Medical Policy
Chromosomal Microarray Testing for the Evaluation of Pregnancy Loss

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Policy Number: 686
BCBSA Reference Number: 2.04.122
NCD/LCD: NA

Related Policies
- Genetic Testing for the Genetic Evaluation of Patients with Developmental Delay/Intellectual Disability or Autism Spectrum Disorder and Congenital Anomalies, #228
- Preimplantation Genetic Testing, #088
- Carrier Testing for Genetic Diseases, #666
- Invasive Prenatal (Fetal) Diagnostic Testing, #708

Policy
Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity Medicare HMO BlueSM and Medicare PPO BlueSM Members

Chromosomal microarray analysis 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.

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 for preimplantation genetic diagnosis or preimplantation genetic screening, or the evaluation of suspected chromosomal abnormalities in the postnatal period.

Prior Authorization Information
Pre-service approval is required for all inpatient services for all products.
See below for situations where prior authorization may be required or may not be required. Yes indicates that prior authorization is required. No indicates that prior authorization is not required. N/A indicates that this service is primarily performed in an inpatient setting.

<table>
<thead>
<tr>
<th>Commercial Managed Care (HMO and POS)</th>
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<tr>
<td>Commercial PPO and Indemnity</td>
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<td>Medicare HMO BlueSM</td>
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CPT Codes / HCPCS Codes / ICD Codes
Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member’s contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member.

Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.

CPT Codes
There is no specific CPT code for this test.

Description
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 products of conception (POC) are examined, it is estimated that 60% of early pregnancy losses are associated with chromosomal abnormalities, particularly trisomies and monosomy X. 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. Recurrent pregnancy loss may be related to cytogenetic abnormalities, particularly balanced translocations, uterine abnormalities, thrombophilies, including antiphospholipid syndrome, and metabolic or 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 evaluate 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; 2012 guidelines on the management of recurrent pregnancy loss from ASRM have indicated 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 found to have
a potential nongenetic underlying cause of recurrent pregnancy loss, such as antiphospholipid syndrome, cytogenetic analysis of pregnancy losses could provide evidence that the miscarriages were not due to treatment failure.\textsuperscript{4}

Genetic testing of POC, if possible, is recommended by several reproductive health organizations. A 2012 committee opinion from ASRM has recommended that the assessment of recurrent pregnancy loss include peripheral karyotyping of the parents and indicated that karyotypic analysis of POC may be useful in the setting of ongoing therapy for recurrent pregnancy loss.\textsuperscript{1} The National Society of Genetic Counselors convened a multidisciplinary working group that recommended, for the genetic evaluation of couples with recurrent pregnancy loss, chromosomal analysis of fetal tissue from POC be pursued (when possible).\textsuperscript{2}

**Late Pregnancy Loss**

Fetal loss that occurs later in pregnancy, after 20 weeks of gestation, may be referred to as intrauterine fetal demise (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. In many cases, the precise cause of IUFD is unidentifiable; however, it 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 thrombophilias), and obstetric complications. Chromosomal or genetic abnormalities can be found in 8% to 13% of IUFD—most commonly aneuploidies. In a large 2012 series of IUFD (N=1025), cytogenic abnormalities were detected in 11.9%.\textsuperscript{5}

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

Reasons for evaluation for a cause of IUFD are similar to those 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 variant in a fetus may prompt testing in the parents; if a heritable variant is identified, parents may pursue preimplantation genetic diagnosis in future pregnancies.

**GENETIC ABNORMALITIES IN MISCARRIAGE AND IUFD**

Genetic disorders are generally categorized into 3 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 on 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. 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 the 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 the target cells, which may fail or be infeasible, particularly for formalin
preserved samples. Further still, 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 a 2009 study that included 103 first
trimester miscarriages, culture failure occurred in 25% of cases.\(^8\)

**CHROMOSOMAL MICROARRAY TESTING**

There is interest in using alternative genetic testing methods, particularly array comparative genomic
hybridization (aCGH), to detect chromosomal or other genetic abnormalities in the evaluation of
miscarriages and IUFD.

**Types of Chromosomal Microarray Technologies**

Several types of microarray technology are in current clinical use, primarily aCGH and single-nucleotide
polymorphism (SNP) microarrays. Comparative genomic hybridization (CGH) chromosomal microarray
(CMA) testing 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 labeled 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 SNVs, which may include hundreds of thousands of SNPs, is
used for hybridization. In contrast with aCGH, 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 or flow cytometry.

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

**CMA Testing Compared With Karyotyping**

CMA testing 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 aCGH cannot
detect balanced translocations or diploid, triploid, and tetraploid states, or sequence inversions because
they are not associated with fluorescence intensity change. SNP-based CMA, in addition to detecting
deletions and duplications, can detect runs of homozygosity, which suggests consanguinity, triploidy, and
uniparental disomy.

Another advantage of CMA is that it does not require successful cell culture, so it may be more likely to
yield a result in cases where karyotyping is technically unsuccessful due to failed culture. In the case of
testing 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.

One distinct disadvantage of CMA is its higher rates of detection of variants of uncertain significance. In
2011, the American College of Medical Genetics (ACMG) published guidelines on the interpretation and
reporting of CNVs in the postnatal setting. ACMG recommended that laboratories performing array-based
assessment of CNVs track their experience with CNVs and document pathogenic CNVs, CNVs of uncertain significance, and CNVs determined to represent benign variations 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 one 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 it 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 submitted11:

- Any whole chromosome aneuploidy.
- Triplody.
- 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 megabase (Mb) pairs.
- Any terminal deletion or duplication, because 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 or 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:
  - 1p36 deletion
  - 1q21.1 deletion (epilepsy)
  - 2q37 deletion
  - 3q29 terminal deletion
  - 4p16.3 deletion (Wolf-Hirschhorn syndrome)
  - 5p15.2 deletion (cri du chat)
  - 7q11.23 deletion (Williams syndrome syndrome)
  - 8q23.2-8q24.1 deletion (Langer-Giedion syndrome)
  - 9q34 deletion
  - 11p13-14 deletion (WAGR syndrome)
  - 11q24.1 deletion (Jacobsen syndrome)
  - 10p13-p14 deletion (DiGeorge syndrome)
  - 15q11-q13 deletion (Prader-Willi syndrome and Angelman syndrome)
  - 16p11.2 deletion (epilepsy)
  - 17p11.2 deletion (Smith-Magenis syndrome)
  - 17p13.3 deletion (Miller-Dieker syndrome)
  - 17q21.31 deletion
  - 22q13 deletion (Phelan-McDermid syndrome)
  - 22q11.2 deletion (DiGeorge syndrome/velocardiofacial syndrome)
  - 22q11.2 duplication
  - Xq28 deletion (MECP2 deletion)
  - Xq28 duplication (MECP2 duplication).

CombiMatrix (Irvine, CA) offers the CombiSNP™ Array for Pregnancy Loss, which is used to test fresh
tissue samples, formalin-fixed, paraffin-embedded tissue samples, or unstained slides. 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 or duplication syndromes, long stretches of homozygosity, which can indicate shared ancestry or uniparental disomy, and maternal cell contamination. The company also offers maternal cell contamination studies.

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

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

Summary
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).
## Policy History

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<th>Date</th>
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<tr>
<td>10/2017</td>
<td>BCBSA National medical policy review. Policy title and statement changed from “analysis” to “testing.” Policy statement otherwise unchanged. 10/1/2017</td>
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## Information Pertaining to All Blue Cross Blue Shield Medical Policies

Click on any of the following terms to access the relevant information:
- Medical Policy Terms of Use
- Managed Care Guidelines
- Indemnity/PPO Guidelines
- Clinical Exception Process
- Medical Technology Assessment Guidelines

## References


