Clinical UM Guideline

Subject:	Preimplantation Genetic Diagnosis Testing		
Guideline #:	CG-GENE-06	**Publish Date:**	05/09/2019
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Description

This document addresses the use of preimplantation genetic diagnosis (PGD) and preimplantation genetic screening (PGS) which is performed as part of an assisted reproductive procedure.

Note: For the purposes of this document, the term "partners" indicates the individuals from whom the sperm and ova originated. That may include the individual members themselves or a gamete donor.

Note: The use of IVF services are subject to separate Benefit Determination, independent of this position statement. Not all benefit contracts or certificates include benefits for IVF services, including PGD. Benefit language supersedes this document.

Note: For additional information regarding the use of perinatal genetic testing, please see:

- CG-GENE-10 Chromosomal Microarray Analysis (CMA) for Developmental Delay, Autism Spectrum Disorder, Intellectual Disability (Intellectual Developmental Disorder) and Congenital Anomalies
- CG-GENE-13 Genetic Testing for Inherited Diseases
- GENE.00026 Cell-Free Fetal DNA-Based Prenatal Testing

Clinical Indications

Medically Necessary:

A. Preimplantation genetic *screening*, when used as a technique to improve the implantation rate of in vitro fertilization (IVF) procedures in infertile couples, is considered **medically necessary** when **any** of the first set of criteria **and all** of the second set of criteria have been met:
   1. Criteria Set 1:
      a. There have been three prior failed attempts at IVF; **or**
      b. There is a history of trisomy in a previous pregnancy;

   and

   2. Criteria set 2:
      Genetic counseling, which encompasses **all** of the following components, has been performed:

a. Interpretation of family and medical histories to assess the probability of disease occurrence or recurrence; **and**
b. Education about inheritance, genetic testing, disease management, prevention and resources; **and**
c. Counseling to promote informed choices and adaptation to the risk or presence of a genetic condition; **and**
d. Counseling for the psychological aspects of genetic testing.

B. Preimplantation genetic *diagnosis,* when used to deselect embryos with genetic mutations, is considered **medically necessary** in partners who meet **any** criteria in Criteria Set 1, **and all** criteria in Criteria Set 2, **and all** criteria in Criteria Set 3:
1. Criteria Set 1 (must meet at **LEAST ONE** of the following):
   a. Both partners are known carriers of the same autosomal recessive disorder; **or**
   b. One partner is a known carrier of an autosomal recessive disorder, and the couple have previously produced offspring affected by that disorder; **or**
   c. One partner is a known carrier of a single gene autosomal dominant disorder; **or**
   d. One of the partners is known to harbor a balanced translocation; **or**
   e. One partner is a known carrier of a single gene X-linked disorder;

and

2. Criteria Set 2 (must meet **ALL** of the following):
   a. A specific mutation, or set of mutations, has been identified, that specifically identifies the genetic disorder with a high degree of reliability; **and**
   b. The genetic disorder is associated with severe disability or has a lethal natural history;

and

3. Criteria set 3:
   Genetic counseling, which encompasses **all** of the following components, has been performed:
   a. Interpretation of family and medical histories to assess the probability of disease occurrence or recurrence; **and**
   b. Education about inheritance, genetic testing, disease management, prevention and resources; **and**
   c. Counseling to promote informed choices and adaptation to the risk or presence of a genetic condition; **and**
   d. Counseling for the psychological aspects of genetic testing.

C. Preimplantation genetic *diagnosis* when used to determine the sex of an embryo is considered **medically necessary** only when there is a documented history of an X-linked disorder, such that deselection of an affected embryo can be made on the basis of sex alone **and** genetic counseling, which encompasses **all** of the following components, has been performed:
1. Interpretation of family and medical histories to assess the probability of disease occurrence or recurrence; **and**
2. Education about inheritance, genetic testing, disease management, prevention and resources; **and**
3. Counseling to promote informed choices and adaptation to the risk or presence of a genetic condition; **and**
4. Counseling for the psychological aspects of genetic testing.

D. Preimplantation genetic *diagnosis* is considered **medically necessary** when used to evaluate human leukocyte antigen (HLA) status alone in families with a child with a bone marrow disorder requiring a hematopoietic cell transplant, **and** in whom there is no other source of a compatible donor other than an HLA matched sibling **and** genetic counseling, which encompasses **all** of the following components, has been performed:
   1. Interpretation of family and medical histories to assess the probability of disease occurrence or recurrence; **and**
   2. Education about inheritance, genetic testing, disease management, prevention and resources; **and**
   3. Counseling to promote informed choices and adaptation to the risk or presence of a genetic condition; **and**
   4. Counseling for the psychological aspects of genetic testing.

E. Preimplantation genetic *screening* for fetal aneuploidy (trisomy 13, 18, and 21) is considered **medically necessary and** genetic counseling, which encompasses **all** of the following components, has been performed:
   1. Interpretation of family and medical histories to assess the probability of disease occurrence or recurrence; **and**
   2. Education about inheritance, genetic testing, disease management, prevention and resources; **and**
   3. Counseling to promote informed choices and adaptation to the risk or presence of a genetic condition; **and**
   4. Counseling for the psychological aspects of genetic testing.

Not Medically Necessary:

Preimplantation genetic *diagnosis* is considered **not medically necessary** for all other indications, including when the criteria above have not been met.

Preimplantation genetic *screening* is considered **not medically necessary** as an adjunct to IVF, except when specified above, including but not limited to the following circumstances:

- To identify the presence or absence of conditions for which an embryo has no known risk factors.

Coding

The following codes for treatments and procedures applicable to this guideline are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

CPT	
89290	Biopsy, oocyte polar body or embryo blastomere, microtechnique (for preimplantation genetic diagnosis); less than or equal to 5 embryos
89291	Biopsy, oocyte polar body or embryo blastomere, microtechnique (for preimplantation genetic diagnosis); greater than 5 embryos

ICD-10 Diagnosis

All diagnoses

Discussion/General Information

Preimplantation genetic diagnosis (PGD) describes a variety of adjunctive techniques to assisted reproductive procedures, in which embryonic DNA is sampled and genetically analyzed, thus permitting deselection of embryos harboring a genetic defect prior to implantation of the embryo into the uterus.

Two general categories of individuals have undergone PGD

Embryos at risk for a specific inherited single gene defect:
When either the mother or father is a known carrier of a genetic defect, embryos can undergo PGD to deselect embryos harboring the defective gene. Sex selection of a female embryo is another strategy when the mother is a known carrier of an X-linked disorder for which there is not yet a specific molecular diagnosis. The most common example is female carriers of fragile X syndrome. In this scenario, PGD is used to deselect male embryos, half of which would be affected. However, in this way half of the normal males will also be deselected. Another strategy, when available, is to perform single diagnosis for specific gene mutations. Single genetic defects for which molecular diagnosis is possible include Tay-Sachs disease, cystic fibrosis, Lesch-Nyhan syndrome, and Duchenne muscular dystrophy. It should be noted that when PGD is used to deselect affected embryos, the treated couple may not be infertile, but are undergoing an assisted reproductive procedure for the sole purpose of PGD. In this setting, PGD may be considered as an alternative to selective termination of an established pregnancy after diagnosis by amniocentesis or chorionic villus sampling.

Embryos at a higher risk of aneuploidy:
Implantation failure of fertilized embryos is a common cause for failure of assisted reproductive procedures; only 20% of morphologically normal embryos implant and produce a viable offspring. Aneuploidy, a condition where there are an abnormal number of chromosomes in an embryo, is thought to contribute to implantation failure. The prevalence of aneuploid oocytes increases in older women, thus explaining the decreased implantation rate in this population. These age-related aneuploidies are mainly due to nondisjunction of chromosomes during maternal meiosis. Therefore, PGD of the extruded polar bodies from the oocyte has been explored as a technique to deselect aneuploid oocytes in older women, with the goal of permitting transfer of those embryos with a higher chance of successful implantation. The evidence regarding the use of this technique has been shown to have a negative effect on pregnancy outcomes when used for women whose only indication is advanced maternal age. However, there are other indications where this technique is beneficial.

Genetic Counseling
According to the National Society of Genetic Counselors (NSGC), genetic counseling is the process of assisting individuals to understand and adapt to the medical, psychological and familial ramifications of a genetic disease. This process typically includes the guidance of a specially trained professional who:

1. Integrates the interpretation of family and medical histories to assess the probability of disease occurrence or recurrence; and
2. Provides education about inheritance, genetic testing, disease management, prevention and resources; and
3. Provides counseling to promote informed choices and adaptation to the risk or presence of a genetic condition; and
4. Provides counseling for the psychological aspects of genetic testing (NSGC, 2006).

Rationale

At this time, there is adequate evidence to support the use of preimplantation genetic testing (PGD) for individuals that are known to be carriers of balanced translocation genetic mutations or are at risk for aneuploidy and who are undergoing assisted reproductive technology (ART) procedures. These types of mutations are known to negatively affect the outcome of ART procedures. The identification and exclusion of embryos harboring these mutations has been demonstrated to improve implantation and birthrates for individuals undergoing ART procedures (Kato, 2016; Kuliev, 2005; Munne, 2005; Scriven, 2013; Shenfeld, 2003).

The evidence demonstrates that PGD identifies embryos harboring specific genetic mutations known to cause various diseases. Furthermore, there is adequate evidence from case series studies that PGD identification of genetic mutations permits deselection of affected embryos and allows successful live birth of healthy unaffected offspring (Chow, 2015; Kuliev, 2005; Shenfeld, 2003).

The addition of human leukocyte antigen (HLA) typing to the PGD procedure is a relatively new innovation. For example, PGD may be performed when a prior child has an inherited disorder, such as Fanconi anemia, which might be treated by a stem cell transplant. The couple may opt for PGD during the next pregnancy in order to deselect an affected embryo, but at the same time select an embryo that is HLA compatible with their affected child. Therefore, the resulting child could serve as a stem cell donor for his/her affected sibling. Additionally, preimplantation diagnosis may be performed solely to select an HLA compatible donor for a sibling requiring a stem cell transplant. For example, a sibling may have a leukemia requiring stem cell transplant, and the parents undergo an assisted reproductive procedure solely for the purposes of creating a suitable sibling as a stem cell donor. While these applications create many ethical issues, they have been shown to be technically feasible (Kuliev, 2004; Verlinsky, 2004).

Specific selection criteria for PGD for otherwise fertile couples are difficult, and must be treated on a case-by-case basis. While PGD has been shown to be technically feasible in general (i.e., the biopsy procedure, implantation and subsequent pregnancy), the diagnostic performance of the individual laboratory tests used to analyze the biopsied genetic material is rapidly evolving. Evaluation of each specific genetic test for each abnormality is beyond the scope of this document. However, in general, in order to assure adequate sensitivity and specificity for the genetic test guiding the embryo deselection process, the genetic defect must be well characterized. For example, the gene or genes responsible for some genetic disorders may be quite large with mutations spread along the entire length of

the gene. The ability to detect all or some of these genes, and an understanding of the clinical significance of each mutation (including its penetration, i.e., whether or not it is expressed in an individual) will affect the diagnostic performance of the test. An ideal candidate for genetic testing would be a condition that is associated with a single well-characterized mutation for which a reliable genetic test has been established. In some situations, PGD may be performed in couples in which the mother is a carrier of an X-linked disease, such as fragile X syndrome. In this case, the genetic test could focus on merely deselecting male embryos (Robertson, 2003).

The severity of the genetic disorder of concern is also a consideration. At the present time, many cases of PGD have involved lethal or severely disabling conditions with limited treatment opportunities such as Huntington's chorea or Tay-Sachs disease. Cystic fibrosis is another. PGD raises many ethical concerns and issues. While some parties may consider that PGD should be allowed to avoid the birth of a baby with diseases that have an immediate effect, such as cystic fibrosis, there are other diseases like Huntington's disease, which occur in the fifth or sixth decade of life and may or may not be appropriate qualifying conditions for PGD. Even though such conditions are unavoidable and untreatable, the offspring with such a genetic predisposition may still have a normal and productive life through their mid to late forties before the onset of disease.

One area of research has been the use of PGD for the screening of embryos with aneuploidy in mothers with advanced maternal age. This use of PGD, also known as preimplantation genetic screening or PGS, has been the topic of several randomized controlled trials with mixed results (Debrock, 2010; Hardarson, 2008; Mastenbroek, 2007; Rubio, 2013; Schoolcraft, 2009; Staessen, 2004). In the trial conducted by Staessen and colleagues, it was reported that there were no differences between the control group (n=141) which received standard care, and the PGD group (n=184) in implantation rate, positive serum HCG per transfer and per cycle. They also note that there were significantly fewer embryos to transfer in the PGD group. In the report by Mastenbroek and others, they found a significantly better ongoing pregnancy rate, live birth rate, and biochemical and clinical pregnancy rate in the control group (n=184) when compared to the PGD group (n=195). In an accompanying editorial by Collins, the author states "Given the findings of Mastenbroek, et al. preimplantation genetic diagnosis for aneuploidy screening should not be performed solely because of advanced maternal age." Hardarson led a group that set out to enroll 320 subjects with advanced maternal age; however, the study was ended prematurely (2008). The final report included only 56 subjects in the PGS group and 53 in the control group, which received no preimplantation diagnostic testing. The clinical pregnancy rate in the PGS group was reported to be 8.9% compared with 24.5% in the control group, a difference of 15.6% (p=0.039). However, due to the early termination of the study these results cannot be generalized to a wider population. Rubio and colleagues described a randomized controlled trial (RCT) involving 274 subjects with either three or more failed IVF cycles (FIVF group; n=91) or advanced maternal age defined as 41-44 years of age (AMA group; n=183). Subjects were assigned to undergo treatment with standard intracytoplasmic sperm injection (ICSI; n=43 FIVF subjects and 90 AMA subjects) or PGD with fluorescence in situ hybridization (FISH; n=48 FIVF subjects and 93 AMA subjects). The authors reported a significant increase in live birth rates per individual in the PGS group compared with the ICSI group for the subjects with AMA (30/93 subjects [32.3%] vs. 14/90 subjects [15.5%]; odds ratio [OR], 2.585; p=0.0099). In FIVF subjects, no significant differences were reported for any outcome measures as a result of PGD. They concluded that PGS with FISH was shown to be beneficial for the AMA group. Finally, a systematic review and meta-analysis by Checa and others looked at 10 RCTs involving 1512 subjects undergoing IVF with and without PGD for aneuploidy (2009). The

authors reported significantly poorer results for the PGS group compared to controls with regard to rate of live births (relative risk [RR], 0.76), ongoing pregnancy (RR, 0.73), and clinical pregnancy (RR, 0.72).

In 2017, Ubaldi and others published the results of a case series study involving 137 subjects aged greater than 43 years who underwent IVF with PGD for aneuploidy and advanced maternal age. All subjects were highly screened and had at least 3 antral follicles on the day prior to starting the stimulation protocol, and no history of failed response to controlled ovarian stimulation. All subjects underwent a single cycle, with an additional 13 undergoing a second, for a total of 150 cycles. Only 21 cycles obtained a transferable embryo. The overall euploidy rate was 11.8% (22/187 blastocysts). This resulted in 12 deliveries (57.1% per transfer, 8.0% per cycle, and 8.8% per subject, respectively). Maternal age was negatively associated with live birth (OR, 0.78), and the number of Metaphase 2 collected at oocyte pickup as positively associated (OR, 1.24). Furthermore, in an ad hoc analysis, fertilization rate was associated with age (44.0-44.9 years of age vs. 46.0-46.9 years of age, p=0.003). No euploidy blastocysts were reported in the eight PGD cycles in subjects older than 46, vs. 14.4% in subjects 44.0-44.9 years of age and 4.5% in subjects vs. 45.0-45.9 years of age. The delivery rate was 10% (11/104) in subjects 44.0-44.9 years of age vs. 2.6% (1/38) in subjects 45.0-45.9 years of age. The authors concluded that their results demonstrated low miscarriage and good delivery rates in women with good ovarian reserve aged 44, which supports the use of PGD for aneuploidy in this population.

Despite this uncertain evidence, the use of PGS for the identification of embryos with aneuploidy has been accepted, and it is believed that PGS may serve a role specifically in identifying trisomy 21, 18, and 13 in individuals undergoing IVF procedures.

PGS has also been proposed as a method of improving IVF outcomes in individuals with no known risk factors in an attempt to improve outcomes. Yang and others (2012) enrolled subjects who were scheduled to undergo first-time IVF. Subjects had a good prognosis, with age under 35, no prior miscarriage, and normal karyotype seeking elective single embryo transfer. All subjects were prospectively randomized to have embryos selected either on the basis of morphology and comprehensive chromosomal screening by array comparative genomic hybridization (aCGH) (n=55) or by morphology only (n=48). All subjects had a single fresh blastocyst transferred on day 6. For aCGH group subjects, 425 blastocysts were biopsied and analyzed (average 7.7 blastocysts/subject). Aneuploidy was detected in 191/425 (44.9%) of blastocysts in this group. For the control group, 389 blastocysts were microscopically examined (average 8.1 blastocysts/ subject). The clinical pregnancy rate was significantly higher in the aCGH group vs. the control group (70.9% vs. 45.8%, respectively; p=0.017); ongoing pregnancy rates were likewise significantly better in the aCGH group (69.1% vs. 41.7%, respectively; p=0.009). There were no twin pregnancies. The miscarriage rate was low for both groups and no significant differences were reported (2.6 vs. 9.2; p=0.0597). Live birth rates were not reported.

Forman (2013) reported the result of an RCT noninferiority trial investigating the benefits of comprehensive chromosome screening (CCS) during elective single embryo transfer. The study involved 205 infertile couples with a female partner less than 43 years old and a serum anti-Müllerian hormone level ≥ 1.2 ng/mL and day 3 FSH < 12 IU/L. Subjects were assigned to undergo real-time CCS biopsy for embryo selection prior to implantation of a single embryo (n=89) or standard selection methodology of two best-quality embryos for implantation (n=86). The

authors reported an ongoing pregnancy rate per randomized subject after the first embryo transfer was similar between groups (60.7% in the CCS group vs. 65.1% control group; RR, 0.9). The risk of multiple gestation was reduced after CCS (53.4% to 0%), and subjects were nearly twice as likely to have an ongoing singleton pregnancy (60.7% vs. 33.7%; RR, 1.8). No data regarding live birth rates were provided. The authors used a 20% noninferiority margin which may not be the most appropriate approach to evaluating the impact of PGS on health outcomes.

Scott and others (2013) reported the results of an RCT designed to determine whether blastocyst biopsy and CCS improved in vitro fertilization (IVF) implantation and delivery rates. Subjects were infertile couples in whom the female partner was between 21 and 42 years of age and undergoing IVF, and were assigned to treatment with CCS (134 blastocysts, n=72) or routine care (163 blastocysts, n=83). Sustained implantation rates were statistically significantly higher in the CCS group (66.4% vs. 47.9%). Delivery rates were also statistically significantly higher in the CCS group with 84.7% vs. 67.5% in the control group (RR, 1.26, p=0.001). The authors concluded that blastocyst biopsy with rapid qPCR-based CCS results in statistically significantly improved IVF outcomes, as evidenced by meaningful increases in sustained implantation and delivery rates.

The results of these three RCTs involved subjects with good prognosis, which does not provide any evidence for the use of PGS for the larger target audience who do not have a good prognosis, such as women of advanced maternal age. Furthermore, two of the three studies did not provide data on live birth rates, which is the ultimate goal of IVF procedures. .

In conclusion, the use of PGD involves a wide variety of complicated scientific, ethical and legal issues. Any application of this technology should be thoroughly and thoughtfully considered with these issues in mind. Decisions regarding PGD should involve careful discussion between the treated couple and the physician. For some couples, the decision may involve the choice between the risks of an in vitro fertilization (IVF) procedure and deselection of embryos as part of the PGD treatment versus normal conception with the prospect of amniocentesis and an elective abortion.

Definitions

Aneuploidy: A condition where there are either fewer or more than the normal number of chromosomes present in cells of a person's body.

Autosomal dominant: A gene mutation located on a non-sex chromosome that is expressed when present as part of a heterozygotic gene pair.

Autosomal recessive: A gene mutation located on a non-sex chromosome that is only expressed when present in homozygous pairs.

Balanced translocation: A chromosomal mutation, where a segment of DNA becomes abnormally attached to the wrong chromosome, which results in two nonhomologous chromosomes being able to cross over, something which normally can occur only between homologous chromosomes.

Genetic counseling: A process involving the guidance of a specially trained professional in the evaluation of family history, medical records, and genetic test results, in assessing the risk of genetic diseases.

HLA typing: Human leukocyte antigen (HLA) typing is the name given to the system used to identify the unique cell markers (antigens) that the immune system recognizes.

In vitro fertilization (IVF): A type of assisted reproductive procedure where an egg is fertilized outside a woman's body and then implanted into the womb.

Preimplantation genetic diagnosis (PGD): Testing of an embryo for a specific genetic disorder, involving a biological couple in which one or both partners are carriers of the disorder.

Preimplantation genetic screening (PGS): Testing of an embryo for a specific genetic disorder, involving a biological couple of no known risk (that is, neither partner is a known carrier of the disorder).

X-linked disorder: A disease associated with a genetic mutation on the X-sex chromosome; X-linked genes are expressed in all males with the gene, but only in females when the same gene is on both X chromosomes.

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History

Status	Date	Action
New	03/21/2019	Medical Policy & Technology Assessment Committee (MPTAC) review. Initial document development. Moved content of GENE.00002 Preimplantation

Genetic Diagnosis Testing to new clinical utilization management guideline document with the same title.