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Medical Policy Manual

Topic: Preimplantation Genetic Testing

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IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION[1]

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.

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 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 villous sampling (CVS) with selective pregnancy termination of affected fetuses. Preimplantation genetic testing can be viewed 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 (PGD), such as Tay Sach's 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 (PGS) 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 (CGH) 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.[2,3]

Three general categories of embryos have undergone PGT:

1. Embryos at risk for a specific inherited single genetic defect (PGD)

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. 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.

3. 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.

MEDICAL POLICY CRITERIA

I. Preimplantation genetic diagnosis (PGD) may be considered **medically necessary** as an adjunct to in vitro fertilization (IVF) in otherwise fertile couples who meet at least one of the following criteria subject to careful consideration of the technical and ethical issues involved:

   A. For evaluation of an embryo at an identified elevated risk of a genetic disorder such as when:

      1. Both partners are known carriers of a single gene autosomal recessive disorder

      2. 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

      3. One partner is a known carrier of a single gene autosomal dominant disorder

      4. One partner is a known carrier of a single X-linked disorder

   B. 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

II. 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.

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

SCIENTIFIC EVIDENCE[1]

Issues addressed in literature includes the technical feasibility of preimplantation genetic testing to deselect embryos for different indications and the impact of the procedure on implantation rates and pregnancy and birth outcomes. Following is a summary of the key literature to date.

Technical Feasibility

Preimplantation genetic diagnosis (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.[4,5] According to the most recent data from a PGD registry initiated by the European Society of Hormone Reproduction and Embryology (ESHRE), the most common indications for PGD were thalassemia, sickle cell syndromes, cystic fibrosis (CF), spinal muscular disease, and Huntington's disease.[6]

Several studies have suggested that the role of preimplantation genetic testing (PGT) has expanded to a broader variety of conditions that have not been considered as an indication for genetic testing via amniocentesis or chorionic villus sampling. The report of PGT used to deselect embryos at risk for early-onset Alzheimer's disease prompted considerable controversy, both in lay and scientific publications.[7-9] Other reports focus on other applications of PGT for *predispositions* to late-onset disorders.[10] This contrasts with the initial use of PGD in deselecting embryos with genetic mutations highly predictive of lethal diseases. PGD has also been used for gender selection and "family balancing."[11-13] A representative sample of case series and reports on the technical feasibility of PGT to deselect embryos for different indications follows.

In 2007 the ESHRE PGD registry reported PGD screening on 3753 oocyte retrievals (OR), resulting in 729 OR chromosomal abnormalities, 110 OR X-linked diseases, 1203 OR with monogenic diseases, and 92 OR for social sexing.[6] These registry data suggest that PGD, using either PCR or FISH, can be used to deselect affected embryos.

Several smaller case series reported on individual diseases. For example, Goossens and colleagues reported on 48 cycles of PGD in 24 couples at risk for cystic fibrosis. Thirteen patients became pregnant, and 12 healthy babies were born.[14] In an additional 2013 study on cystic fibrosis, there were 44 PGD cycles performed for 25 CF-affected homozygous or double-heterozygous CF patients (18 male and seven female partners), which involved testing simultaneously for three mutations, resulting in the birth of 13 healthy CF-free children and no misdiagnosis. PGD was also performed for six couples at a combined risk of producing offspring with CF and another genetic disorder. Concomitant testing for CFTR and other mutations resulted in birth of six healthy children, free of both CF and another genetic disorder in all but one cycle.[15] Other anecdotal studies have reported successful PGD in patients with osteogenesis imperfecta,[16] Lesch-Nyhan syndrome,[17] bulbar muscular atrophy,[18] and phenylketonuria.[19]

Efficacy and Safety

Preimplantation Genetic Diagnosis with In Vitro Fertilization in Otherwise Fertile Couples

An area of clinical concern is the impact of PGT on overall IVF success rates. For example, is the use of PGT 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 2011.[20] 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 PGT with genetic material from the polar body.[21] All preimplantation genetic diagnoses were confirmed postnatally; there were no diagnostic errors. The incidence of multiple gestations was similar to that seen with IVF. Preimplantation genetic diagnosis did not appear to be associated with an increased risk of obstetric complications compared to data reported for obstetric outcomes for in vitro fertilization. However, it should be noted that biopsy of the polar body is extra-embryonic material, and thus one might not expect an impact on obstetric outcomes. The patients in this study had undergone PGT 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.[22] 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.

Munne and colleagues reviewed 35 couples in which 1 partner was known to carry a translocation.[23] Of the 47 cycles of PGD, there were 13 completed or ongoing pregnancies (27%). There was no embryo transfer in 14 of the cycles; thus the pregnancy rate per embryo transfer was 39%. A total of 15 patients in this group had 16 pregnancies, only 2 of which ended in spontaneous abortion. Prior to PGD, this same group of patients had 38 previous pregnancies of which 35 ended in spontaneous abortion.

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.[24] 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 evaluated PGD for couples carrying reciprocal translocations.[25] 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.

Conclusion: 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 with In Vitro Fertilization

Technology Assessments

A 2008 technology assessment published by the Agency for Healthcare Research and Quality (AHRQ) found 2 randomized controlled trials that assessed the use of PGS for embryo selection in women 35 years or older.[26] The first study reported lower pregnancy and live birth rates in the PGS group compared with the control group which did not undergo PGS, though this difference was not statistically significant (p=0.09).[27] About 25% of the embryos biopsied were genetically abnormal; therefore, fewer embryos were transferred in the PGD group. In the second study, which also studied women 35 years or older, Mastenbroek et al. reported significantly lower pregnancy and live birth rates in the PGS group.[28] In this study, all women had 2 embryos transferred; thus, the between-group difference could not be attributed to differences in the number of transferred embryos.

Systematic Reviews and Meta-Analyses

- A 2006 Cochrane review included 2 randomized controlled trials and concluded that the available data on PGS with women of advanced maternal age showed no difference in live birth rate and ongoing pregnancy rates.[29]
- An additional meta-analysis was published in 2009 by Checa and colleagues.[30] The investigators identified 10 trials with a total of 1,512 women. 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.
- A systematic review and meta-analysis was published in 2011 by Mastenbroek and colleagues.[31] They 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.

Randomized Controlled Trials (RCTs)

Several RCTs on PGS are summarized below:

- In 2007, Mastenbroek et al., found that PGS reduced the rates of ongoing pregnancies and live births after IVF in women of advanced maternal age (aged 35 through 41 years).[28] In this study, 408 women (206 assigned to PGD and 202 assigned to the 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, 0.69; 95% confidence interval [CI]: 0.51–0.93). The women assigned to PGS also had a significantly lower live-birth rate (24% vs. 35%, respectively; rate ratio, 0.68; 95% CI: 0.50–0.92).
- In 2011, a follow-up study was published when surviving children were 2 years-old.[32] Forty-nine pregnancies in the PGS group and 71 in the control group resulted in live births of at least one child. Forty-five couples with 54 children (36 singletons and 9 twins) in the PGS group and 63 couples with 77 children (49 singletons and 14 twins) in the control group were available for follow-up. The groups of children did not differ significantly in scores on an infant development scale and child development checklist variables. For example, median scores on the total Child Behavior Checklist were 43.0 among children born after PGS and 46.0 in control children, p=0.44. However, the neurologic optimality score (NOS) was significantly lower in the PGS group than the control group, p=0.20.
- Morphological abnormalities at 2 years were reported by Beukers and colleagues in 2013.[28] Data were available on 50 children born after PGS and 72 children born without PGS. Fourteen out 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 one 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 one major abnormality. Developmental outcomes at 2 and 4 years have also been reported.
- In 2013, Schendelaar and colleagues reported on outcomes when children were 4 years old. 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.[33] The primary outcome of this analysis was the child's neurological condition, as assessed by the fluency of motor behavior. The fluency score ranged from 0 to 15 and is a sub-scale of the neurological 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 were similar between non-PGS and PGS groups.
- In 2013, Rubio and colleagues published findings of 2 RCTs evaluating PGS.[34] Studies designs were similar but one included women of advanced maternal age (41-44 years old) and the other included couples under 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 patients 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 and colleagues published a trial in 2010 that included women of advanced maternal age (at least 35 years) who were undergoing in vitro fertilization.[35] 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 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.

Conclusion: 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.

Clinical Practice Guidelines and Position Statements

American College of Obstetricians and Gynecologists (ACOG)

In 2009, ACOG issued an opinion statement on preimplantation genetic screening for aneuploidy.[36] ACOG 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.

American Society for Reproductive Medicine

A 2008 practice committee opinion issued by the American Society for Reproductive Medicine concluded the following:[37]

- PGD can reduce the risk of conceiving a child with genetic abnormality carried by one or both parents if that abnormality can be identified from a single cell.
- Available evidence does not support the use of PGS as currently performed to improve live birth rates in patients with advanced maternal age, previous implantation failure, recurrent pregnancy loss, or male factor infertility.

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. Therefore, 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 insufficient evidence that preimplantation genetic screening improves ongoing pregnancy and live birth rates. Therefore, preimplantation genetic screening as an adjunct to in vitro fertilization is considered investigational.

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CROSS REFERENCES

None

CODES	NUMBER	DESCRIPTION
CPT	88271 – 88275	Molecular cytogenetics (i.e., FISH), code range
	89290	Biopsy, oocyte polar body or embryo blastomere, microtechnique (for preimplantation genetic diagnosis), less than or equal to 5 embryo(s)
	89291	; greater than 5 embryo(s)
HCPCS	None	