Chromosomal Microarray Testing for the Evaluation of Pregnancy Loss

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Origination: 6/2015
Last Review: 3/2018
Next Review: 3/2019

Policy

Blue Cross and Blue Shield of Kansas City (Blue KC) will provide coverage for Chromosomal Microarray Analysis for the Evaluation of Pregnancy Loss when it is determined to be medically necessary because the criteria shown below are met.

When Policy Topic is covered

Chromosomal microarray testing of fetal tissue may be considered medically necessary for the evaluation of pregnancy loss in patients with indications for genetic analysis of the embryo or fetus (see Considerations).

When Policy Topic is not covered

Chromosomal microarray testing of fetal tissue not meeting guidelines (see Considerations below) is considered not medically necessary.

Considerations

Guidelines for cases of miscarriage or intrauterine fetal demise (IUFD) where genetic analysis of the embryo, fetus, or stillborn infant is indicated are based on guidelines from several reproductive health organizations, including the American Society for Reproductive Medicine (ASRM, 2013; ASRM, 2012), the National Society of Genetic Counselors (Laurino, 2005), and the American College of Obstetrics and Gynecology (ACOG, 2009), regarding the use of karyotyping and/or microarray testing in miscarriage or IUFD. Genetic testing may be indicated (if desired by parents):

- In cases of pregnancy loss at 20 weeks of gestation or earlier when there is a maternal history of recurrent miscarriage (defined as a history of 2 or more failed pregnancies); OR
- In all cases of pregnancy loss after 20 weeks of gestation.

The decision to obtain genetic testing should be made jointly between the mother or parents and the treating clinician.
This policy does not address the use of chromosomal microarray testing (CMA) for preimplantation genetic diagnosis or preimplantation genetic screening, or the evaluation of suspected chromosomal abnormalities in the postnatal period.

**Genetics Nomenclature Update**

Human Genome Variation Society (HGVS) nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. Such nomenclature is being implemented for genetic testing medical evidence review updates starting in 2017 (see Table PG1). HGVS nomenclature is recommended by HGVS, the Human Variome Project, and the HUman Genome Organization (HUGO).

The American College of Medical Genetics and Genomics (ACMG) and Association for Molecular Pathology (AMP) standards and guidelines for interpretation of sequence variants represent expert opinion from ACMG, AMP, and the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table PG2 shows the recommended standard terminology—“pathogenic,” “likely pathogenic,” “uncertain significance,” “likely benign,” and “benign”—to describe variants identified that cause Mendelian disorders.

**Table PG1. Nomenclature to Report on Variants Found in DNA**

<table>
<thead>
<tr>
<th>Previous</th>
<th>Updated</th>
<th>Definition</th>
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<tr>
<td><strong>Mutation</strong></td>
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<tr>
<td>Disease-associated variant</td>
<td>Disease-associated change in the DNA sequence</td>
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<tr>
<td>Variant</td>
<td>Change in the DNA sequence</td>
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<tr>
<td>Familial variant</td>
<td>Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives</td>
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**Table PG2. ACMG-AMP Standards and Guidelines for Variant Classification**

<table>
<thead>
<tr>
<th>Variant Classification</th>
<th>Definition</th>
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<tbody>
<tr>
<td><strong>Pathogenic</strong></td>
<td>Disease-causing change in the DNA sequence</td>
</tr>
<tr>
<td><strong>Likely pathogenic</strong></td>
<td>Likely disease-causing change in the DNA sequence</td>
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<tr>
<td><strong>Variant of uncertain significance</strong></td>
<td>Change in DNA sequence with uncertain effects on disease</td>
</tr>
<tr>
<td><strong>Likely benign</strong></td>
<td>Likely benign change in the DNA sequence</td>
</tr>
<tr>
<td><strong>Benign</strong></td>
<td>Benign change in the DNA sequence</td>
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ACMG: American College of Medical Genetics and Genomics; AMP: Association for Molecular Pathology.

**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.

**Definitions**
Fetal tissue may consist of fetal tissue, a formed fetus, or placental tissue derived from the fetal genotype, depending on the stage of pregnancy at the time of the fetal loss.

Early pregnancy loss or miscarriage is considered to be a pregnancy loss that occurred at or before 20 weeks gestational age.

Intrauterine fetal demise (IUFD) is defined as delivery of a non-live-born fetus after 20 weeks gestational age.

**Description of Procedure or Service**

<table>
<thead>
<tr>
<th>Populations</th>
<th>Interventions</th>
<th>Comparators</th>
<th>Outcomes</th>
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<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 pregnancy loss with indications for genetic analysis of the embryo/fetus</td>
<td>• Chromosomal microarray analysis testing of fetal tissue</td>
<td>• Karyotype of fetal tissue</td>
<td>• Test accuracy</td>
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<td>• Test validity</td>
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<td>• Other test performance measures</td>
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<td>• Morbid events</td>
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<td>• Quality of life</td>
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Chromosomal microarray (CMA) testing of fetal tissue or placental tissue derived from the fetal genotype has been proposed as a technique to evaluate the cause of isolated and recurrent early pregnancy loss (miscarriages) and later pregnancy loss (intrauterine fetal demise [IUFD]). The evaluation of both recurrent and isolated miscarriages and IUFD may involve genetic testing of the products of conception (POC). Such testing has typically been carried out through cell culture and karyotyping of cells in metaphase. However, the analysis of fetal or placental tissue has been inhibited by the following limitations: the need for fresh tissue, the potential for cell culture failure, and the potential for maternal cell contamination.

For individuals who have pregnancy loss with indications for genetic analysis of the embryo or fetus who receive CMA testing of fetal tissue, the evidence includes prospective and retrospective cohort studies that report on the yield of CMA testing. Relevant outcomes are test accuracy and validity, other test performance measures, changes in reproductive decision making, morbid events, and quality of life. The available evidence has suggested that CMA testing has a high rate of concordance with standard karyotyping. For both early and late pregnancy loss, CMA is more likely to yield a result than karyotyping. Other studies have reported that CMA testing detects a substantial number of abnormalities in patients with normal karyotypes, although the precise yield is uncertain and likely varies based on gestational age. Rates of variants of uncertain significance in CMA testing of miscarriage samples are not well characterized. Potential benefits from identifying a genetic abnormality in a miscarriage or IUFD include reducing emotional distress...
for families, altering additional testing undertaken to assess for other causes of pregnancy loss, and changing reproductive decision making for future pregnancies. The potential for clinical utility with CMA testing of fetal tissue in pregnancy loss is parallel to that for obtaining a karyotype of fetal tissue in pregnancy loss, which is recommended by a number of organizations. None of the studies identified directly demonstrated whether (or how) patient management would change based on CMA testing of POC from early or late pregnancy losses, nor did they demonstrate how patient outcomes would improve; however, the available evidence suggests that, for situations in which a genetic evaluation is indicated, CMA testing would be expected to perform as well as (or better) than standard karyotyping. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

There was strong support from clinical input that CMA testing is medically necessary for the evaluation of IUFD and likely offers incremental benefits over karyotyping for genetic evaluation in pregnancy loss. Although there was no consensus on a specific gestational age at which CMA testing for pregnancy loss should be used, some reviewers did note a lack of data on the testing yield in early losses. Since clinical input was obtained, additional studies in large cohorts have added to the available data on the feasibility and yield of testing. Therefore, CMA testing may be considered medically necessary in the evaluation of pregnancy loss when fetal genetic evaluation is desired, either as an alternative to conventional karyotyping or when conventional karyotyping is normal or unable to be performed (ie, in case of cell culture failure or maternal cell overgrowth).

Background

Pregnancy Loss: Etiology and Evaluation

Early Pregnancy Loss
Pregnancy loss is common, occurring in at least 15% to 25% of recognized pregnancies. Most pregnancy loss occurs early in the pregnancy, most often by the end of the first trimester or early second trimester. Pregnancy loss that occurs before the 20th week of gestation is referred to as a spontaneous abortion, early pregnancy loss, or miscarriage. While a wide range of factors can lead to early pregnancy loss, genetic causes are thought to be the predominant cause: when POC are examined, it is estimated that 60% of early pregnancy losses are associated with chromosomal abnormalities, particularly trisomies and monosomy X.(1,2) The increasing risk of trisomies with maternal age contributes to the increased risk of early pregnancy loss with increasing maternal age.

Recurrent pregnancy loss, defined by the American Society for Reproductive Medicine (ASRM) as 2 or more failed pregnancies, is less common, occurring in approximately 5% of women.(3) Recurrent pregnancy loss may be related to cytogenetic abnormalities, particularly balanced translocations, uterine abnormalities, thrombophilias, including antiphospholipid syndrome, and metabolic/endocrinologic disorders such as uncontrolled diabetes and thyroid disease. Estimates for the frequency of various underlying causes of recurrent pregnancy loss vary widely, with ranges from 2% to 6% for cytogenetic
abnormalities, 8% to 42% for antiphospholipid antibody syndrome, and 1.8% to 37.6% for uterine abnormalities. It is likely that the risk of cytogenetic abnormalities is lower in recurrent early pregnancy loss than in isolated spontaneous early pregnancy loss.

Clinicians and patients may undertake an evaluation for the cause of a single or recurrent early pregnancy loss for several reasons. The knowledge that an early pregnancy loss is secondary to a sporadic genetic abnormality may provide parents with reassurance that there was nothing that they did or did not do that contributed to the loss, although the magnitude of this benefit is difficult to quantify. For couples with recurrent pregnancy loss and evidence of a structural genetic abnormality in one of the parents, preimplantation genetic diagnosis with transfer of unaffected embryos or the use of donor gametes might be considered for therapy. These therapies might be considered for couples with recurrent pregnancy loss without evidence of a structural genetic abnormality in one of the parents; guidelines on the management of recurrent pregnancy loss from ASRM state that “treatment options should be based on whether repeated miscarriages are euploid, aneuploid, or due to an unbalanced structural rearrangement and not exclusively on the parental carrier status.” Finally, among patients who are found to have a potential nongenetic underlying cause of recurrent pregnancy loss, such as antiphospholipid syndrome, cytogenetic analysis of pregnancy losses may provide evidence that the miscarriages were not due to treatment failure.

Genetic testing of POC, if possible, is recommended by several reproductive health organizations. A committee opinion from ASRM recommends that the assessment of recurrent pregnancy loss include peripheral karyotyping of the parents and states that karyotypic analysis of POC may be useful in the setting of ongoing therapy for recurrent pregnancy loss. The American College of Obstetrics and Gynecology recommends that evaluation after an IUFD includes examination of the stillborn fetus, along with examination of the placenta and umbilical cord, along with genetic testing for all IUFD (after

Late Pregnancy Loss
Fetal loss that occurs later in pregnancy, after 20 weeks gestation, may be referred to as IUFD, stillbirth, or intrauterine fetal death. In 2004, IUFD occurred in 6.2 of 1000 births in the United States, representing about 60% of perinatal mortality. IUFD may be related to a range of disorders, including genetic disorders in the fetus, maternal infection, coexisting maternal medical disorders (eg, diabetes, antiphospholipid antibody syndrome, heritable thrombophilies) and obstetric complications, although in many cases, the precise cause is unable to be identified. Chromosomal or genetic abnormalities can be found in 8% to 13% of IUFD, most commonly aneuploidies. In 1 large series of IUFD (N=1025), cytogenic abnormalities were detected in 11.9%.

The American College of Obstetrics and Gynecology recommends that evaluation after an IUFD includes examination of the stillborn fetus, along with examination of the placenta and umbilical cord, along with genetic testing for all IUFD...
parental permission is obtained). Other evaluation should be based on maternal history and may include evaluation for thyroid disorders, systemic lupus erythematosus, and infections.(6)

Some of the motivations for evaluation for a cause of IUFD are the same as for earlier pregnancy loss. Although both early and later pregnancy losses may cause grief for the mother and her family, IUFD can be particularly devastating. Information about the cause of the pregnancy loss may be important in counseling women about their recurrence risk. In low-risk women with an unexplained IUFD, the risk of recurrence is 7.8 to 10.5 of 1000 live births, but this increases to 21.8 per 1000 live births in women with a history of fetal growth restriction. Identification of a heritable genetic mutation in a fetus may prompt testing in the parents; if a heritable mutation is identified, parents may pursue preimplantation genetic diagnosis in future pregnancies.

**Genetic Abnormalities in Miscarriage and IUFD**

Genetic disorders are generally categorized into 3 main groups: single gene, chromosomal, and multifactorial. Single gene disorders (also known as monogenic disorders) result from errors in a specific gene, whereas those that are chromosomal include larger aberrations that are numerical or structural. Evidence about specific abnormalities in miscarriages and IUFD is somewhat limited. However, it is estimated that 60% of early pregnancy losses are associated with chromosomal abnormalities, particularly trisomies and monosomy X. For later pregnancy losses, aneuploidies are most common in the 8% to 13% of tested IUFD that have an identified chromosomal or genetic abnormality. Karyotypic abnormalities are identified in 6% to 12% of IUFD.(7) Rates of single gene disorders in IUFD are less well quantified. However, of stillborn fetuses who undergo autopsy, 25% to 35% are identified to have single or multiple malformations or deformations; of these, 25% have an abnormal karyotype, but other single gene disorders are suspected to occur in a high proportion of stillborn fetuses with malformations.

Traditionally, genetic evaluation of the POC after a miscarriage is conducted by karyotyping of metaphase cells after cells are cultured in tissue. Karyotyping can identify whole chromosome aneuploidies and large structural rearrangements. However, only visible rearrangements are likely to be identified using this method (down to a resolution of 5-10 Mb), so smaller genetic variants may not be detected. In addition, karyotype requires culturing of the target cells, which may fail or be infeasible, particularly for formalin preserved samples. In addition, there is the potential for maternal cell contamination, which may occur if the POC tissue is not separated from the maternal decidua before culturing, or if there is poor growth of noneuploid cells from the POC tissue, thereby allowing maternal cell overgrowth. The potential for maternal cell contamination makes it impossible to know if a normal female (46 XX) karyotype testing result is due to a normal fetal karyotype or a maternal karyotype. In 1 study that included 103 first trimester miscarriages, culture failure occurred in 25% of cases.(8)
CMA Testing
There has been interest in using alternative genetic testing methods, particularly array comparative genomic hybridization (CGH), to detect chromosomal or other genetic abnormalities in the evaluation of miscarriages and IUFD.

Types of CMA Technologies
Several types of microarray technology are in current clinical use, primarily array CGH) and single nucleotide polymorphism (SNP) microarrays. CGH CMA analysis detects copy number variants (CNVs) by comparing a reference genomic sequence with the patient ("unknown") sequence in terms of binding to a microarray of cloned (from bacterial artificial chromosomes) or synthesized DNA fragments with known sequences. The reference DNA and the unknown sample are labelled with different fluorescent tags, and both samples are cohybridized to the fragments of DNA on the microarray. Computer analysis is used to detect the array patterns and intensities of the hybridized samples. If the unknown sample contains a deletion or duplication of genetic material in a region contained on the reference microarray, the sequence imbalance is detected as a difference in fluorescence intensity.

In SNP-based CMA testing, a microarray of SNPs, which may include hundreds of thousands of SNPs, is used for hybridization. In contrast with array CGH, a reference genomic sequence is not used. Instead, only the “unknown” sample is hybridized to the array platform, and the presence or absence of specific known DNA sequence variants is evaluated by signal intensity to provide information about copy numbers. In some cases, laboratories confirm CNVs detected on CMA with an alternative technique, such as fluorescence in situ hybridization (FISH) or flow cytometry.

Microarrays also vary in breadth of coverage of the genome that they include. Targeted CMA analysis provides coverage of the genome with a concentration of sequences in areas with known, clinically significant CNVs. In contrast, whole-genome CMA allows the characterization of large numbers of genes, but with the downside that analysis may identify large numbers of CNVs of undetermined significance.

CMA Compared With Karyotyping
CMA has several advantages over karyotyping, including improved resolution (detection of smaller chromosomal variants that are undetectable using standard karyotyping) and therefore can result in potentially higher rates of detection of pathogenic chromosomal abnormalities. Array CGH can detect CNVs for larger deletions and duplications, including trisomies. However, CMA based on array CGH cannot detect balanced translocations or diploid, triploid and tetraploid states or sequence inversions because these are not associated with fluorescence intensity change. SNP-based CMA analysis, in addition to detecting deletions and duplications, can detect runs of homozygosity, which suggests consanguinity, triploidy, and uniparental disomy.
CMA also has the advantage of not requiring successful cell culture, so may be more likely to yield a result in cases where karyotyping is technically unsuccessful due to failed culture. In the case of testing of specimens from early miscarriage, CMA may also be used to rule out maternal cell contamination, if a fetal sample is compared with a maternal sample.

CMA has the disadvantage of higher rates of detection of variants of uncertain significance. The American College of Medical Genetics has published guidelines regarding the interpretation and reporting of CNVs in the postnatal setting that recommend that laboratories that perform array-based assessment of CNVs track their experience with CNVs and document pathogenic CNVs, CNVs of uncertain significance, and CNVs that have been determined to represent benign variation based on comparisons with internal and external databases.(9)

**Commercially Available Tests**

Natera Inc. (San Carlos, CA) offers the Anora™ miscarriage test, which uses a SNP-based array system for testing of POC. The test includes the company’s proprietary “Parental Support Technology,” which uses a DNA sample from 1 or both parents as a reference to the POC sample. This comparison can identify maternal cell contamination, uniparental disomy, and the parent of origin of a fetal chromosome abnormality. According to a description of the “Parental Support” algorithm,(10) the algorithm uses the

“SNP array data to calculate the relative amounts of each of the 2 alleles at each SNP. At heterozygous loci, disomic chromosomes are expected to have SNP ratios of approximately 50%, trisomic chromosomes are expected to have SNP ratios of approximately 33% and 66%, and monosomic chromosomes are expected to have only homozygous loci. For each chromosome, the algorithm compares the observed SNP data to each of the expected alleles for the possible ploidy states and determines which is most likely.”

According to the manufacturer’s website, the test reports the following abnormalities, including the parent of origin of any anomaly when a parental sample has been submitted(11):

- Any whole chromosome aneuploidy.
- Triploidy.
- Tetraploidy where 1 parent contributed 1 set of chromosomes and the other parent contributed the other 3. Tetraploidy when parental contribution is equal cannot be detected.
- Uniparental disomy.
- Interstitial deletions and duplications greater than 5 Mb.
- Any terminal deletion or duplication, as it could be an indication for a balanced translocation.
- Deletions of 1 Mb or greater and duplications of 2 mB or greater are reviewed individually by a genetic counselor/geneticist and reported if the potential cause of a miscarriage or recurrence risk implications are identified.
- Any of the following deletions and duplications, when identified:
CombiMatrix (Irvine, CA) offers 2 SNP-based microarray systems for testing POC, the CombiSNP™ Array for Pregnancy Loss, which is used for testing fresh tissue samples and the CombiBAC™ Array, which is used for testing formalin-fixed, paraffin-embedded tissue samples. According to the manufacturer’s website, the CombiSNP Array is a high resolution SNP microarray that can detect triploidy, numeric chromosome abnormalities, unbalanced structural rearrangements, microdeletion/ duplication syndromes, long stretches of homozygosity, which can indicate shared ancestry or uniparental disomy, and maternal cell contamination. The CombiBAC Array is an array CGH method that can detect numeric chromosome abnormalities, unbalanced structural rearrangements and microdeletion/microduplication syndromes.

GeneDx offers the Whole Genome Chromosomal Microarray for Products of Conception test, which is a SNP- and CGH-array that has whole-genome CGH-array coverage with oligonucleotide probes for the detection of CNVs and SNP probes to detect runs of homozygosity, which may indicate uniparental disomy.

Multiple laboratories offer CMA testing for prenatal samples that is not specifically designed for testing of POC.

**Rationale**
This evidence review was created in June 2014 and has been updated regularly with searches of the MEDLINE database. The most recent literature update was
performed through June 22, 2017 (see Appendix Table 1 for genetic testing categories). The following is a summary of the key literature to date.

The evaluation of the evidence related to the use of chromosomal microarray (CMA) testing of products of conception (POC) for the evaluation of miscarriage or intrauterine fetal demise (IUFD) can be structured around several related questions.

First, what are the test performance characteristics of CMA testing in the testing of POC, either as an alternative or in addition to standard karyotyping? Most genetic tests are evaluated based on their analytic validity (ie, technical accuracy of the test in detecting a variant that is present, or in excluding a mutation that is absent) and their clinical validity (ie, diagnostic performance of the test [sensitivity, specificity, positive and negative predictive values] in detecting clinical disease). Although the clinical validity of most diagnostic genetic tests is evaluated based on their ability to diagnosing clinically defined disease, for the purposes of assessment of POC, the diagnosis of a known chromosomal or genetic abnormality in the setting of pregnancy loss may serve as a surrogate end point. The results of CMA testing can be compared directly with karyotyping, but there is no independent reference standard that can be used to determine the performance characteristics of each test.

The clinical utility of CMA testing in miscarriage or IUFD is determined by whether results from CMA testing affect patient management and are associated with improved patient outcomes.

**Chromosomal microarray testing of fetal tissue**

**Analytic Validity**
No studies were identified in the peer-reviewed literature that addressed the technical performance of CMA testing for POC. In general, CMA testing has a high analytic validity for detecting copy number variants (CNVs), in most instances greater than 95%.

**Clinical Validity**

**Diagnostic Accuracy of CMA**
In 2014, Dhillon et al reported results from a systematic review and meta-analysis of studies that compared CMA testing with conventional karyotyping in the evaluation of miscarriage. Reviewers included 9 studies that reported results from CMA on POC following miscarriage alongside conventional karyotyping. There were 314 miscarriage samples in the included studies. In pooled analysis, the overall agreement between karyotype and CMA results was 86.0% (95% confidence interval [CI], 77.0% to 96.0%), with high homogeneity across the studies (Cochrane Q, $I^2=0.2$). CMA detected 13% (95% CI, 8.0% to 21.0%) additional chromosomal abnormalities not detected by karyotyping (including both likely pathogenic variants and variants of uncertain significance [VUS]). Conventional karyotyping detected 3% (95% CI, 1.0% to 10.0%) additional
abnormalities not detected by CMA. Among 5 studies that reported VUS, the pooled chance of having a VUS was 2% (95% CI, 1.0% to 10.0%). This systematic review demonstrated good overall agreement between CMA and karyotype in the analysis of miscarriage specimens. However, the confidence interval around the estimate of the VUS rate was large, indicating uncertainty regarding the true rate. Further research is required to determine whether CNVs found in POC are pathogenic or benign.

A number of additional studies not included in the Dhillon systematic review have compared CMA with karyotyping. For example, in 2014, Lathi et al reported results from a comparison of a single-nucleotide polymorphism (SNP)–based array with informatics assistance (“Parental Support” algorithm previously described) with conventional karyotyping in 30 first-trimester miscarriage samples. CMA testing was conducted using a SNP-based microarray, which measures about 300,000 SNPs across the genome (≈1 every 10 kilobase [Kb] pairs). The “Parental Support” technique compares results from the POC sample with parental samples to determine the number and origin of each chromosome in the POC sample. On conventional karyotype, 63% of samples were chromosomally abnormal, with autosomal trisomies as the most common abnormality. All 46 XX samples on karyotyping were confirmed to be from fetal tissue on microarray analysis. Four samples were discordant between CMA and karyotype, including a case of whole-genome duplication and a balanced translocation, both of which would not be expected to be detected on microarray; and 2 additional discrepancies that were attributed to sampling error, tissue mosaicism, or culture artifact.

In 2009, Menten et al reported results of an evaluation of 100 pregnancy losses with conventional karyotyping, flow cytometry, and array comparative genomic hybridization (aCGH). Array CGH was performed using an investigator-developed bacterial artificial CMA at a resolution of approximately 1 megabase (Mb). On conventional karyotyping, normal karyotypes were found in 11 male and 44 female cases. In 28 cases, karyotyping was not possible due to culture failure. Chromosomal abnormalities were found in 17 cases (9 autosomal trisomies, 2 cases of monosomy X, 3 triploidy cases, 1 balanced and 1 unbalanced translocation). On aCGH, 23 abnormal results were found: 15 autosomal trisomies, 5 cases of monosomy X, and 3 structural abnormalities. Ten of the abnormalities on aCGH were not detected with conventional karyotyping. In 1 case, balanced translocation was not detected on aCGH. In 2 additional cases, a triploidy was suspected due to aberrant ratios for the sex chromosomes. Due to poor DNA quality, no result could be obtained for 2 samples.

In 2006, Hu et al conducted genetic analysis by both CGH and karyotyping in 38 POC from early pregnancy losses. Culture of chorionic villi and examination of metaphase chromosomes were attempted in all samples, but cytogenic analysis was technically successful in only 31 samples. Of the 31 samples successfully karyotyped, 14 were diagnosed to be aneuploidies, including 4 with trisomy 21, 2 each with trisomies 13 and 16, 2 with monosomy X, and 1 each with trisomies 3, 7, 18, and 20. An additional 2 cases of triploidy were detected. On CGH analysis, 17 aneuploidies were identified (14 of those found on the karyotyped samples,
along with 3 cases in samples for which cell culture failed), along with 1 structural chromosomal abnormality. For the 31 samples that had both tests conducted, there was generally good concordance between the approaches—with the exception that CGH did not detect the 2 cases of triploidy.

**Yield of CMA Testing in Pregnancy Loss**

**CMA Testing in Early Pregnancy Loss**

Several studies have assessed the use of CMA in the evaluation of early pregnancy loss when standard karyotyping was unsuccessful, or have evaluated the incremental benefit of CMA testing in the detection of maternal cell contamination.

Viaggi et al (2013) used a whole-genome aCGH to evaluate 40 POC samples from first-trimester miscarriages that had normal karyotypes to assess for the presence and prevalence of CNVs. Frozen samples were evaluated with aCGH at a resolution of 100 Kb. CNVs were compared with those present in the Database of Genomic Variants, Decipher, and the Database of Human CNVs to differentiate between benign CNVs and possibly pathogenic CNVs. Forty-five CNVs, corresponding to 22 different CNVs, were identified in 31 samples (31/40 [77.5%]). Thirty-one (68%) of the 45 CNVs identified were defined as common CNVs. When the CNVs were compared with control CNVs reported in the Database of Genomic Variants, 7 CNV frequencies were considered statistically different from the control population.

Benkhalifa et al (2005) evaluated 26 samples from first-trimester miscarriages that failed to divide in routine cytogenetic studies with array used CMA methods with aCGH. The aCGH method used involved human genomic microarrays containing 2600 cloned areas spanning chromosome subtelomeric regions and critical areas spaced about 1 Mb along each chromosome. Of the 26 samples that failed to divide in routine cytogenetics, 15 had an abnormal genetic profile on aCGH. Abnormalities that are highly prevalent on routine karyotyping (trisomy 16, monosomy X, triploidy, which are estimated to account for >55% of cytogenetically abnormal findings in routine karyotyping) were relatively uncommon among the 15 abnormal samples, with an instance of monosomy 16 and 2 instances of monosomy X.

Doria et al (2009) evaluated aCGH as part of a sequential protocol in the genetic evaluation of 232 spontaneous miscarriages or fetal deaths, 186 of which were from the first trimester, 24 from the second trimester, and 22 from the third trimester. Tissue culture and karyotype was attempted on all specimens; samples that could not be karyotyped were tested with aCGH, followed by additional confirmation with fluorescence in situ hybridization (FISH). Culture failure occurred in 25.4% of the cases. Of the 173 (74.6%) with valid karyotypes, 66 (38.2%) of 173 were abnormal: 62 of 66 with numerical abnormalities (single, double, or triple trisomies, monosomy X, polyploidy, or mosaicism), and 5 of 66 with structural abnormalities. Array CGH was performed in 58 of 59 cases with culture failure (1 case with insufficient DNA for CGH). Fifteen of the 58 cases were abnormal, with 3 cases of monosomy X, 1 case of XY with gain for X, 7 cases of...
trisomy 15, 2 cases of trisomy 16, and 1 case each of trisomies 18 and 21. With the addition of FISH testing, 4 new cases of triploidy were detected. This study suggested that the use of aCGH increases the yield of testing of genetic testing of POC beyond that of standard karyotyping.

Barrett et al (2001) evaluated aCGH-based CMA testing in 368 specimens from first- and second-trimester spontaneous abortions, of which gestational age and degree of tissue maceration were available for 276. Genetic abnormalities were detected in 206 cases, with complete or partial aneuploidy involving trisomy in 85.5%, monosomy X in 9.2%, and structural rearrangements in 5.3%. Samples were also analyzed with traditional cytogenetics, but direct comparisons between CGH and cytogenetics were not reported.

In 2014, Lathi et al reported results of a retrospective analysis of the use of CMA in detecting maternal cell contamination on conventional karyotyping in 1222 POC samples from first-trimester miscarriages that were evaluated at a Natera laboratory from January 2010 to August 2011. The POC samples, along with maternal peripheral blood samples, were evaluated with a SNP-based CMA. When CMA results for the POC were 46 XX, a comparison with the maternal genotype fingerprint allowed investigators to determine whether results were due to maternal cell contamination. On initial analysis, before comparison with the maternal genotype fingerprint, 48% of POC specimens were chromosomally abnormal, 37% were 46 XX, and 14% were 46 XY. Comparison with maternal bloody genotype indicated that 59% of the 46 XX results were due to maternal cell contamination. The authors suggested that the use of CMA testing might improve accurate detection of fetal chromosomal abnormalities.

A number of studies have reported outcomes from CMA of POC in various patient populations where karyotyping was not performed.

In the largest such study identified, Levy et al (2014) reported on results of SNP microarray analysis of 2447 consecutively received POC samples, of which 2400 were fresh samples. Of the fresh samples, 2392 (99.7%) were 20 weeks of gestation or less, and 1861 (77.6%) had no or negligible maternal cell contamination. The authors used a 10-Mb cutoff to estimate the threshold of detection for routine karyotyping in POC samples. At a resolution of conventional karyotyping, 1106 (59.4%) showed classical cytogenetic abnormalities. Of the remaining 755 samples considered normal at the karyotype level, 33 (4.4%) had a CNV (microdeletion or microduplication); 12 (36.4%) were considered clinically significant and the remaining were considered VUS.

In 2015, Maslow et al evaluated the yield of SNP-based array for determining chromosome number in paraffin-fixed POC compared with a standard evaluation for couples with recurrent first-trimester pregnancy losses. Eligible patients had been previously analyzed for chromosome number and screening tests recommended by the American Society for Reproductive Medicine (ASRM) for recurrent pregnancy loss, including parental karyotypes, maternal serum testing for antiphospholipid antibodies, thyrotropin, and prolactin, and a uterine cavity
evaluation via sonohysterogram or hysterosalpingogram. Forty-two women with a total of 178 first-trimester losses were included, with 62 paraffin-embedded POC samples available. SNP-based microarray was able to determine a fetal chromosome number in 44 (71%) of 62 of samples, 25 (57%) of which were noneuploid. Recurrent pregnancy loss screening was normal in 35 (83%) of 42 participants. The detection rate for any cause of pregnancy loss was significantly higher with SNP microarray (0.50; 95% CI, 0.36 to 0.64) than with the ASRM-recommended recurrent pregnancy loss evaluation (0.17; 95% CI, 0.08 to 0.31, p=0.002).

Also in 2015, Romero et al reported on types of genetic abnormalities found on CMA testing in early pregnancy losses (<20 weeks of gestation) among 86 women.25 Thirteen (14.9%) of POC samples were excluded because placental villi or fetal tissue could not be identified with certainty and 9 were excluded due to complete maternal cell contamination, leaving a sample of 64 for analysis. The overall prevalence of aneuploidy and pathogenic CNV or VUS was 43.8% (28/64). Excluding the 2 cases with VUS, rates of pathogenic CNV or aneuploidy differed by gestational age: 9.1%, 69.2%, and 28.0% of pre-embryonic, embryonic, and fetal samples, respectively (p<0.01). Aneuploidy was the most common abnormality, occurring in 37.5% (24/64) cases.

In 2014, Mathur et al reported on results from CMA testing in preserved POC samples from 58 women with 77 miscarriage specimens who were evaluated at a single recurrent pregnancy loss clinic.26 All women had a history of recurrent pregnancy loss, defined as 2 or more ultrasound-documented miscarriages at less than 10 weeks of gestation. Samples were evaluated with CGH; if results were 46 XX, the genotype of the POC was compared with the maternal genotype at several highly polymorphic loci through microsatellite analysis (MSA) to determine whether the 46 XX results were consistent with maternal cell contamination. Sixteen (21%) samples yielded uninformative results due to minimal pregnancy tissue (n=9), poor quality DNA (n=2), or confirmed maternal cell contamination (n=2). CGH was considered informative in 61 (79%) cases, with 22 noneuploid and 39 euploid. Thirty-three of the euploid specimens were 46 XX, 11 of which were not sent for reflex MSA. The author concluded that CMA testing of preserved POC is technically feasible, including cases where karyotyping has failed due to cell growth failure, which had occurred in 8 samples evaluated.

Warren et al (2009) conducted a prospective case series to evaluate results from aCGH in POC from 35 women who had pregnancy loss between 10 and 20 weeks of gestation with either normal karyotype (n=9) or no conventional cytogenetic testing (n=26).27 Thirty-five samples were from fresh tissue obtained at the time of pregnancy loss when dilatation and curettage was performed; the remainder was from paraffin-embedded tissue. Samples were assessed with a whole-genome bacterial artificial chromosome array chip. Clones that demonstrated copy number changes in the fetal tissue were compared with known copy number change regions in the Database of Genomic Variants, and the internal database of apparently benign copy number changes maintained by the University of Utah CGH laboratory. When CNVs were detected, parental samples were assessed with the
same array chip, and CNVs present in fetal tissue but not parental DNA were defined as de novo CNVs. Samples with de novo CNVs on the bacterial artificial chromosome chip were further analyzed with an oligonucleotide microarray chip with an average resolution of 6.4 Kb for more accurate characterization. DNA was successfully isolated in 30 cases (all from the fresh tissue samples). De novo CNVs were detected in 6 (20%) of the 30 cases using the bacterial artificial chromosome array and confirmed in 4 (13%) of 30 cases using the oligonucleotide array.

In 2007, Azmanov et al evaluated samples from 106 first- (n=83) and second-trimester (n=23) miscarriages with aCGH-based CMA testing. Although the specific weeks of gestational age were not reported, most samples were from early miscarriages, including 8 blighted ova and 75 missed abortions, with 23 second-trimester spontaneous abortions. In the entire sample, 40 (37.7%) of 106 demonstrated chromosomal abnormalities, with 82.5% numerical abnormalities (47.5% aneuploidy, 25.0% monosomy X, 10.0% hyperdiploidy) and 17.6% structural aberrations.

**CMA Testing in IUFD**

Relatively few studies have reported on the yield of CMA testing for IUFD, either in addition to or as an alternative to standard karyotyping. In the largest study identified, Reddy et al (2012) compared CMA testing with karyotyping in the evaluation of 532 cases of IUFD. Of the karyotypes attempted, 375 (70.5%) yielded a result. Of those, 31 (8.3%) of 375 were classified as abnormal, with trisomy 21 (n=9), trisomy 18 (n=8), trisomy 13 (n=2), and monosomy X (n=5) representing the most common abnormalities. CMA testing yielded results in 465 (87.4%) of samples, significantly more than were successfully karyotyped (p<0.001). Of those, 32 (6.9%) were aneuploidy, 12 (2.6%) were considered a pathogenic variant, and 25 (5.4%) were considered a VUS. Nine pathogenic variants on CMA testing were detected in stillbirths with normal karyotypes. CMA testing detected aneuploidy in 7 cases of the 157 in which karyotyping was unsuccessful.

Sahlin et al (2014) evaluated CMA testing in a sample of 90 IUFD cases (after 22 weeks of gestation) with no known genetic diagnosis based on karyotype and quantitative fluorescence polymerase chain reaction. CMA testing yielded results in all cases, 77% of which were benign or likely benign CNVs. Three variants were detected in genes known to be associated with IUFD or other disorders. Twenty-six VUS were identified in 21 cases of IUFD.

Harris et al (2011) reported on rates of structural abnormalities detected with aCGH-based CMA testing in IUFD after 22 weeks of gestation. From a cohort of 54 stillbirths, 29 were prospectively determined to be “unexplained” or to have a normal conventional karyotype. Of those, 24 novel CNVs were detected.

Raca et al (2009) evaluated the yield of CMA testing in a sample of stillborn fetuses from a statewide repository of data on IUFD cases, which included tissue samples for 573 cases from 1994 to 2002. The authors identified 26 cases with tissue or cell samples available that met the following criteria: (1) the cause of
death was thought to have been fetal; (2) the fetal phenotype suggested that a chromosomal imbalance might be present because of the presence of multiple congenital anomalies (at least 2 abnormalities of 2 different organs or parts of the body); and (3) cytogenetic results were either normal or were not obtained due to culture failure. In 15 cases with good-quality DNA available for analysis, aCGH detected 2 abnormalities (trisomy 21, an unbalanced translocation between chromosomes 3 and 10).

**Section Summary: Clinical Validity**

The evidence on the clinical validity of CMA testing comes primarily from studies that have compared genetic testing results from CMA with conventional karyotype, and from several studies that have evaluated the yield of CMA in patients with a normal or unsuccessful karyotype. These studies suggest that CMA has good concordance with karyotype for detection of aneuploidy and is more likely to yield results than conventional karyotyping given the need for cell culture for karyotyping. Studies on the testing yield in early pregnancy losses have suggested that aneuploidies are the most common abnormality detected, CMA may detect abnormalities not detected on karyotype. Relatively few studies have reported CMA outcomes in late pregnancy losses, but they do suggest that CMA testing is more likely to yield a result than conventional karyotyping.

**Clinical Utility**

**Changes in Patient Management Following CMA Testing**

Changes in management that could result from CMA testing include changes in additional testing to evaluate for causes of a pregnancy loss or changes in the management of future pregnancies, such as the decision to undertake preimplantation genetic testing. No empirical studies identified evaluated changes in management that occurred as a result of CMA testing in miscarriage or IUFD.

One argument for genetic evaluation (karyotype or CMA) in POC in cases of recurrent pregnancy loss is that an abnormal genetic evaluation could forestall an evaluation for other causes of recurrent pregnancy loss, which might include assessment of the uterine cavity, thyroid function testing, and testing for antiphospholipid antibodies. In the 2015 study by Maslow et al (described above), the testing yield using a SNP microarray in recurrent pregnancy loss was higher than the yield of other recommended testing (some of which are potentially invasive).\(^{25}\) Bernardi et al (2012) developed a decision analytic model to compare the cost of two strategies for recurrent pregnancy loss evaluation: (1) selective recurrent pregnancy loss evaluation, defined as an evaluation if the second miscarriage is euploid; or (2) universal recurrent pregnancy loss evaluation, defined as recurrent pregnancy loss evaluation after the second miscarriage of less than 10 weeks of size.\(^ {33}\) Genetic analysis in the study’s decision model in the “selected” recurrent pregnancy loss evaluation was stepwise, beginning with cytogenetic analysis. If the cytogenetic testing results were abnormal, no further evaluation would be needed. If the results were consistent with an unbalanced translocation, cytogenetic analysis of the parents would be indicated. If results on cytogenetics were consistent with 46 XX, MSA would be indicated to evaluate for maternal cell
contamination. If the 46 XX result was of maternal origin, CGH of stored miscarriage tissue would be indicated. Similarly, if there was no result from cytogenetic analysis, CGH of stored miscarriage tissue would be indicated. If results on CGH were consistent with unbalanced translocation, cytogenetic analysis of the parents would be indicated; if results were consistent with normal 46 XY on either karyotype or CGH or confirmed fetal normal 46 XX on karyotype or CGH, or an unbalanced translocation, further workup for recurrent pregnancy loss would be indicated.

Although this decision analysis would suggest a way in which CMA testing of POC could be used in an algorithm to determine testing for recurrent pregnancy loss, it does not demonstrate that use of CMA testing improves outcomes. Further research evaluating the implementation of such a decision tool in practice is needed.

**Improvement in Patient Outcomes Following CMA Testing**

Several potential health-related outcomes could result from CMA testing of POC in pregnancy loss. Knowledge of the cause of the loss might lead to reduced parent distress or anxiety. For couples with recurrent pregnancy loss, preimplantation genetic diagnosis with transfer of unaffected embryos or the use of donor gametes might be considered for therapy. No studies identified reported whether the use of CMA is associated with changes in parental mental health outcomes.

No studies identified addressed whether CMA testing of POC is associated with changes in management or future successful pregnancies.

**Section Summary: Clinical Utility**

Although there are several ways in which CMA testing of fetal tissue in pregnancy losses could have clinical utility, including leading to changes in diagnostic testing, reduced parental distress, or preimplantation genetic diagnosis, no studies identified directly demonstrated changes in outcomes.

**Summary of Evidence**

For individuals who have pregnancy loss with indications for genetic analysis of the embryo or fetus who receive CMA testing of fetal tissue, the evidence includes prospective and retrospective cohort studies that report on the yield of CMA testing. Relevant outcomes are test accuracy and validity, other test performance measures, changes in reproductive decision making, morbid events, and quality of life. The available evidence has suggested that CMA testing has a high rate of concordance with standard karyotyping. For both early and late pregnancy loss, CMA is more likely to yield a result than karyotyping. Other studies have reported that CMA testing detects a substantial number of abnormalities in patients with normal karyotypes, although the precise yield is uncertain and likely varies based on gestational age. Rates of variants of uncertain significance in CMA testing of miscarriage samples are not well characterized. Potential benefits from identifying a genetic abnormality in a miscarriage or IUFD include reducing emotional distress for families, altering additional testing undertaken to assess for other causes of pregnancy loss, and changing reproductive decision making for future pregnancies.
The potential for clinical utility with CMA testing of fetal tissue in pregnancy loss is parallel to that for obtaining a karyotype of fetal tissue in pregnancy loss, which is recommended by a number of organizations. None of the studies identified directly demonstrated whether (or how) patient management would change based on CMA testing of POC from early or late pregnancy losses, nor did they demonstrate how patient outcomes would improve; however, the available evidence suggests that, for situations in which a genetic evaluation is indicated, CMA testing would be expected to perform as well as (or better) than standard karyotyping. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Supplemental Information

Clinical Input From Physician Specialty Societies and Academic Medical Centers
While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

In response to requests, input was received from 3 academic medical centers, one of which provided 2 responses, and 3 physician specialty societies, one of which provided 3 responses, while this policy was under review in 2015. There was consensus that chromosomal microarray (CMA) testing is medically necessary in the evaluation of intrauterine fetal demise. Most reviewers noted that there are specific clinical scenarios in which the yield of CMA testing is likely to be higher, including later term losses and for fetuses with congenital anomalies. However, there was no consensus about specific criteria that should be used to limit the use of CMA testing. While many reviewers noted that the CMA testing yield is likely to be higher in later term losses, there was no consensus about a specific gestational age that should be used.

Practice Guidelines and Position Statements

American College of Obstetrics and Gynecologists
In 2013, the American College of Obstetrics and Gynecologists and the Society for Maternal-Fetal Medicine published a joint opinion on the use of chromosomal microarray testing in prenatal diagnosis. The guidelines made the following recommendations about the evaluation of fetal losses:

- “In cases of intrauterine fetal demise or stillbirth when further cytogenetic analysis is desired, chromosomal microarray analysis on fetal tissue (ie, amniotic fluid, placenta, or products of conception) is recommended because of its increased likelihood of obtaining results and improved detection of causative abnormalities.”
“Limited data are available on the clinical utility of chromosomal microarray analysis to evaluate first-trimester and second-trimester pregnancy losses; therefore, this is not recommended at this time.”

**American Society for Reproductive Medicine**

In 2012, the American Society for Reproductive Medicine issued an opinion on the evaluation and treatment of recurrent pregnancy loss. The statement makes the following conclusions about the evaluation of recurrent pregnancy loss:

- “Evaluation of recurrent pregnancy loss can proceed after 2 consecutive clinical pregnancy losses.”
- “Assessment of recurrent pregnancy loss focuses on screening for genetic factors and antiphospholipid syndrome, assessment of uterine anatomy, hormonal and metabolic factors, and lifestyle variables. These may include:
  - Peripheral karyotype of the parents.
  - Screening for lupus anticoagulant, anticardiolipin antibodies, and anti-β2 glycoprotein I.
  - Sonohysterogram, hysterosalpingogram, and/or hysteroscopy.
  - Screening for thyroid and prolactin abnormalities.”
- “Karyotypic analysis of products of conception may be useful in the setting of ongoing therapy for recurrent pregnancy loss.”

**Royal College of Obstetricians and Gynaecologists**

In 2011, the Royal College of Obstetricians and Gynaecologists issued guidelines on the evaluation and treatment of couples with recurrent first-trimester and second-trimester miscarriage. The guidelines made the following recommendations on karyotyping in recurrent miscarriage (see Table 1).

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>GOE</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>“Cytogenetic analysis should be performed on products of conception of the third and subsequent consecutive miscarriage(s).”</td>
<td>D (evidence level 3 or 4; or extrapolated from studies rated 2+)</td>
<td>4 (expert opinion)</td>
</tr>
<tr>
<td>“Parental peripheral blood karyotyping of both partners should be performed in couples with recurrent miscarriage where testing of products of conception reports an unbalanced structural chromosomal abnormality.”</td>
<td>D</td>
<td>3 (nonanalytic studies, eg, case reports, case series)</td>
</tr>
</tbody>
</table>

**GOE:** grade of evidence; **LOE:** level of evidence.

**U.S. Preventive Services Task Force Recommendations**

Not applicable.

**Medicare National Coverage**

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.
Ongoing and Unpublished Clinical Trials
A search of ClinicalTrials.gov in September 2015 did not identify any ongoing or unpublished trials that would likely influence this review.

References

Billing Coding/Physician Documentation Information

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

ICD-10 Codes

N96  Recurrent pregnancy loss (Investigation or care in a nonpregnant woman with history of recurrent pregnancy loss)
O26.20- O26.23  Pregnancy care for patient with recurrent pregnancy loss code range

There is no specific CPT code for this test.
Additional Policy Key Words
N/A

Policy Implementation/Update Information
6/1/15 New Policy considered investigational.
3/1/16 Gestational age requirement removed from medically necessary statement. Title changed to “Chromosomal Microarray Analysis for the Evaluation of Pregnancy Loss”
3/1/17 No policy statement changes.
3/1/18 Policy title and statement changed from “analysis” to “testing”.

Appendix Table 1. Categories of Genetic Testing Addressed in 2.04.122

<table>
<thead>
<tr>
<th>Category</th>
<th>Addressed</th>
</tr>
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</table>
| 1. Testing of an affected individual’s germline to benefit the individual | 1a. Diagnostic  
1b. Prognostic  
1c. Therapeutic |
| 2. Testing cancer cells from an affected individual to benefit the individual | 2a. Diagnostic  
2b. Prognostic  
2c. Therapeutic |
| 3. Testing an asymptomatic individual to determine future risk of disease | |
| 4. Testing of an affected individual’s germline to benefit family members | 5a. Carrier testing: preconception  
5b. Carrier testing: prenatal |
| 5c. In utero testing: aneuploidy  
5d. In utero testing: familial variants  
5e. In utero testing: other X | 5f. Preimplantation testing with in vitro fertilization |

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.