Preimplantation Genetic Testing

Policy Number: 4.02.05  Last Review: 6/2017

Policy
Blue Cross and Blue Shield of Kansas City (Blue KC) will provide coverage for preimplantation genetic testing when it is determined to be medically necessary because the criteria shown below are met.

For fetal DNA testing of an embryo, verify infertility treatment benefits before applying medical policy

When Policy Topic is covered
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 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 1 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

When Policy Topic is not covered
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.
Considerations
In some cases involving a single X-linked disorder, determination of the sex 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.

Genetic Counseling
Genetic counseling is primarily aimed at patients who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual’s family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

Some plans may have contract or benefit exclusions for genetic testing.

Plans may consider reviewing their contract language to determine if such restrictions would apply to those patients undergoing preimplantation genetic diagnosis, not as an adjunct to treatment for infertility but as an alternative to selective termination of an established pregnancy. This latter group of patients is not infertile.

Description of Procedure or Service

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<thead>
<tr>
<th>Populations</th>
<th>Interventions</th>
<th>Comparators</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Individuals:</td>
<td>Interventions of interest are:</td>
<td>Comparators of interest are:</td>
<td>Relevant outcomes include:</td>
</tr>
<tr>
<td>With an identified elevated risk of a genetic disorder</td>
<td>• Preimplantation genetic diagnosis</td>
<td>• In vitro fertilization without preimplantation</td>
<td>• Health status measures</td>
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<tr>
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<td></td>
<td></td>
<td>• Treatment-related</td>
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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.

For individuals who have an identified elevated risk of a genetic disorder undergoing in vitro fertilization who receive PGD, the evidence includes observational studies and systematic reviews. Relevant outcomes are health status measures and treatment-related morbidity. The available data from observational studies and a systematic review have suggested that PGD is associated with the birth of unaffected fetuses when performed for detection of single genetic defects and is associated with a decrease in spontaneous abortions for patients with structural chromosomal abnormalities. Moreover, PGD performed for single gene defects does not appear to be associated with increased risk of obstetric complications. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

For individuals who have no identified elevated risk of a genetic disorder undergoing in vitro fertilization who receive PGS, the evidence includes randomized controlled trials (RCTs) and meta-analyses. Relevant outcomes are health status measures and treatment-related morbidity. RCTs and meta-analyses of RCTs on initial PGS methods (eg, fish in situ hybridization) tended to find lower or similar ongoing pregnancy and live birth rates compared with in vitro fertilization without PGS. There are fewer RCTs on newer PGS methods, and findings are mixed. Meta-analyses of RCTs have found higher implantation rates with PGS than with standard care, but not live birth rates. One meta-analysis, but not the other, found significantly higher ongoing pregnancy rates after PGS than after standard care. Well-conducted RCTs evaluating PGS in the target population (eg, women of advanced maternal age) are needed before conclusions can be drawn about the impact on the net health benefit. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Background**
PGT describes a variety of adjuncts to an assisted reproductive procedure (see separate policy) in which either maternal or embryonic DNA is sampled and

<table>
<thead>
<tr>
<th>Preimplantation Genetic Testing</th>
<th>Genetic Diagnosis</th>
<th>Morbidity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Undergoing in vitro fertilization</td>
<td>Prenatal genetic testing</td>
<td>Health status measures</td>
</tr>
<tr>
<td>Interventions of interest are:</td>
<td></td>
<td>Treatment-related morbidity</td>
</tr>
<tr>
<td>With no identified elevated risk of a genetic disorder undergoing in vitro fertilization</td>
<td>Preimplantation genetic screening</td>
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<td>Comparators of interest are:</td>
<td>In vitro fertilization without preimplantation genetic screening</td>
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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 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 eg, 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 (ie, 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, sex 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 has been explored as a
technique to deselect aneuploid oocytes in older women. FISH analysis of extruded polar bodies from the oocyte or no blastomeres at day 3 of embryo development was the initial method used to detect aneuploidy. A limitation of FISH is that analysis is limited to a restricted number of proteins. More recently, newer PGS methods have been developed and are known collectively as PGS version 2 (PGSv.2) or PGS#2. These methods allow for all chromosomes analysis with genetic platforms including array comparative genomic hybridization and single-nucleotide polymorphism chain reaction analysis. Moreover, in addition to older women, PGS has been proposed for women with repeated implantation failure.

Rationale

Literature Review

This evidence review was originally created in November 1998 and has been updated regularly with searches of the MEDLINE database. Most recently, the literature was reviewed through July 7, 2016.

Following is a summary of the key literature to date. (see Appendix Table 1 for genetic testing categories).

Note: The complicated technical and ethical issues associated with preimplantation genetic testing (PGT) will frequently require case by case consideration. 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 evidence review. 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, ie, 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 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. This review is not designed to analyze every possible genetic defect. Therefore, implementation 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.

Preimplantation Genetic Diagnosis With In Vitro Fertilization

Relevant outcomes of preimplantation genetic diagnosis (PGD) are the live birth rate per cycle and embryo transfer. In 2011, Franssen et al conducted 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 and natural conception. (3) No controlled studies were identified. The reviewers 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 rates 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%); after PGD, miscarriage rates ranged from 0% to 50% (median, 0%). Findings of this review apply only to couples with both recurrent miscarriage and a known structural chromosome abnormality.

Studies have been published since the Franssen systematic review and are described next.

**Observational Studies**  
A 2016 study by Kato et al included 52 couples with a reciprocal translocation (n=46) or Robersonian translocation (n=6) in at least 1 partner. (4) All couples had a history of at least 2 miscarriages. The average live birth rate was 76.9% over 4.6 oocyte retrieval cycles. In the subgroups of young (<38 years) female carriers, young male carriers, older (≥38 years) female carriers, and older male carriers, live birth rates were 77.8%, 72.7%, 66.7%, and 50.0%, respectively.

In 2015, Chow et al reported on 124 cycles of PGD in 76 couples with monogenetic diseases (X-linked recessive, autosomal recessive, autosomal dominant). (5) The most common genetic conditions were α-thalassemia (64 cycles) and β-thalassemia (23 cycles). Patients were not required to have a history of miscarriage. A total of 92 PGD cycles resulted in embryo transfer, with an ongoing pregnancy rate (beyond 8-10 weeks of gestation) in 28.2% of initiated cycles and an implantation rate of 35%. The live birth rate was not reported.

In 2012, Keymolen et al in Belgium reported clinical outcomes of 312 cycles performed for 142 couples with reciprocal translocations. (6) Seventy-five (53%) of 142 couples had PGD for infertility, 40 (28%) couples for a history of miscarriage, and the remainder for other reasons. The live birth rate per cycle was 12.8% (40/312), and the live birth rate per cycle with embryo transfer was 26.7% (40/150).

A 2013 study by Scriven et al in the United Kingdom evaluated PGD for couples carrying reciprocal translocations. (7) This prospective analysis included the first 59 consecutive couples who completed treatment at a single center. Thirty-two (54%) of the 59 couples had had recurrent miscarriages. The 59 couples underwent a total of 132 cycles. The estimated live birth rate per couple was 30 (51%) of 59 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 returned.
**Adverse Events**

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. All PGDs were confirmed postnatally; there were no diagnostic errors. The incidence of multiple gestations was similar to that seen with in vitro fertilization (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. Patients in this study had undergone PGD for both unspecified chromosomal disorders and various disorders associated with a single-gene defect (ie, cystic fibrosis, sickle cell disease, others).

**Section Summary: Preimplantation Genetic Diagnosis With In Vitro Fertilization**

A systematic review of observational studies found a median live birth rate of 31% after PGD compared with 55.5% after natural conception. The median miscarriage rate was 0% after PGD and 34% after natural conception. Findings of this review apply only to patients with recurrent miscarriage. Other observational studies have found reasonable live birth rates, and have found that PGD in patients with a genetic disorder does not appear to be associated with adverse obstetric outcomes.

**Preimplantation Genetic Screening With In Vitro Fertilization**

**Systematic Reviews**

A number of randomized controlled trials (RCTs) evaluating preimplantation genetic screening (PGS) using fluorescent in situ hybridization (FISH)-based technology have been published, and findings for these trials have been pooled in meta-analyses. In 2011, a meta-analysis by Mastenbroek et al included RCTs that compared the live birth rates in women undergoing IVF with and without PGS for aneuploidies. Fourteen potential trials were identified; 5 trials were excluded, leaving 9 eligible trials (total N=1589 women). 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%) than in the control group (26%; p<0.001). There was no 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 reviewers 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.

Previously, in 2009, a meta-analysis by Checa et al identified 10 trials (total N=1512 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 than in the control group. The unweighted live birth rates were 151 (21%) of 704 in the PGS group and 195 (27%) of 715 in the control group (p=0.003). Findings were similar in subanalyses, including only studies of the general IVF population and only trials including women in higher risk situations. The continuing pregnancy rate was also significantly lower in the PGS group than in the control group in meta-analysis of 8 trials. The unweighted rates were 160 (23%) of 707 in the PGS group and 210 (30%) of 691 in the control group (p=0.004). Again, findings were similar in subgroup analyses.

**Randomized Controlled Trials**
A key RCT evaluating outcomes of FISH analysis was published in 2007 by Mastenbroek et al.(11) The trial found that PGS reduced the rates of ongoing pregnancies and live births after IVF in women of advanced maternal age (age range, 35-41 years). In this study, 408 women (206 PGD, 202 control) 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 (52/206 [25%] women) than in those not assigned to PGS (74/202 [37%] women; rate ratio, 0.69; 95% confidence interval [CI], 0.51 to 0.93). Women assigned to PGS also had a significantly lower live birth rate (24% vs 35%, respectively; rate ratio, 0.68; 95% CI, 0.50 to 0.92).

More recently, studies on newer methods of PGS have been published. There are several systematic reviews, including a 2015 review of RCTs on PGS by Dahdouh et al.(12) RCTs were eligible for inclusion if they compared women undergoing IVF with PGS using one of the newer techniques on trophectodermic blastocyst cells to standard care without PGS. The reviewers did not distinguish between studies using fresh or frozen embryos, or between the various PGS version 2 techniques. Three RCTs met eligibility criteria.(13-15) Study characteristics and results are described in Table 1. All trials conducted embryo biopsies on day 5 or 6 of development. One trial (Yang et al) used array comparative genomic hybridization and the other 2 used quantitative polymerase chain reaction PCR. None targeted women of advanced maternal age or women with repeated implantation failure. Instead, Yang et al included good prognosis patients younger than age 35 with no history of spontaneous abortion, Forman et al included women younger than age 43, and Scott et al included women between the ages of 21 and 42 years with no more than 1 failed IVF attempt. One of the trials (Forman et al) transferred 1 embryo in the intervention group and 2 embryos in the control group, which might have introduced bias. Two studies were superiority trials and the other (Forman et al) a noninferiority trial. Forman used a 20% noninferiority margin, which may not be the most appropriate approach for evaluating the impact of PGS on health outcomes.

**Table 1: Randomized Controlled Trials Evaluating PGS Methods**

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<tr>
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<td>Noninferiority trial</td>
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<tr>
<td>Sample size</td>
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<td>205 couples</td>
<td>155 patients</td>
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<tr>
<td>Patient population</td>
<td>Female partner &lt;35 y with no history of spontaneous abortion and with normal karyotype</td>
<td>Female partner &lt;43 y</td>
<td>Female partner between 21 and 42 y with no more than 1 failed IVF attempt</td>
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<td>Intervention</td>
<td>• Blastocyst biopsy (day 5/6) and analyzed via aCGH • Single euploid embryo selected for transfer based on PGS</td>
<td>• Blastocyst biopsy (day 5/6) and analyzed via qPCR • Single euploid embryo selected for transfer based on PGS</td>
<td>• Blastocyst biopsy (day 5/6) and analyzed via qPCR • Single euploid embryo selected for transfer based on PGS</td>
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<tr>
<td>Comparator</td>
<td>Single embryo selected for transfer on day 5/6 based on morphologic assessment</td>
<td>Two embryos selected for transfer on day 5/6 based on morphologic assessment</td>
<td>Single embryo selected for transfer on day 5/6 based on morphologic assessment</td>
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<tr>
<td>Implantation rate</td>
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<td>• Intervention group: 63.2% • Control group: 51.7% (p=0.08)</td>
<td>• Intervention group: 66.4% • Control group: 47.9% (p&lt;0.001)</td>
</tr>
<tr>
<td>Clinical pregnancy rate</td>
<td>• Intervention group: 70.9% • Control group: 45.8% (p=0.017)</td>
<td>• Intervention group: 69% • Control group: 81% (not inferior)</td>
<td>• Intervention group: 93.1% • Control group: 80.7% (p=0.03)</td>
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<tr>
<td>Ongoing pregnancy rate (≥24 wk of gestation)</td>
<td>• Intervention group: 69.1% • Control group: 41.7% (p=0.009)</td>
<td>• Intervention group: 60.7% • Control group: 65.1% (not inferior)</td>
<td>Not reported</td>
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aCGH: array comparative genomic hybridization; IVF: in vitro fertilization; PGS: preimplantation genetic screening; qPCR: quantitative polymerase chain reaction PCR.

In a subsequent meta-analysis, Dahdouh et al pooled findings of the above 3 RCTs.(16) Primary outcomes of the meta-analysis were implantation rates and ongoing pregnancy rates (ie, beyond 20 weeks). In pooled analyses, rates of both primary outcomes were significantly higher after use of the newer PGS techniques compared to standard care without PGS. For clinical implantation rate, the pooled relative risk (RR) was 1.29 (95% CI, 1.15 to 1.45); for sustained implantation rate, the pooled relative risk was 1.39 (95% CI, 1.21 to 1.60). The meta-analysis did not address the live birth rate or adverse obstetric outcomes.

Another 2015 meta-analysis on newer PGS methods was published by Chen et al.(17) Four RCTs and 7 cohort studies were identified. In addition to the 3 RCTs described in Table 1, Chen included a 2012 RCT that used single-nucleotide polymorphism microarray analysis. A pooled analysis of the 4 RCTs found a significantly higher implantation rate with PGS than control (RR=1.32; 95% CI, 1.18 to 1.47). However, in additional pooled analyses of the RCTs, other outcomes were not significantly better with PGS than with control. For example, for the ongoing pregnancy rate, a pooled analysis of 2 RCTs had a relative risk of 1.31.
(95% CI, 0.64 to 2.66). Two RCTs reported a lower miscarriage rate (RR=0.53; 95% CI, 0.24 to 1.15). Meta-analyses of the cohort studies found significantly improved ongoing pregnancy rates (RR=1.61; 95% CI, 1.30 to 2.00; 6 studies) and miscarriage rates (RR=0.31; 95% CI, 0.21 to 0.46; 5 studies), but not live birth rate (RR=1.35; 95% CI, 0.85 to 2.13; 3 studies). The cohort studies were subject to limitations such as selection bias.

Several RCTs have reported longer term outcomes after PGS. Beukers et al reported morphologic abnormalities in surviving children at 2 years.(18) Data were available on 50 children born after PGS and 72 children born without PGS. Fourteen (28%) of 50 children in the PGS group and 25 (35%) of 72 children in the non-PGS group had at least 1 major abnormality; the difference between groups was not statistically significant (p=0.43). Skin abnormalities (eg, capillary hemangioma, 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 (30%) children had at least 1 major abnormality.

In 2013, Schendelaar et al reported on outcomes when children were 4 years old.(19) 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 was the child’s neurologic condition, as assessed by the fluency of motor behavior. The fluency score ranged from 0 to 15, as measured using a subscale of the Neurological Optimality Score. In the sample as a whole, and among singletons, the fluency score did not differ among children in the PGS and the 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 PGS and non-PGS groups.

Section Summary: Preimplantation Genetic Screening With In Vitro Fertilization

RCTs and meta-analyses are available. A meta-analysis of PGS using FISH-based technology found a significantly lower live birth rate after PGS compared with controls in women of advanced maternal age, and there was no significant between-group difference in good prognosis patients. Fewer RCTs using newer PGS techniques have been published. Meta-analyses of RCTs on newer methods found higher implantation rates with PGS than with standard care, but not live birth rates. One meta-analysis, but not the other, found a significantly higher ongoing pregnancy rate after PGS than with standard care. The RCTs on newer PGS methods tended to include good prognosis patients, and results may not be generalizable to other populations. Moreover, individual RCTs on newer PGS methods had potential biases (eg lack of blinding, choice of noninferiority margin). Well-conducted RCTs evaluating PGS in the target population (eg, women of advanced maternal age) are needed before conclusions can be drawn about the impact on the net health benefit.
Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 2.

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<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
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<td>NCT02265614a</td>
<td>PGS Using Microarray in IVF Patients With Repeated Implantation Failure</td>
<td>130</td>
<td>Jun 2016 (ongoing)</td>
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NCT: national clinical trial.

Summary of Evidence

For individuals who have an identified elevated risk of a genetic disorder undergoing in vitro fertilization who receive preimplantation genetic diagnosis (PGD), the evidence includes observational studies and systematic reviews. Relevant outcomes are health status measures and treatment-related morbidity. The available data from observational studies and a systematic review have suggested that PGD is associated with the birth of unaffected fetuses when performed for detection of single genetic defects and is associated with a decrease in spontaneous abortions for patients with structural chromosomal abnormalities. Moreover, PGD performed for single gene defects does not appear to be associated with increased risk of obstetric complications. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

For individuals who have no identified elevated risk of a genetic disorder undergoing in vitro fertilization who receive preimplantation genetic screening (PGS), the evidence includes randomized controlled trials (RCTs) and meta-analyses. Relevant outcomes are health status measures and treatment-related morbidity. RCTs and meta-analyses of RCTs on initial PGS methods (eg, fish in situ hybridization) tended to find lower or similar ongoing pregnancy and live birth rates compared with in vitro fertilization without PGS. There are fewer RCTs on newer PGS methods, and findings are mixed. Meta-analyses of RCTs have found higher implantation rates with PGS than with standard care, but not live birth rates. One meta-analysis, but not the other, found significantly higher ongoing pregnancy rates after PGS than after standard care. Well-conducted RCTs evaluating PGS in the target population (eg, women of advanced maternal age) are needed before conclusions can be drawn about the impact on the net health benefit. The evidence is insufficient to determine the effects of the technology on health outcomes.
SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

American Society for Reproductive Medicine
In 2013, the ethics committee of the American Society for Reproductive Medicine (ASRM) published a committee opinion on use of PGD for serious adult-onset conditions.(20) 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.

A 2007 ASRM practice committee opinion 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)

American College of Obstetricians and Gynecologists
In 2009 (reaffirmed 2014), the American College of Obstetricians and Gynecologists (ACOG) issued an opinion on PGS for aneuploidy.(22) 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; it recommended that use be limited to research studies.

U.S. Preventive Services Task Force Recommendations
Not applicable.

Medicare National Coverage
There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.
References:


**Billing Coding/Physician Documentation Information**

81161 DMD (dystrophin) (eg, Duchenne/Becker muscular dystrophy) deletion analysis, and duplication analysis, if performed

81235 EGFR (epidermal growth factor receptor) (eg, non-small cell lung cancer) gene analysis, common variants (eg, exon 19 LREA deletion, L858R, T790M, G719A, G719S, L861Q)

81240 F2 (prothrombin, coagulation factor II) (eg, hereditary hypercoagulability) gene analysis, 20210G>A variant

81241 F5 (coagulation factor V) (eg, hereditary hypercoagulability) gene analysis, Leiden variant

81242 FANCC (Fanconi anemia, complementation group C) (eg, Fanconi anemia, type C) gene analysis, common variant (eg, IVS4+4A>T)

81243 FMR1 (fragile X mental retardation 1) (eg, fragile X mental retardation) gene analysis; evaluation to detect abnormal (eg, expanded) alleles

81244 FMR1 (Fragile X mental retardation 1) (eg, fragile X mental retardation) gene analysis; characterization of alleles (eg, expanded size and methylation status)

81245 FLT3 (fms-related tyrosine kinase 3) (eg, acute myeloid leukemia), gene analysis; internal tandem duplication (ITD) variants (ie, exons 14, 15)

81246 FLT3 (fms-related tyrosine kinase 3) (eg, acute myeloid leukemia), gene analysis; tyrosine kinase domain (TKD) variants (eg, D835, I836)

81250 G6PC (glucose-6-phosphatase, catalytic subunit) (eg, Glycogen storage disease, type 1a, von Gierke disease) gene analysis, common variants (eg, R83C, Q347X)

81251 GBA (glucosidase, beta, acid) (eg, Gaucher disease) gene analysis, common variants (eg, N370S, 84GG, L444P, IVS2+1G>A)

81252 GJB2 (gap junction protein, beta 2, 26kDa, connexin 26) (eg, nonsyndromic hearing loss) gene analysis; full gene sequence

81253 GJB2 (gap junction protein, beta 2, 26kDa, connexin 26) (eg, nonsyndromic hearing loss) gene analysis; known familial variants

81254 GJB6 (gap junction protein, beta 6, 30kDa, connexin 30) (eg, nonsyndromic hearing loss) gene analysis, common variants (eg, 309kb [del(GJB6-D13S1830)] and 232kb [del(GJB6-D13S1854)])

81255 HEXA (hexosaminidase A [alpha polypeptide]) (eg, Tay-Sachs disease) gene analysis, common variants (eg, 1278insTATC, 1421+1G>C, G269S)

81256 HFE (hemochromatosis) (eg, hereditary hemochromatosis) gene
analysis, common variants (eg, C282Y, H63D)

81257 HBA1/HBA2 (alpha globin 1 and alpha globin 2) (eg, alpha thalassemia, Hb Bart hydrops fetalis syndrome, HbH disease), gene analysis, for common deletions or variant (eg, Southeast Asian, Thai, Filipino, Mediterranean, alpha3.7, alpha4.2, alpha20.5, and Constant Spring)

81260 IKBKAP (inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase complex-associated protein) (eg, familial dysautonomia) gene analysis, common variants (eg, 2507+6T>C, R696P)

81261 IGH@ (Immunoglobulin heavy chain locus) (eg, leukemias and lymphomas, B-cell), gene rearrangement analysis to detect abnormal clonal population(s); amplified methodology (eg, polymerase chain reaction)

81262 IGH@ (Immunoglobulin heavy chain locus) (eg, leukemias and lymphomas, B-cell), gene rearrangement analysis to detect abnormal clonal population(s); direct probe methodology (eg, Southern blot)

81263 IGH@ (Immunoglobulin heavy chain locus) (eg, leukemia and lymphoma, B-cell), variable region somatic mutation analysis

81264 IGK@ (Immunoglobulin kappa light chain locus) (eg, leukemia and lymphoma, B-cell), gene rearrangement analysis, evaluation to detect abnormal clonal population(s)

81265 Comparative analysis using Short Tandem Repeat (STR) markers; patient and comparative specimen (eg, pre-transplant recipient and donor germline testing, post-transplant non-hematopoietic recipient germline [eg, buccal swab or other germline tissue sample] and donor testing, twin zygosity testing, or maternal cell contamination of fetal cells)

81266 Comparative analysis using Short Tandem Repeat (STR) markers; each additional specimen (eg, additional cord blood donor, additional fetal samples from different cultures, or additional zygosity in multiple birth pregnancies) (List separately in addition to code for primary procedure)

81267 Chimerism (engraftment) analysis, post transplantation specimen (eg, hematopoietic stem cell), includes comparison to previously performed baseline analyses; without cell selection

81268 Chimerism (engraftment) analysis, post transplantation specimen (eg, hematopoietic stem cell), includes comparison to previously performed baseline analyses; with cell selection (eg, CD3, CD33), each cell type

81270 JAK2 (Janus kinase 2) (eg, myeloproliferative disorder) gene analysis, p.Val617Phe (V617F) variant

81275 KRAS (v-Ki-ras2 Kirsten rat sarcoma viral oncogene) (eg, carcinoma) gene analysis, variants in codons 12 and 13

81287 MGMT (O-6-methylguanine-DNA methyltransferase) (eg, glioblastoma multiforme), methylation analysis

81288 MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; promoter methylation analysis

81290 MCOLN1 (mucolipin 1) (eg, Mucolipidosis, type IV) gene analysis,
common variants (eg, IVS3-2A>G, del6.4kb)

81291 MTHFR (5,10-methylenetetrahydrofolate reductase) (eg, hereditary hypercoagulability) gene analysis, common variants (eg, 677T, 1298C)

81292 MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis

81293 MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants

81294 MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants

81295 MSH2 (mutS homolog 2, colon cancer, nonpolyposis type 1) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis

81296 MSH2 (mutS homolog 2, colon cancer, nonpolyposis type 1) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants

81297 MSH2 (mutS homolog 2, colon cancer, nonpolyposis type 1) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants

81298 MSH6 (mutS homolog 6 [E. coli]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis

81299 MSH6 (mutS homolog 6 [E. coli]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants

81300 MSH6 (mutS homolog 6 [E. coli]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants

81301 Microsatellite instability analysis (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) of markers for mismatch repair deficiency (eg, BAT25, BAT26), includes comparison of neoplastic and normal tissue, if performed

81302 MECP2 (methyl CpG binding protein 2) (eg, Rett syndrome) gene analysis; full sequence analysis

81303 MECP2 (methyl CpG binding protein 2) (eg, Rett syndrome) gene analysis; known familial variant

81304 MECP2 (methyl CpG binding protein 2) (eg, Rett syndrome) gene analysis; duplication/deletion variants

81310 NPM1 (nucleophosmin) (eg, acute myeloid leukemia) gene analysis, exon 12 variants

81313 PCA3/KLK3 (prostate cancer antigen 3 [non-protein coding]/kallikrein-related peptidase 3 [prostate specific antigen]) ratio (eg, prostate cancer)

81315 PML/RARalpha, (t(15;17)), (promyelocytic leukemia/retinoic acid receptor alpha) (eg, promyelocytic leukemia) translocation analysis; common breakpoints (eg, intron 3 and intron 6), qualitative or
<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>81316</td>
<td>PML/RARalpha, (t(15;17)), (promyelocytic leukemia/retinoic acid receptor alpha) (eg, promyelocytic leukemia) translocation analysis; single breakpoint (eg, intron 3, intron 6 or exon 6), qualitative or quantitative</td>
</tr>
<tr>
<td>81317</td>
<td>PMS2 (postmeiotic segregation increased 2 [S. cerevisiae]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis</td>
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<tr>
<td>81318</td>
<td>PMS2 (postmeiotic segregation increased 2 [S. cerevisiae]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants</td>
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<tr>
<td>81319</td>
<td>PMS2 (postmeiotic segregation increased 2 [S. cerevisiae]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants</td>
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<tr>
<td>81321</td>
<td>PTEN (phosphatase and tensin homolog) (eg, Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; full sequence analysis</td>
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<tr>
<td>81322</td>
<td>PTEN (phosphatase and tensin homolog) (eg, Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; known familial variant</td>
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<tr>
<td>81323</td>
<td>PTEN (phosphatase and tensin homolog) (eg, Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; duplication/deletion variant</td>
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<tr>
<td>81324</td>
<td>PMP22 (peripheral myelin protein 22) (eg, Charcot-Marie-Tooth, hereditary neuropathy with liability to pressure palsies) gene analysis; duplication/deletion analysis</td>
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<tr>
<td>81325</td>
<td>PMP22 (peripheral myelin protein 22) (eg, Charcot-Marie-Tooth, hereditary neuropathy with liability to pressure palsies) gene analysis; full sequence analysis</td>
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<tr>
<td>81326</td>
<td>PMP22 (peripheral myelin protein 22) (eg, Charcot-Marie-Tooth, hereditary neuropathy with liability to pressure palsies) gene analysis; known familial variant</td>
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<tr>
<td>81330</td>
<td>SMPD1 (sphingomyelin phosphodiesterase 1, acid lysosomal) (eg, Niemann-Pick disease, Type A) gene analysis; common variants (eg, R496L, L302P, fsP330)</td>
</tr>
<tr>
<td>81331</td>
<td>SNRPN/UBE3A (small nuclear ribonucleoprotein polypeptide N and ubiquitin protein ligase E3A) (eg, Prader-Willi syndrome and/or Angelman syndrome), methylation analysis</td>
</tr>
<tr>
<td>81332</td>
<td>SERPINA1 (serpin peptidase inhibitor, clade A, alpha-1 antiproteinase, antitrypsin, member 1) (eg, alpha-1-antitrypsin deficiency), gene analysis; common variants (eg, *S and *Z)</td>
</tr>
<tr>
<td>81340</td>
<td>TRB@ (T cell antigen receptor, beta) (eg, leukemia and lymphoma), gene rearrangement analysis to detect abnormal clonal population(s); using amplification methodology (eg, polymerase chain reaction)</td>
</tr>
<tr>
<td>81341</td>
<td>TRB@ (T cell antigen receptor, beta) (eg, leukemia and lymphoma), gene rearrangement analysis to detect abnormal clonal population(s); using direct probe methodology (eg, Southern blot)</td>
</tr>
<tr>
<td>81342</td>
<td>TRG@ (T cell antigen receptor, gamma) (eg, leukemia and lymphoma), gene rearrangement analysis, evaluation to detect abnormal clonal population(s)</td>
</tr>
</tbody>
</table>

VKORC1 (vitamin K epoxide reductase complex, subunit 1) (eg, warfarin metabolism), gene analysis, common variants (eg, -1639/3673)

HLA Class I and II typing, low resolution (eg, antigen equivalents); HLA-A, -B, -C, -DRB1/3/4/5, and -DQB1

HLA Class I and II typing, low resolution (eg, antigen equivalents); HLA-A, -B, and -DRB1 (eg, verification typing)

HLA Class I typing, low resolution (eg, antigen equivalents); complete (ie, HLA-A, -B, and -C)

HLA Class I typing, low resolution (eg, antigen equivalents); one locus (eg, HLA-A, -B, or -C), each

HLA Class I typing, low resolution (eg, antigen equivalents); one antigen equivalent (eg, B*27), each

HLA Class II typing, low resolution (eg, antigen equivalents); HLA-DRB1/3/4/5 and -DQB1

HLA Class II typing, low resolution (eg, antigen equivalents); one locus (eg, HLA-DRB1, -DRB3/4/5, -DQB1, -DQA1, -DPB1, or -DPA1), each

HLA Class II typing, low resolution (eg, antigen equivalents); one antigen equivalent, each

HLA Class I and II typing, high resolution (ie, alleles or allele groups), HLA-A, -B, -C, and -DRB1

HLA Class I typing, high resolution (ie, alleles or allele groups); complete (ie, HLA-A, -B, and -C)

HLA Class I typing, high resolution (ie, alleles or allele groups); one locus (eg, HLA-A, -B, or -C), each

HLA Class I typing, high resolution (ie, alleles or allele groups); one allele or allele group (eg, B*57:01P), each

HLA Class II typing, high resolution (ie, alleles or allele groups); one locus (eg, HLA-DRB1, -DRB3/4/5, -DQB1, -DQA1, -DPB1, or -DPA1), each

HLA Class II typing, high resolution (ie, alleles or allele groups); 1 allele or allele group (eg, HLA-DQB1*06:02P), each

Molecular pathology procedure, Level 1 (eg, identification of single germline variant [eg, SNP] by techniques such as restriction enzyme digestion or melt curve analysis)

Molecular pathology procedure, Level 2 (eg, 2-10 SNPs, 1 methylated variant, or 1 somatic variant [typically using nonsequencing target variant analysis], or detection of a dynamic mutation disorder/triplet repeat)

Molecular pathology procedure, Level 3 (eg, >10 SNPs, 2-10 methylated variants, or 2-10 somatic variants [typically using nonsequencing target variant analysis], immunoglobulin and T-cell receptor gene rearrangements, duplication/deletion variants of 1 exon, loss of heterozygosity [LOH], uniparental disomy [UPD])

Molecular pathology procedure, Level 4 (eg, analysis of single exon by
DNA sequence analysis, analysis of >10 amplicons using multiplex PCR in 2 or more independent reactions, mutation scanning or duplication/deletion variants of 2-5 exons

81404 Molecular pathology procedure, Level 5 (eg, analysis of 2-5 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 6-10 exons, or characterization of a dynamic mutation disorder/triplet repeat by Southern blot analysis)

81405 Molecular pathology procedure, Level 6 (eg, analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons, regionally targeted cytogenomic array analysis)

81406 Molecular pathology procedure, Level 7 (eg, analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons, cytogenomic array analysis for neoplasia)

81407 Molecular pathology procedure, Level 8 (eg, analysis of 26-50 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of >50 exons, sequence analysis of multiple genes on one platform)

81408 Molecular pathology procedure, Level 9 (eg, analysis of >50 exons in a single gene by DNA sequence analysis)

81479 Unlisted molecular pathology procedure

88271 Molecular cytogenetics; DNA probe, each (eg, FISH)

88272 Molecular cytogenetics; chromosomal in situ hybridization, analyze 3-5 cells (eg, for derivatives and markers)

88273 Molecular cytogenetics; chromosomal in situ hybridization, analyze 10-30 cells (eg, for microdeletions)

88274 Molecular cytogenetics; interphase in situ hybridization, analyze 25-99 cells

88275 Molecular cytogenetics; interphase in situ hybridization, analyze 100-300 cells

88291 Cytogenetics and molecular cytogenetics, interpretation and report

89290 Biopsy, oocyte polar body or embryo blastomere, microtechnique (for pre-implantation genetic diagnosis); less than or equal to 5 embryos

89291 Biopsy, oocyte polar body or embryo blastomere, microtechnique (for pre-implantation genetic diagnosis); greater than 5 embryos

ICD-10 Codes

Z31.430; Encounter for genetic testing of female for procreative management; code list

Z31.438 Encounter for genetic testing of male for procreative management;

Z31.448 code list

Z31.449 Encounter for other procreative investigation and testing

Specific CPT codes exist to describe the embryo biopsy procedure (89290-89291). Additional CPT codes will be required for the genetic analysis. CPT codes used will vary according to the technique used to perform the genetic analysis. As appropriate, specific codes from the CPT molecular pathology section (81161-81479) or molecular cytogenetics section (88271-88275) would be reported.
Codes 81280, 81281 and 81282 were deleted as of 1/1/2017

Additional Policy Key Words
N/A

Policy Implementation/Update Information
6/1/15  New Policy; considered investigational.
6/1/16  No policy statement changes.
6/1/17  No policy statement changes.

State and Federal mandates and health plan contract language, including specific provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. The medical policies contained herein are for informational purposes. The medical policies do not constitute medical advice or medical care. Treating health care providers are independent contractors and are neither employees nor agents Blue KC and are solely responsible for diagnosis, treatment and medical advice. No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, photocopying, or otherwise, without permission from Blue KC.