I. POLICY

Preimplantation genetic diagnosis (PGD) testing may be considered medically necessary as an adjunct to invitro fertilization (IVF) in otherwise fertile couples who meet one of the following criteria:

For evaluation of an embryo at an identified elevated risk of a genetic disorder such as when
- Both partners are known carriers of a single gene autosomal recessive disorder;
- One partner is a known carrier of a single gene autosomal recessive disorder, and the partners have one offspring that has been diagnosed with that recessive disorder;
- One partner is a known carrier of a single gene autosomal dominant disorder;
- One partner is a known carrier of a single X-linked disorder; or

For evaluation of an embryo at an identified elevated risk of structural chromosomal abnormality, such as for a Parent with balanced or unbalanced chromosomal translocation

Preimplantation genetic diagnosis (PGD) as an adjunct to IVF is considered investigational in patients/couples who are undergoing IVF in all situations other than those specified above. There is insufficient evidence to support a conclusion concerning the health outcomes or benefits associated with this procedure.

Preimplantation genetic screening (PGS) as an adjunct to IVF is considered investigational in patients/couples who are undergoing IVF in all situations, as there is insufficient evidence to support a conclusion concerning the health outcomes or benefits associated with this procedure.
Policy Guidelines

In some cases involving a single X-linked disorder, determination of the gender of the embryo provides sufficient information for excluding or confirming the disorder.

The severity of the genetic disorder is also a consideration. At the present time, many cases of preimplantation genetic diagnosis (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 condition for which PGD has been frequently performed. However, cystic fibrosis has a variable presentation and can be treatable. The range of genetic testing that is performed on amniocentesis samples as a possible indication for elective abortion may serve as a guide.

This policy does not attempt to address the myriad ethical issues associated with PGT that, it is hoped, have involved careful discussion between the treated couple and the physician. For some couples, the decision may involve the choice between the risks of an IVF procedure and deselection of embryos as part of the PGT treatment versus normal conception with the prospect of amniocentesis and an elective abortion.

Cross-reference:
MP-7.002 Reproductive Techniques
MP-2.232 Genetic Testing for Inheritable Disease

II. PRODUCT VARIATIONS

| [N] = No product variation, policy applies as stated |
| [Y] = Standard product coverage varies from application of this policy, see below |

| [N] Capital Cares 4 Kids | [N] Indemnity |
| [N] PPO | [N] SpecialCare |
| [N] HMO | [N] POS |
| [Y] SeniorBlue HMO* | [N] FEP PPO** |
| [Y] SeniorBlue PPO* |

*In-Vitro Fertilization (IVF) is a non-covered service.

**Services and supplies related to ART and assisted insemination procedures are non-covered.
Preimplantation genetic testing (PGT) involves analysis of biopsied cells as part of an assisted reproductive procedure. It is generally considered to be divided into two categories. Preimplantation genetic diagnosis (PGD) is used to detect a specific inherited disorder and aims to prevent the birth of affected children in couples at high risk of transmitting a disorder. Preimplantation genetic screening (PGS) uses similar techniques to screen for potential genetic abnormalities in conjunction with in vitro fertilization for couples without a specific known inherited disorder.

Preimplantation genetic testing (PGT) describes a variety of adjuncts to an assisted reproductive procedure in which either maternal or 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. The ability to identify preimplantation embryos with genetic defects before the initiation of pregnancy provides an attractive alternative to amniocentesis or chorionic villus sampling (CVS), with selective pregnancy termination of affected fetuses. Preimplantation genetic testing is generally categorized as either diagnostic (PGD) or screening (PGS). PGD is used to detect genetic evidence of a specific inherited disorder, in the oocyte or embryo, derived from mother or couple, respectively, that has a high risk of transmission. PGS is not used to detect a specific abnormality but instead uses similar techniques to identify genetic abnormalities to identify embryos at risk. This terminology, however, is not used consistently e.g., some authors use the term preimplantation genetic diagnosis when testing for a number of possible abnormalities in the absence of a known disorder.

Biopsy for PGD can take place at 3 stages; the oocyte, the cleavage stage embryo or the blastocyst. In the earliest stage, the first and second polar bodies are extruded from the oocyte as it completes meiotic division after ovulation (first polar body) and fertilization (second polar body). This strategy thus focuses on maternal chromosomal abnormalities. If the mother is a known carrier of a genetic defect and genetic analysis of the polar body is normal, then it is assumed that the genetic defect was transferred to the oocyte during meiosis.

Biopsy of cleavage stage embryos or blastocysts can detect genetic abnormalities arising from either the maternal or paternal genetic material. Cleavage stage biopsy takes place after the first few cleavage divisions when the embryo is composed of 6-8 cells (i.e., blastomeres). Sampling involves aspiration of 1 and sometimes 2 blastomeres from the embryo. Analysis of 2 cells may improve diagnosis but may also affect the implantation of the embryo. In addition, a potential disadvantage of testing at this phase is that mosaicism might be present. Mosaicism refers to genetic differences among the cells of the embryo that could result in an incorrect interpretation if the chromosomes of only a single cell are examined.

The third option is sampling the embryo at the blastocyst stage when there are about 100 cells. Blastocysts form 5 to 6 days after insemination. Three to 10 cells trophectoderm cells (outer layer of the blastocyst) are sampled. A disadvantage is that not all embryos develop to the
blastocyst phase in vitro and, if they do, there is a short time before embryo transfer needs to take place. Blastocyst biopsy has been combined with embryonic vitrification to allow time for test results to be obtained before the embryo is transferred.

The biopsied material can be analyzed in a variety of ways. Polymerase chain reaction (PCR) or other amplification techniques can be used to amplify the harvested DNA with subsequent analysis for single genetic defects. This technique is most commonly used when the embryo is at risk for a specific genetic disorder such as Tay Sachs disease or cystic fibrosis. Fluorescent in situ hybridization (FISH) is a technique that allows direct visualization of specific (but not all) chromosomes to determine the number or absence of chromosomes. This technique is most commonly used to screen for aneuploidy, gender determination or to identify chromosomal translocations. FISH cannot be used to diagnose single genetic defect disorders. However, molecular techniques can be applied with FISH (such as microdeletions and duplications) and thus, single-gene defects can be recognized with this technique.

Another approach that is becoming more common is array comparative genome hybridization testing at either the 8-cell or more often, the blastocyst stage. Unlike FISH analysis, this allows for 24 chromosome aneuploidy screening, as well as more detailed screening for unbalanced translocations and inversions and other types of abnormal gains and losses of chromosomal material.

Next-generation sequencing such as massively parallel signature sequencing has potential applications to prenatal genetic testing, but use of these techniques is in a relatively early stage of development compared to other methods of analyzing biopsied material. (1, 2)

Three general categories of embryos have undergone PGT:

1. Embryos at risk for a specific inherited single genetic defect
   Inherited single-gene defects fall into 3 general categories: autosomal recessive, autosomal dominant, and X-linked. 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. Gender 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. PGD could also be used to deselect affected male embryos. While there is a growing list of single genetic defects for which molecular diagnosis is possible, the most common indications include cystic fibrosis, beta thalassemia, muscular dystrophy, Huntington's disease, hemophilia, and fragile X disease. It should be noted that when PGD is used to deselect affected embryos, the treated couple is not technically infertile but are undergoing an assisted reproductive procedure for the sole purpose of PGD. In this setting, PGD may be considered an alternative to selective termination of an established pregnancy after diagnosis by amniocentesis or chorionic villus sampling.
2. Embryos at a higher risk of translocations
   Balanced translocations occur in 0.2% of the neonatal population but at a higher rate in infertile couples or in those with recurrent spontaneous abortions. PGD can be used to deselect those embryos carrying the translocations, thus leading to an increase in fecundity or a decrease in the rate of spontaneous abortion.

3. Identification of aneuploid embryos
   Implantation failure of fertilized embryos is a common cause for failure of assisted reproductive procedures; aneuploidy of embryos is thought to contribute to implantation failure and may also be the cause of recurrent spontaneous abortion. The prevalence of aneuploid oocytes increases in older women. These age-related aneuploidies are mainly due to nondisjunction of chromosomes during maternal meiosis. Therefore, PGS of the extruded polar bodies from the oocyte has been explored as a technique to deselect aneuploid oocytes in older women. The FISH technique is most commonly used to detect aneuploidy.

IV. RATIONALE

   Literature Review

   This policy was originally created in 1998 and was updated regularly with searches of the MEDLINE database. The most recent literature search was performed for the period May 2012 through June 10, 2013. Following is a summary of the key literature to date.

   Preimplantation Genetic Diagnosis (PGD)

   Technical Feasibility

   PGD has been shown to be a feasible technique to detect genetic defects and to deselect affected embryos. Recent reviews continue to state that PGD using either polymerase chain reaction (PCR) or fluorescent in situ hybridization (FISH) can be used to identify numerous single gene disorders and unbalanced chromosomal translocation. (3, 4) According to the most recent data from a PGD registry initiated by the European Society of Hormone Reproduction and Embryology (ESHRE) in 1997, the most common indications for PGD were thalassemia, sickle cell syndromes, cystic fibrosis, spinal muscular disease, and Huntington’s disease. (5)

   This policy is not designed to perform a separate analysis on every possible genetic defect. Therefore, implementation of this policy will require a case by case approach to address the many specific technical and ethical considerations inherent in testing for genetic disorders, based on an understanding of the penetrance and natural history of the genetic disorder in question and
the technical capability of genetic testing to identify affected embryos. (Guidance is provided in the Policy Guidelines section.)

Efficacy and Safety

_Preimplantation genetic diagnosis with in vitro fertilization in otherwise fertile couples_

An area of clinical concern is the impact of PGD on overall IVF success rates. For example, is the use of PGD associated with an increased number of in vitro fertilization (IVF) cycles required to achieve pregnancy or a live birth? There is a lack of direct evidence comparing IVF success rates with and without PGD. A rough estimate can be obtained by comparing data from the Centers for Disease Control and Prevention literature review.

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registry data reporting on success rates after PGD. The most recent CDC data were collected in 2010. (6) Using fresh embryos from non-donor eggs, the percentage of cycles resulting in pregnancies was 47.6% for women <35 years-old, 38.8% for women aged 35-37 and 29.9% for women aged 38-40. (These 3 age groups comprised approximately 85% of cycles). The percentage of cycles resulting in live births was 41.5% for women <35 years old, 31.9% for women aged 35-37, and 22.1% for women aged 38-40. According to ESHRE data from 2007, with PGD the clinical pregnancy rate was 23% per oocyte retrieval and 32% per embryo transfer. (5) The delivery rate was 19% per oocyte retrieval and 26% per embryo transfer. Although this comparison only provides a very rough estimate, the data suggest that use of PGD lowers the success rate of an in vitro fertilization cycle, potentially due to any of a variety of reasons such as inability to biopsy an embryo, inability to perform genetic analysis, lack of transferable embryos, and effect of PGT itself on rate of clinical pregnancy or live birth. It is important to note that the CDC database presumably represents couples who are predominantly infertile compared to the ESHRE database, which primarily represents couples who are not necessarily infertile but are undergoing IVF strictly for the purposes of PGD.

An important general clinical issue is whether PGD is associated with adverse obstetric outcomes, specifically fetal malformations related to the biopsy procedure. Strom and colleagues addressed this issue in an analysis of 102 pregnant women who had undergone PGD with genetic material from the polar body. (7) All preimplantation genetic diagnoses were confirmed postnatally; there were no diagnostic errors. The incidence of multiple gestations was similar to that seen with IVF. PGD did not appear to be associated with an increased risk of obstetric complications compared to the risk of obstetric outcomes reported in data for IVF. However, it should be noted that biopsy of the polar body is considered biopsy of extra-embryonic material, and thus one might not expect an impact on obstetric outcomes. The patients in this study had undergone PGD for both unspecified chromosomal disorders and various disorders associated with a single gene defect (i.e., cystic fibrosis, sickle cell disease, and others).

In the setting of couples with known translocations, the most relevant outcome of PGD is the live birth rate per cycle or embryo transfer. In 2011, Franssen and colleagues published a systematic review of literature on reproductive outcomes in couples with recurrent miscarriage (at least 2) who had a known structural chromosome abnormality; the review compared live birth rates after PGD or natural conception. (8) No controlled studies were identified. The investigators identified 4 observational studies on reproductive outcome in 469 couples after natural conception and 21 studies on reproductive outcome of 126 couples after PGD. The live birth rate per couple ranged from 33-60% (median 55.5%) after natural conception and between 0 and 100% (median 31%) after PGD. Miscarriage rate was a secondary outcome. After natural conception, miscarriage rates ranged from 21% to 40% (median 34%) and after PGD, miscarriage rates ranged from 0 to 50% (median 0%). Findings of this study apply only to couples with both recurrent miscarriage and a known structural chromosome abnormality.

Several additional studies have been published since the 2011 systematic review. In 2012, Keymolen and colleagues in Belgium reported clinical outcomes of 312 cycles performed for
142 couples with reciprocal translocations. (9) Data were collected at one center over 11 years. Seventy-five of 142 couples (53%) had PGD due to infertility, 40 couples (28%) due to a history of miscarriage, and the remainder due to a variety of other reasons. Embryo transfer was feasible in 150 of 312 cycles and 40 women had a successful singleton or twin pregnancy. The live birth rate per cycle was thus 12.8% (40 of 312), and the live birth rate per cycle with embryo transfer was 26.7% (40 of 150). A 2013 study by Scriven and colleagues in the United Kingdom evaluated PGD for couples carrying reciprocal translocations. (10) This prospective analysis included the first 59 consecutive couples who completed treatment at a single center. Thirty-two out of the 59 couples (54%) had a history of recurrent miscarriages. The 59 couples underwent a total of 132 cycles. Twenty-eight couples (47%) had at least one pregnancy, 21 couples (36%) had at least 1 live birth and 10 couples (36%) had at least one pregnancy loss. The estimated live birth rate per couple was 30 of 59 (51%) after 3 to 6 cycles. The live birth rate estimate assumed that couples who were unsuccessful and did not return for additional treatment would have had the same success rate as couples who did return.

No studies were identified that specifically addressed PGD for evaluation of embryos when parents have a history of aneuploidy in a previous pregnancy.

Section summary: Studies have shown that PGD for evaluation of an embryo at identified risk of a genetic disorder or structural chromosomal abnormality is feasible and does not appear to increase the risk of obstetric complications.

Preimplantation Genetic Screening (PGS) With In Vitro Fertilization

A number of randomized controlled trials (RCTs) and several meta-analyses on PGS have been published. Meta-analyses have included studies using PGS for a variety of indications. In 2009, Checa and colleagues identified 10 trials with a total of 1,512 women. (11) PGS was performed for advanced maternal age in 4 studies, for previous failed IVF cycles in 1 study, and for single embryo transfer in 1 study; the remaining 4 studies included the general IVF population. A pooled analysis of data from 7 trials (346 events) found a significantly lower rate of live birth in the PGS group compared to the control group. The unweighted live birth rates were 151 of 704 (21%) in the PGS group and 195 of 715 (27%) in the control group, p=0.003. Findings were similar in subanalyses including only studies of the general IVF population and only the trials including women in higher-risk situations. The continuing pregnancy rate was also significantly lower in the PGS group compared to the control group in a meta-analysis of 8 trials. The unweighted rates were 160 of 707 (23%) in the PGS group and 210 of 691 (30%) in the control group, p=0.004. Again, findings were similar in subgroup analyses.

Another meta-analysis was published in 2011 by Mastenbroek and colleagues. (12) The investigators included RCTs that compared the live birth rate in women undergoing IVF with and without PGS for aneuploidies. Fourteen potential trials were identified; 5 trials were excluded after detailed inspection, leaving 9 eligible trials with 1,589 women. All trials used FISH to analyze the aspirated cells. Five trials included women of advanced maternal age, 3 included “good prognosis” patients, and 1 included women with repeated implantation failure.
When data from the 5 studies including women with advanced maternal age were pooled, the live birth rate was significantly lower in the PGS group (18%) compared to the control group (26%), \( p=0.0007 \). There was not a significant difference in live birth rates when data from the 3 studies with good prognosis patients were pooled; rates were 32% in the PGS group and 42% in the control group, \( p=0.12 \). The authors concluded that there is no evidence of a benefit of PGS as currently applied in practice; they stated that potential reasons for inefficacy include possible damage from the biopsy procedure and the mosaic nature of analyzed embryos PGS group and 12 of 43 patients (28%) in the non-PGS groups had live births. (The exact \( p \)-value was not provided). However, the live birth rate was significantly higher with PGS in the advanced maternal age study. Thirty of 93 patients (32%) in the PGS group and 14 of 90 patients (16%) in the non-PGS group had live births: The difference between groups was statistically significant, \( p=0.001 \).

Debrock and colleagues published a trial in 2010 that included women of advanced maternal age (at least 35 years) who were undergoing \textit{in vitro} fertilization. (17) Randomization was done by cycle; 52 cycles were randomized to a PGS group and 52 to a control group that did not undergo PGS. Cycles were excluded if 2 or fewer fertilized oocytes were available on day 1 after retrieval or if 2 or fewer embryos of 6 or more cells were available on day 3. Individuals could participate more than once, and there was independent randomization for each cycle. More cycles were excluded postrandomization in the control group; outcome data were available for 37 cycles (71%) in the PGS group and 24 cycles (46%) in the control group. Study findings did not confirm the investigators’ hypothesis that the implantation rate would be higher in the group receiving PGS. The implantation rate was 15.1% in the PGS group and 14.9% in the control group; \( p=1 \). Moreover, the live-birth rate per embryo transferred did not differ significantly between groups; rates were 9.4% in the PGS group and 14.9% in the control group; \( p=0.76 \). An intention-to-treat (ITT) analysis of all randomized cycles (included and excluded) did not find any significant differences in outcomes including the implantation rate which was 11 of 76 (14.5%) in the PGS group and 16 of 88 (18.2%) in the control group, \( p=0.67 \). In the ITT, the live-birth rate per embryo transferred was 7 of 47 (14.9%) in the PGS group and 10 of 49 (20.4%) in the control group, \( p=0.60 \).

**Section summary:** Most RCTs and meta-analyses of RCTs tended to find similar or lower ongoing pregnancy and/or live birth rates after IVF with PGS compared to IVF without PGS. One recent RCT found a significantly higher live birth rate after IVS with PGS among women of advanced maternal age and no significant difference between groups among couples with repeated implantation failure. There is a lack of consistent evidence of benefit of PGS.

**Summary**

Preimplantation genetic testing has been shown to be technically feasible in detecting single gene defects, structural chromosomal abnormalities, and aneuploid embryos using a variety of biopsy and molecular diagnostic techniques. In terms of health outcomes, small case series have suggested that preimplantation genetic diagnosis is associated with the birth of unaffected fetuses.
when performed for detection of single genetic defects and a decrease in spontaneous abortions for patients with structural chromosomal abnormalities. For couples with single genetic defects, these beneficial health outcomes are balanced against the probable overall decreased success rate of the PGD procedure compared to in vitro fertilization alone. However, the alternative for couples at risk for single genetic defects is prenatal genetic testing, i.e., amniocentesis or chorionic villus sampling, with pregnancy termination contemplated for affected fetuses. (It should be noted that many patients undergoing PGD will also undergo a subsequent amniocentesis or chorionic villus sampling to verify PGD accuracy.) Ultimately, the choice is one of the risks (both medical and psychologic) of undergoing IVF with PGD, compared to the option of normal fertilization and pregnancy with the possibility of a subsequent elective abortion. Thus, PGD is considered medically necessary, as noted in the policy statements, when the evaluation is focused on a known disease or disorder, and the decision to undergo PGD is made upon careful consideration of the risks and benefits. There is a lack of consistent evidence from RCTs that preimplantation genetic screening improves ongoing and live birth rates in any patient population. Thus, preimplantation genetic screening as an adjunct to in vitro fertilization is considered investigational.

Practice Guidelines and Position Statements
In 2009, the American College of Obstetricians and Gynecologists (ACOG) issued an opinion on preimplantation genetic screening for aneuploidy. (18) They state that current data do not support the use of preimplantation genetic screening to screen for aneuploidy due solely to maternal age. ACOG also does not recommend PGS for recurrent unexplained miscarriage and recurrent implantation failures in the clinical setting; they recommended that use be limited to research studies.

A 2007 practice committee opinion issued by the American Society for Reproductive Medicine concluded that available evidence did not support the use of preimplantation genetic screening as currently performed to improve live birth rates in patients with advanced maternal age, previous implantation failure, or recurrent pregnancy loss, or to reduce miscarriage rates in patients with recurrent pregnancy loss related to aneuploidy. (19)

V. DEFINITIONS

ANEUPLOIDY is a condition of having an abnormal number of chromosomes for the species indicated.

ASSISTED FERTILIZATION is also referred to as assisted reproduction technology (ART). Refers to the process of aiding or supporting the union of the female egg and the male sperm to achieve conception, including artificial insemination (AI), in vitro fertilization (IVF), gamete intra-fallopian transfer (GIFT), and zygote intra-fallopian transfer (ZIFT).
**Chorionic Villus** are the vascular (blood-vessel like) projections from the chorion, which form the fetal portion of the placenta.

**DNA** is a large nucleic acid molecule, found principally in the chromosomes of the nucleus of a cell that is the carrier of genetic information.

**In Vitro Fertilization-Embryo Transfer (IVF-ET)** is a method of fertilizing human ova outside the body by collecting the mature ova and placing them in a dish with a sample of sperm. After an incubation period of forty-eight hours to seventy-two hours, the fertilized ova are injected into the uterus through the cervix.

**Oocyte** refers to the early or primitive ovum (egg cell) before it has developed completely.

VI. **Benefit Variations**

The existence of this medical policy does not mean that this service is a covered benefit under the member's contract. Benefit determinations should be based on the applicable contract language. Medical policies do not constitute a description of benefits. A member's individual or group customer benefits govern which services are covered, which are excluded, and which are subject to benefit limits and which require preauthorization. Members and providers should consult the member’s benefit information or contact Capital for benefit information.

VII. **Disclaimer**

Capital’s medical policies are developed to assist in administering a member’s benefits, do not constitute medical advice and are subject to change. Treating providers are solely responsible for medical advice and treatment of members. Members should discuss any medical policy related to their coverage or condition with their provider and consult their benefit information to determine if the service is covered. If there is a discrepancy between this medical policy and a member’s benefit information, the benefit information will govern. Capital considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.

VIII. **Coding Information**

Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.
**Covered when medically necessary:**

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Additional CPT codes will be required for the genetic analysis. The CPT codes used will vary according to the test and technique used to perform the genetic analysis.


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*If applicable, please see Medicare LCD or NCD for additional covered diagnoses.

**The following ICD-10 diagnosis codes will be effective October 1, 2014:**

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<td>Z31.49</td>
<td>Encounter for other procreative investigation and testing</td>
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*If applicable, please see Medicare LCD or NCD for additional covered diagnoses.

**IX. REFERENCES**


20. Taber’s Cyclopedic Medical Dictionary, 20th edition
X. POLICY HISTORY

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<td>CAC 2/28/12</td>
<td>Adopt BCBSA. Statement regarding preimplantation genetic diagnosis testing as an adjunct to in vitro fertilization (IVF) considered not medically necessary in patients/couples who are undergoing IVF due to infertility when there is no identified elevated risk of genetic disorder or chromosomal abnormality in the embryo was removed from the policy. New policy statement added that preimplantation genetic diagnosis is considered investigational in all situations other than those specified in the medically necessary policy statement. In addition, the phrase “in all situations” added to the policy statement on preimplantation genetic screening.</td>
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<td>Minor revision. In the medically necessary statement, the word “structural” was added to “chromosomal abnormality” for clarification and “e.g., unbalanced translocation” was removed because it was repetitive. Added FEP variation to indicate services and supplies related to ART and assisted insemination procedures are non-covered. Added rationale section and policy guidelines.</td>
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