Medical Policy
Chromosomal Microarray Analysis 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, Including Chromosomal Microarray Analysis and Next-Generation Sequencing Panels, for the Evaluation of Developmental Delay-Intellectual Disability, Autism Spectrum Disorder, and/or 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 analysis (CMA) 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>
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<tr>
<th>Outpatient</th>
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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.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.1 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, aneuploidy, 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 National Society of Genetic Counselors convened a multidisciplinary Inherited Pregnancy Loss Working Group. It recommended that, for the genetic evaluation of couples with recurrent pregnancy loss, when possible, chromosomal analysis on fetal tissue from POC should be pursued.

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. 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 thrombophilias), and obstetric complications, although, in many cases, the precise cause is unidentifiable. Chromosomal or genetic abnormalities can be found in 8% to 13% of IUFD, most commonly aneuploidies. In 1 large series of IUFD (N=1025), cytogenetic 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 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.

Some motivations 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 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. Rates of single-gene disorders in IUFD are less wellquantified. 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 singlegene 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 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.  

**Chromosomal Microarray Analysis Testing**

There has been 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 Analysis 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 analysis (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 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 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 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.

CMA also has the advantage of not requiring 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 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 (ACMG) has published guidelines on the interpretation and reporting of CNVs in the postnatal setting. ACMG recommends 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 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 submitted11:
- 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:
  - 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)
  - 8q23.2-8q24.1 deletion (Langer-Giedion)
  - 9q34 deletion
  - 11p13-14 deletion (WAGR)
  - 11q24.1 deletion (Jacobsen syndrome)
  - 10p13-p14 deletion (DiGeorge 2)
  - 15q11-q13 deletion (Prader-Willi/Angelman region)
  - 16p11.2 deletion (epilepsy)
  - 17p11.2 deletion (Smith-Magenis)
  - 17p13.3 deletion (Miller-Dieker)
  - 17q21.31 deletion
  - 22q13 deletion (Phelan-McDermid syndrome)
  - 22q11.2 deletion (DiGeorge/VCFS)
  - 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/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.\textsuperscript{12}

GeneDx offers the Whole Genome Chromosomal Microarray for Products of Conception test, which 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, 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 analysis (CMA) 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, this technique is limited by the need for fresh tissue, the potential for cell culture failure, and the potential for maternal cell contamination, limitations which may be addressed with CMA.

The evidence for the use of CMA testing of fetal tissue in individuals who have pregnancy loss with indications for genetic analysis of the embryo/fetus includes prospective and retrospective cohort studies that report on the yield of CMA testing, sometimes compared with standard karyotyping. 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 suggests that CMA has a high rate of concordance with karyotyping. For both early and late pregnancy loss, CMA is more likely to yield a result than karyotyping. Other studies have reported that CMA 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 unknown 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 that is undertaken to assess for other causes of pregnancy loss, and changing reproductive decision making for future pregnancies. The potential for clinical utility for 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. While no studies identified directly demonstrated whether or how patient management is changed based on CMA testing of POC from early or late pregnancy losses, or how patient outcomes are improved, the available evidence suggests that, for situations in which a genetic evaluation is indicated, CMA would be expected to perform as well as or better than standard karyotyping. The evidence is sufficient to determine qualitatively 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 testing with karyotyping for genetic evaluation in pregnancy loss. Although there was not consensus about a specific gestational age at which CMA testing for pregnancy loss should be used, some reviewers noted a lack of data on the yield of testing 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 medical 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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<td>5/2016</td>
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6/2015


11/2014

New medical policy describing investigational indications.

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