IVF without PGT-A were eligible for inclusion. Two review authors independently selected studies for inclusion, assessed risk of bias, and extracted study data. The primary outcome was the cLBR; secondary outcomes were LBR after the 1st ET, miscarriage rate, ongoing pregnancy rate, clinical pregnancy rate, multiple pregnancy rate, proportion of women reaching an ET, and mean number of embryos per transfer.

These researchers included 13 trials involving 2,794 women. The quality of the evidence ranged from low-to-moderate. The main drawbacks were imprecision, inconsistency, and risk of publication bias. IVF with PGT-A versus IVF without PGT-A with the use of genome-wide analyses. One trial used polar body biopsy with aCGH. It is uncertain whether the addition of PGT-A by polar body biopsy increases the cLBR compared to IVF without PGT-A (OR 1.05, 95 % CI: 0.66 to 1.66, 1 RCT, n = 396, low-quality evidence). The evidence suggested that for the observed cLBR of 24 % in the control group, the chance of livebirth following the results of 1 IVF cycle with PGT-A was between 17 % and 34 %. It was unclear if the LBR after the 1st ET improved 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 was uncertain (OR 0.77, 95 % CI: 0.50 to 1.16, 1 RCT, n = 396, low-quality evidence). One trial used blastocyst stage biopsy with next-generation sequencing (NGS). It was unclear if IVF with the addition of PGT-A by blastocyst stage biopsy increased cLBR compared to IVF without PGT-A, since no data were available. It was uncertain if LBR after the 1st ET improved 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 was unclear if PGT-A with blastocyst stage biopsy reduced 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; a total of 11 trials were included in this comparison. It was unclear if IVF with addition of PGT-A increased cLBR (OR 0.59, 95 % CI: 0.35 to 1.01, 1 RCT, n = 408, low-quality evidence). The evidence suggested that for the observed average cLBR of 29 % in the control group, the chance of livebirth following the results of 1 IVF cycle with PGT-A was between 12 % and 29 %. PGT-A performed with FISH probably reduced livebirths after the 1st ET 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 suggested that for the observed average LBR per 1st ET of 31 % in the control group, the chance of livebirth after the 1st ET with PGT-A was between 16 % and 29 %. There was 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 reduced 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 there is insufficient good-quality evidence of a difference in cumulative livebirth rate, livebirth rate after the 1st embryo transfer, or miscarriage rate between IVF with and IVF without PGT-A as currently performed. No data were available on ongoing pregnancy rates. The effect of PGT-A on clinical pregnancy rate is uncertain. Women need to be aware that it is unclear if PGT-A with the use of genome-wide analyses is an effective addition to IVF, especially in view of the invasiveness and costs involved in PGT-A. Moreover, PGT-A using FISH for the genetic analysis is probably harmful. The currently available evidence is insufficient to support PGT-A in routine clinical practice.

The Practice Committee and Genetic Counseling Professional Group (GCPG) of the ASRM’ Committee Opinion on “Clinical management of mosaic results from preimplantation genetic testing for aneuploidy (PGT-A) of blastocysts” (2020) stated that since the advent of PGT-A in the 1990s, substantial changes in test methodology and technology now allow the detection and reporting of intermediate chromosome copy number (commonly referred to as mosaicism) for aneuploidy in a trophectoderm biopsy sample. Clinicians are grappling with how to interpret such findings and how to counsel patients regarding ET decision-making. This document reviewed the available literature and outlined the various issues regarding the reporting of intermediate copy number and consideration of storage or transfer of blastocysts with intermediate copy number results. This document did not endorse, nor did it suggest that PGT-A is appropriate for all cases of IVF. This Committee Opinion noted that current data suggest that embryos deemed mosaic by PGT-A resulted in fewer ongoing pregnancies and more spontaneous abortions (SABs) compared with euploid embryos. However, those patients who have had embryos transferred with mosaic results to-date may have included an over-representation of poor prognosis patients, which introduced a population bias into these comparisons; thus, these data should be interpreted with caution. They also noted that several studies reporting livebirths after transfer of an embryo with mosaic results have been documented, and the resulting newborns appeared to be healthy. Although this is encouraging, there is a lack of accompanying post-natal correlation of chromosomal studies, and no formal evaluations or longitudinal studies have been conducted; thus, these data should be interpreted with caution. The field would greatly benefit from an improved effort to collect and publish the findings of laboratory and clinical genetic follow-up evaluations. Moreover, these researchers stated that there is currently no evidence-based classification system for prioritizing embryos according to the type of mosaic result. It remains to be determined whether pre-natal or post-natal mosaicism data could be used to predict outcomes for pre-implantation embryos identified as mosaic. They stated that future studies should focus on providing detailed information correlating the specific mosaic result (i.e., type of aneuploidy and level of mosaicism) of the embryos transferred with clinical outcomes, and report on documented pre-natal and post-natal chromosomal data (karyotype, chromosomal microarray, uniparental disomy studies) in addition to phenotypic information whenever possible.

The ACOG's Committee Opinion on "Preimplantation genetic testing" (2020) noted that pre-implantation genetic testing comprises a group of genetic assays used to evaluate embryos prior to transfer to the uterus. Pre-implantation genetic testing-monogenic is targeted to single gene disorders, and PGT-A is a broader test that screens for aneuploidy in all chromosomes, including the 22 pairs of autosomes and the sex chromosomes X and Y. To test embryos that are at risk for chromosome gains and losses related to parental structural chromosomal abnormalities (e.g., translocations, inversions, deletions, and insertions), pre-implantation genetic testing-structural re-arrangements is employed. Independent of the pre-implantation genetic testing modality employed, false-positive (FP) and false-negative (FN) results are possible. Patients and health care providers should be aware that a "normal" or negative pre-implantation genetic test result is not a guarantee of a newborn without genetic abnormalities. 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. It is especially important to offer diagnostic testing or screening for aneuploidy after pre-implantation genetic testing-monogenic or pre-implantation genetic testing-structural re-arrangements if concurrent PGT-A is not carried out. Many limitations exist to pre-implantation genetic testing and include challenges in detecting micro-deletions and micro-duplications, de-novo variants, and imprinting disorders. An emerging problem has been detection of mosaicism during PGT-A. The clinical use of pre-implantation genetic testing-monogenic and pre-implantation genetic testing-structural re-arrangements is firmly established; however, the best use of PGT-A remains to be determined. The authors concluded that future research is needed to establish the overall clinical utility for PGT-A, the subset of patients that may benefit from PGT-A, the clinical significance of mosaicism, and residual risk for aneuploidy in PGT-A screened embryos.

Bhatt and associates (2021) noted that euploid ET is thought to optimize outcomes in some couples with infertility; however, there is insufficient evidence supporting this approach to management of RPL. These researchers examined if PGT-A would improve the LBR in patients with RPL. This study included data collected by the Society of Assisted Reproductive Technologies Clinical Outcomes Reporting System (SART-CORS) for IVF-FET cycles between years 2010 through 2016. A total of 12,631 FET cycles in 10,060 couples were included in this analysis designed to examine the use of PGT-A in couples with RPL undergoing FET, including 4,287 cycles in couples with tubal disease who formed a control group. The experimental group included couples with RPL (strictly defined as a history of 3 or more pregnancy losses) undergoing FET with or without PGT-A. The primary outcome was LBR; secondary outcomes included rates of clinical pregnancy, SAB, and biochemical pregnancy loss. Differences were analyzed using generalized estimating equations logistic regression models to account for multiple cycles per patient. Co-variates included in the model were age, gravidity, geographic region, race/ethnicity, smoking history, and indication for ART. Analyses were stratified for age groups as defined by SART: less than 35 years, 35 to 37 years, 38 to 40 years, 41 to 42 years, and greater than 42 years. In women with a diagnosis of RPL, the adjusted OR comparing IVF-FET with PGT-A versus without PGT-A for livebirth outcome was 1.31 (95 % CI: 1.12 to 1.52) for age of less than 35 years, 1.45 (95 % CI: 1.21 to 1.75) for ages 35 to 37 years, 1.89 (95 % CI: 1.56 to 2.29) for ages of 38 to 40, 2.62 (95 % CI: 1.94 to 3.53) for ages 41 to 42, and 3.80 (95 % CI: 2.52 to 5.72) for ages greater than 42 years. For clinical pregnancy, the OR was 1.26 (95 % CI: 1.08 to 1.48) for age of less than 35 years, 1.37 (95 % CI: 1.14 to 1.64) for ages 35 to 37 years, 1.68 (95 % CI: 1.40 to 2.03) for ages 38 to 40 years, 2.19 (95 % CI: 1.65 to 2.90) for ages 41 to 42, and 2.31 (95 % CI: 1.60 to 3.32) for ages greater than 42 years. Finally, for SAB, the OR was 0.95 (95 % CI: 0.74 to 1.21) for age of less than35 years, 0.85 (95 % CI: 0.65 to 1.11) for ages 35 to 37 years, 0.81 (95 % CI: 0.60 to 1.08) for ages 38 to 40, 0.86 (95 % CI: 0.58 to 1.27) for ages 41 to 42, and 0.58 (95 % CI: 0.32 to 1.07) for ages greater than 42 years. The authors concluded that this was the largest study to-date examining the use of PGT-A in women with RPL. PGT-A was associated with improvement in livebirth and clinical pregnancy in women with RPL, with the largest difference noted in the group of women with age greater than 42 years.

The drawbacks of this study included the retrospective collection of data including only women with RPL undergoing FET; and results may not be generalizable to all couples with RPL. Furthermore, data regarding evaluation and treatment for RPL for the included women were unavailable.

Natera Spectrum Preimplantation Genetic Testing for Monogenic Disorders (PGT-M)

Natera offers the Spectrum PGT-M test, a preimplantation genetic test that evaluates 300,000 DNA single-nucleotide polymorphisms (SNPs) by microarray from embryonic tissue, and uses an algorithm to report probability for single-gene germline conditions. PGT-M tests embryos for inherited single gene conditions, such as cystic fibrosis, spinal muscular atrophy, and hemophilia.

A search for published peer-reviewed literature for this test did not return any results.

IriSight Prenatal Analysis

IriSight Prenatal Analysis (Variantyx, Inc.) is a diagnostic test designed to identify genetic variants that correlate with clinical symptoms manifested in a fetus or a pregnancy, or that results in severe, early-onset genetic disorders. It employs the whole genome platform, providing a full, phenotypically-driven analysis of all relevant genes and variant types. According to its website, IriSight Prenatal Analysis can be ordered when amniocentesis has been determined to be medically necessary due to ultrasound (US) abnormalities. It may also be ordered for pregnancies without a medical indication; however, variants of uncertain significance (VUS) will not be reported. However, there is a lack of evidence regarding the clinical benefits of the IriSight Prenatal Analysis.

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