MEDICAL POLICY – 12.04.122
Chromosomal Microarray Testing for the Evaluation of Pregnancy Loss

BCBSA Ref. Policy: 2.04.122
Effective Date: Oct. 1, 2017
Last Revised: Sept. 21, 2017
Replaces: 2.04.122

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Introduction

Chromosomal microarray (CMA) testing is one way of testing chromosomes. “Microarray” refers to testing and analyzing many pieces of DNA at one time. CMA testing focuses on parts of a chromosome that are too small to see with a microscope. It can detect small areas of extra or missing parts of a chromosome. In miscarriages, there are many reasons why a pregnancy may end. CMA testing looks at fetal chromosomes to determine if a chromosomal problem, such as too many or too few chromosomes, caused the loss of the pregnancy. This policy describes when CMA testing may be considered medically necessary after the loss of a pregnancy.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.

Policy Coverage Criteria
### Analysis

<table>
<thead>
<tr>
<th>Chromosomal microarray testing</th>
<th>Medical Necessity</th>
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<tbody>
<tr>
<td>Chromosomal microarray testing of fetal tissue may be considered medically necessary:</td>
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<tr>
<td>• 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) AND</td>
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<tr>
<td>• In all cases of pregnancy loss after 20 weeks of gestation</td>
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### Additional Guidelines

**The decision to obtain genetic testing should be made jointly between the mother or parents and the treating clinician.**

**Note:** This policy does not address the use of chromosomal microarray (CMA) testing for preimplantation genetic diagnosis or preimplantation genetic screening, or the evaluation of suspected chromosomal abnormalities in the postnatal period.

### Coding

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
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<tr>
<td>CPT</td>
<td>Cytogenomic constitutional (genome-wide) microarray analysis; interrogation of genomic regions for copy number and single nucleotide polymorphism (SNP) variants for chromosomal abnormalities</td>
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### Related Information

#### Definition of Terms

**Early pregnancy loss or miscarriage:** This is considered to be a pregnancy loss that occurred at or before 20 weeks gestational age.
**Fetal tissue:** This term may include fetal tissue, a formed fetus, or placental tissue, depending on the stage of pregnancy at the time of the fetal loss.

**Intrauterine fetal demise:** This is defined as delivery of a non-live-born fetus after 20 weeks gestational age.

**Genetic Counseling**

Experts recommend formal genetic counseling for patients who are at risk for inherited disorders and who wish to undergo genetic testing. Interpreting the results of genetic tests and understanding risk factors can be difficult for some patients. Genetic counseling helps individuals understand the impact of genetic testing, including the possible effects the test results could have on the individual or their family members. It should be noted that genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. Further, genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

**Evidence Review**

**Description**

Chromosomal microarray (CMA) testing of fetal tissue or placental tissue 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.
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 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. The risk of trisomies increases with maternal age and helps to explain why there are more early pregnancy losses as a woman ages.

Recurrent pregnancy loss, defined by the American Society for Reproductive Medicine (ASRM) as 2 or more failed pregnancies, occurs in fewer than 5% of women. 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 choose to investigate 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. These therapies might be considered for couples with recurrent pregnancy loss without evidence of a structural genetic abnormality in one of the parents. Guidelines published in 2012 by the ASRM on the management of recurrent pregnancy loss 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.\textsuperscript{4}

Genetic testing of POC, if possible, is recommended by several reproductive health organizations. A 2012 committee opinion from ASRM recommended that the assessment of recurrent pregnancy loss include peripheral karyotyping of the parents and indicated that karyotypic analysis of products of conception may be useful in the setting of ongoing therapy for recurrent pregnancy loss.\textsuperscript{5} The National Society of Genetic Counselors convened a multidisciplinary working group that recommended that chromosomal analysis of fetal tissue from POC be pursued (when possible) for couples with recurrent pregnancy loss.\textsuperscript{2}

**Late Pregnancy Loss**

Fetal loss that occurs later in pregnancy, after 20 weeks 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 U.S., 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 (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 after an IUFD, an examination of the stillborn fetus, along with examination of the placenta and umbilical cord, be performed, as well as 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 wanting to determine the cause of an IUFD are similar to those for an 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 1,000 live births, but this increases to 21.8 per 1,000 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 three 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, 25% to 35% of stillborn fetuses who undergo autopsy 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. Further still, there is the potential for maternal cell contamination, which may occur if the products of conception tissue are not separated from the maternal decidua before culturing, or if there is poor growth of noneuploid cells from the products of conception 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.

**Chromosomal Microarray 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.
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 these 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 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.

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 regarding the interpretation and reporting of CNVs in the postnatal setting. ACMG recommend that laboratories that 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 products of conception. 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 products of conception sample. This comparison can identify maternal cell contamination, uniparental disomy, and the parent of origin of a fetal chromosome abnormality.

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 (single nucleotide polymorphism) 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.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, the results of which may indicate uniparental disomy.

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

**Summary of Evidence**

For individuals who have pregnancy loss with indications for genetic analysis of the embryo/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 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 intrauterine fetal demise 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. When looking at fetal tissue in pregnancy loss, the clinical utility of CMA testing is parallel to that of karyotyping. None of the studies identified directly demonstrated whether (or how) patient management is changed based on CMA testing of POC from early or late pregnancy losses, nor did they demonstrate how patient outcomes are improved. However, 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 that the technology results in a meaningful improvement in the net health outcome.

**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.
Clinical Input Received from Physician Specialty Societies and Academic Medical Centers

While the various physician specialty societies and academic medical centers may provide appropriate reviewers who collaborate with and make recommendations during this process, 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 on the policy from three academic medical centers, one of which provided two responses, and three physician specialty societies, one of which provided three responses, while this policy was under review in 2015. There was consensus that 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 not consensus about specific criteria that should be used to limit the use of CMA testing. While many reviewers noted that the yield of CMA testing is likely to be higher in later term losses, there was not 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 Committee 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 testing 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 testing 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 investigation and treatment of couples with recurrent first-trimester and second-trimester miscarriage. The guidelines make the following recommendations related to karyotyping in recurrent miscarriage:

- Cytogenetic analysis should be performed on products of conception of the third and subsequent consecutive miscarriage(s). (Grade of evidence D [evidence level 3 or 4; or extrapolated from studies rated as 2+]; Evidence level 4 [expert opinion]).

- 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. (Grade of evidence D; Evidence level 3 [nonanalytical studies, eg, case reports, case series]).
Medicare National Coverage

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

Regulatory Status

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA). The Anora™ miscarriage test, the CombiSNP™ Array for Pregnancy Loss, the CombiBAC™ Array, and the GeneDx Whole Genome Chromosomal Microarray for Products of Conception, along with other chromosomal microarray testing platforms currently available are LDTs available under the auspices of CLIA. Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

References


<table>
<thead>
<tr>
<th>Date</th>
<th>Comments</th>
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<tbody>
<tr>
<td>12/08/14</td>
<td>New Policy. Policy created with literature review through May 14, 2014. Chromosomal microarray analysis of products of conception (fetal tissue or placental tissue derived from the fetal genotype) is considered investigational for the evaluation of early pregnancy loss.</td>
</tr>
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<td>03/10/15</td>
<td>Annual Review. Policy updated with literature review through September 10, 2014, with scope expanded to include late pregnancy losses. References 5-7, 20, and 23-27 added. Clinical input reviewed; CMA testing of fetal tissue may be considered medically necessary for 3rd trimester pregnancy losses. Title changed to “Chromosomal Microarray Testing for the Evaluation of Early Pregnancy Loss and Intrauterine Fetal Demise”</td>
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<td>05/27/15</td>
<td>Coding update: CPT code 81229 added.</td>
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<tr>
<td>02/09/16</td>
<td>Annual Review. Policy updated with literature review through September 23, 2015; references 21-23 added; gestational age requirement removed from medically necessary statement. Two criteria from Guidelines incorporated into policy statement. Title changed to “Chromosomal Microarray Analysis for the Evaluation of Pregnancy Loss”</td>
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<tr>
<td>10/07/16</td>
<td>Minor formatting update. Removed hyperlink from coding section.</td>
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<tr>
<td>11/08/16</td>
<td>Minor update. Language added to support the age application of this policy applies to those with pregnancy loss at 20 weeks is based on recommendations from several reproductive health organizations and the American College of Obstetrics and Gynecology. No change in policy statements.</td>
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U.S. Department of Health and Human Services
200 Independence Avenue SW, Room S09F, HHH Building
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