4.02.05	Preimplantation Genetic Testing	
Section 4.0 OB/Gyn/Reproduction	**Effective Date** August 29, 2014	
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Description

Preimplantation genetic testing (PGT) involves analysis of biopsied cells as part of an assisted reproductive procedure. It is generally considered to be divided into 2 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.

Related Policies

- General Approach to Evaluating the Utility of Genetic Panels
- Genetic Testing - Overview

Policy

Preimplantation genetic diagnosis (PGD) may be considered **medically necessary** as an adjunct *to in vitro* fertilization (IVF) in couples not known to be infertile who meet **one** of the following criteria:

- For evaluation of an embryo at an identified elevated risk of a genetic disorder
    - 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
- For evaluation of an embryo at an identified elevated risk of structural chromosomal abnormality

- 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.

Preimplantation genetic *screening* (PGS) as an adjunct to IVF is considered **investigational** in patients/couples who are undergoing IVF in all situations.

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 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.

Coding

There are specific CPT codes describing the embryo biopsy procedure:

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

As appropriate, specific codes from the CPT molecular pathology section or molecular cytogenetics section would be reported:

- 81200-81479: Molecular pathology code range
- 88271-88275: Molecular cytogenetics code range

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

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. 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.

Some state or federal mandates (e.g., Federal Employee Program (FEP)) prohibit Plans from denying Food and Drug Administration (FDA) - approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

Rationale

Background

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 before implantation of the embryo into the uterus. The ability to identify preimplantation embryos with genetic defects before the initiation of pregnancy provides an alternative to amniocentesis or chorionic villus sampling (CVS), with selective pregnancy termination of affected fetuses. PGT is generally categorized as either Preimplantation genetic diagnostic (PGD) or Preimplantation genetic 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 PGD 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, cleavage stage embryo, or the blastocyst. In the earliest stage, both 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 to 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 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 with 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 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 is 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 CVS.

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.

Note: The complicated technical and ethical issues associated with preimplantation genetic testing (PGT) will frequently require case by case consideration. For example, such consideration may be required, particularly for couples who are known carriers of potentially lethal or disabling genetic mutations and are seeking preimplantation genetic diagnosis (PGD) as an alternative to conventional conception, with the possibility of an elective abortion if a subsequent amniocentesis identifies an affected fetus. The diagnostic performance of the individual laboratory tests used to analyze the biopsied genetic material is rapidly evolving, and evaluation of each specific genetic test for each abnormality is beyond the scope of this policy. However, in general, 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 penetrance, i.e., the probability that an individual with the mutation will express the associated disorder), will affect the diagnostic performance of the test. An ideal candidate for genetic testing would be a person who has a condition that is associated with a single well- characterized mutation for which a reliable genetic test has been established. In some situations, PGT 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.

Following is a summary of the key literature to date.

Preimplantation Genetic Diagnosis (PGD)

Technical Feasibility

Preimplantation genetic diagnostic (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 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 couples not known to be infertile

An area of clinical concern is the impact of PGD on overall in vitro fertilization (IVF) success rates. For example, is the use of PGD associated with an increased number of 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

(CDC) on IVF success rates overall and ESHRE registry data reporting on success rates after PGD. The most recent CDC data were collected in 2010.(6) Using fresh embryos from nondonor eggs, the percentage of cycles resulting in pregnancies was 47.6% for women younger than 35 years-old, 38.8% for women aged 35 to 37, and 29.9% for women aged 38 to 40. (These 3 age groups comprised approximately 85% of cycles.) The percentage of cycles resulting in live births was 41.5% for women younger than 35 years-old, 31.9% for women aged 35 to 37, and 22.1% for women aged 38 to 40. According to European Society of Hormone Reproduction and Embryology (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, data suggest that use of PGD lowers the success rate of an IVF 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 with 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 et al. addressed this issue in an analysis of 102 pregnant women who had undergone PGD with genetic material from the polar body.(7) All PGDs 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 with 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, 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. Franssen et al. (2011) 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% to 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. Keymolen et al. (2012), 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 study by Scriven et al. (2013), 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 1 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, including fetal malformations related to the biopsy procedure.

Preimplantation Genetic Screening With In Vitro Fertilization

A number of randomized controlled trials (RCTs) and several meta-analyses on preimplantation genetic screening (PGS) have been published. Meta-analyses have included studies using PGS for a variety of indications. Checa et al. (2009) identified 10 trials with a total of 1512 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 with 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 with 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.

Mastenbroek et al. (2011) published another meta-analysis.(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 1589 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 woman 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 with 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.

A systematic review by Gleicher et al. (2014) considered studies using newer PGS methods that they called PGS#2. This consists of biopsy on day 5 to 6 and aneuploidy assessment of all 24 chromosome pairs (as opposed to PGS#1 that involves biopsy on day 3 and FISH assessment of limited numbers of chromosomes).(13) The authors did not identify any randomized controlled trials (RCTs) that used these newer methods and met the methodologic criterion of using an intention-to-treat (ITT) analysis with IVF cycle as the denominator. Studies claiming that PGS using day 5 to 6 biopsy had a positive impact on health outcomes were not randomized, and they evaluated pregnancy outcomes per the embryo transfer rate rather than per the number of IVF cycles. The authors asserted the data analysis methods used in the available studies misrepresent outcomes and that there are insufficient data that PGS#2 improves health outcomes compared with PGS#1.

Key recent randomized trials on PGS are summarized next.

Mastenbroek et al. (2007), in an RCT, found that PGS reduced the rates of ongoing pregnancies and live births after IVF in women of advanced maternal age (aged 35- 41 years).(14) In this study, 408 women (206 PGD and 202 control group) underwent 836 cycles of IVF (434 cycles with and 402 cycles without PGS). The ongoing pregnancy rate was significantly lower in the women assigned to PGS (52 of 206 women [25%]) than in those not assigned to PGS (74 of 202 women [37%]; rate ratio [RR], 0.69; 95% confidence interval [CI]: 0.51 to 0.93). The women assigned to PGS also had a significantly lower live

birth rate (24% vs. 35%, respectively; RR, 0.68; 95% CI: 0.50 to 0.92). Beukers et al. reported morphologic abnormalities in surviving children at 2 years.(15) Data were available on 50 children born after PGS and 72 children born without PGS. Fourteen of 50 children (28%) in the PGS group and 25 of 72 children (35%) in the group that did not receive PGS had at least 1 major abnormality; the difference between groups was not statistically significant, p=0.43. Skin abnormalities (e.g., capillary hemangioma and hemangioma plana) were the most common, affecting 5 children after PGS and 10 children in the non-PGS group. In a control group of 66 age-matched children born without assisted reproduction, 20 children (30%) had at least 1 major abnormality. Developmental outcomes at 2 and 4 years have also been reported. Schendelaar et al. (2013) reported on outcomes when children were 4 years-old.(16) Data were available on 49 children (31 singletons, 9 sets of twins) born after IVF with PGS and 64 children (42 singletons, 11 sets of twins) born after IVF without PGS. The primary outcome of this analysis was the child's neurologic condition, as assessed by the fluency of motor behavior. The fluency score ranged from 0 to 15 and is a subscale of the neurologic optimality score (NOS). In the sample as a whole, and among singletons, the fluency score did not differ among children in the PGS and non-PGS groups. However, among twins, the fluency score was significantly lower among those in the PGS group (mean score, 10.6, 95% CI: 9.8 to 11.3) and non-PGS group (mean score, 12.3, 95% CI: 11.5 to 13.1). Cognitive development, as measured by IQ score, and behavioral development, as measured by the total problem score, was similar between non-PGS and PGS groups.

Rubio et al. (2013) published findings of 2 RCTs evaluating PGS.(17) Studies' designs were similar, but one included women of advanced maternal age (41-44 years-old), and the other included couples younger than 40 years-old with repetitive implantation failure (RIF), defined as failing 3 or more previous attempts at implantation. All couples were infertile and did not have a history of pregnancy or miscarriage with chromosomal abnormality. In all cases, blastocysts were transferred at day 5. In the groups receiving PGS, single-cell biopsies were done at the cleavage stage. A total of 91 patient

enrolled in the RIF study (48 in the PGS group and 43 in the non-PGS group) and 183 patients in the advanced maternal age study (93 patients in the PGS group and 90 patients in the non-PGS group). Among RIF patients, the live birth rate did not differ significantly between groups. Twenty-three of 48 patients (48%) in the 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 et al. (2010) published a trial that included women of advanced maternal age (at least 35 years) who were undergoing IVF.(18) 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. Subjects 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 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 date 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 with 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 preimplantation genetic diagnosis (PGD) procedure compared with in vitro fertilization (IVF) alone. However, the alternative for couples at risk for single genetic defects is prenatal genetic testing, i.e., amniocentesis or chorionic villus sampling (CVS), with pregnancy termination contemplated for affected fetuses. (It should be noted that many patients undergoing PGD will also undergo a subsequent amniocentesis or

CVS to verify PGD accuracy.) Ultimately, the choice is one of the risks (both medical and psychologic) of undergoing IVF with PGD, compared with 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 (PGS) improves ongoing and live birth rates in any patient population. Thus, PGS as an adjunct to IVF is considered investigational.

Practice Guidelines and Position Statements

The Ethics Committee of the American Society for Reproductive Medicine (2013) published a committee opinion on use of PGD for serious adult onset conditions.(19) The main points included:

"- Preimplantation genetic diagnosis (PGD) for adult-onset conditions is ethically justifiable when the conditions are serious and when there are no known interventions for the conditions or the available interventions are either inadequately effective or significantly burdensome.

- For conditions that are less serious or of lower penetrance, PGD for adult onset conditions is ethically acceptable as a matter of reproductive liberty. It should be discouraged, however, if the risks of PGD are found to be more than merely speculative."

The committee opinion also stated that physicians and patients should be aware that much remains unknown about the long-term effects of embryo biopsy on the developing fetus and that experienced genetic counselors should be involved in the decision process.

The American College of Obstetricians and Gynecologists (ACOG) (2009) issued an opinion on PGS for aneuploidy.(20) They stated that current data do not support the use of PGS to screen for aneuploidy due solely to maternal age. ACOG also did 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 the available evidence did not support the use of PGS 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.(21)

U.S Preventive Services Task Force

No relevant guidelines were found.

Medicare National Coverage

No national coverage determination.

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21. Preimplantation genetic testing: a Practice Committee opinion. Fertil Steril 2007; 88(6):1497-504.
22. Blue Cross Blue Shield Association. Medical Policy Reference Manual, No. 04.02.05 (November 1998).

Documentation Required for Clinical Review

- History and physical and/or consultation notes including:
  - Reason for performing test
  - Signs/symptoms/test results related to reason for genetic testing
  - Family history if applicable
  - How test result will impact clinical decision making
- Lab results documenting one/both partners carrier status or genetic disorder
- Physician order for genetic test
- Name and description of genetic test
- CPT codes billed for the particular genetic test

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to benefit design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement.

MN/IE

The following service/procedure may be considered medically necessary in certain instances and investigational in others. Services may be medically necessary when policy criteria are met. Services are considered investigational when the policy criteria are not met or when the code describes application of a product in the position statement that is investigational.

Type	Code	Description
CPT®	81161 - 81479	Molecular pathology code range
	88271 - 88275	Molecular cytogenetics (i.e., FISH), code range
	88291	Cytogenetics and molecular cytogenetics, interpretation and report
	89290 - 89291	Biopsy, oocyte polar body or embryo blastomere, microtechnique (for preimplantation genetic diagnosis), less than or equal to, or greater than 5 embryo(s), respectively
HCPC	None	
ICD-9 Procedure	None	
ICD-10 Procedure	***For dates of service on or after 10/01/2015***	
	None	
ICD-9 Diagnosis	V26.31 - V26.39	Genetic counseling and testing
	V28.89	Other specified antenatal screening
ICD-10 Diagnosis	***For dates of service on or after 10/01/2015***	
	Z31.430	Encounter of female for testing for genetic disease carrier status for procreative management
	Z31.438	Encounter for other genetic testing of female for procreative management
	Z31.440	Encounter of male for testing for genetic disease carrier status for procreative management
	Z31.448	Encounter for other genetic testing of male for procreative management
	Z31.49	Encounter for other procreative investigation and testing

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action	Reason
August 29, 2014	BCBSA Medical Policy adoption	Medical Policy Committee

Definitions of Decision Determinations

Medically Necessary: A treatment, procedure or drug is medically necessary only when it has been established as safe and effective for the particular symptoms or diagnosis, is not investigational or experimental, is not being provided primarily for the convenience of the patient or the provider, and is provided at the most appropriate level to treat the condition.

Investigational/Experimental: A treatment, procedure or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California / Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a Split Evaluation, where a treatment, procedure or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements

This service (or procedure) is considered **medically necessary** in certain instances and **investigational** in others (refer to policy for details).

For instances when the indication is **medically necessary**, clinical evidence is required to determine **medical necessity**.

For instances when the indication is **investigational**, you may submit additional information to the Prior Authorization Department.

Within five days before the actual date of service, the Provider MUST confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should also be directed to the Prior Authorization Department. Please call 1-800-541-6652 or visit the Provider Portal www.blueshieldca.com/provider.

The materials provided to you are guidelines used by this plan to authorize, modify, or deny care for persons with similar illness or conditions. Specific care and treatment may vary depending on individual need and the benefits covered under your contract. These Policies are subject to change as new information becomes available.