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

BCBSA Ref. Policy: 2.04.122
Effective Date: Oct. 1, 2018
Last Revised: Sept. 20, 2018
Replaces: 2.04.122

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POLICY CRITERIA | CODING | RELATED INFORMATION
EVIDENCE REVIEW | REFERENCES | HISTORY

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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. CMA testing can detect small areas of extra chromosome, 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
Chromosomal microarray testing of fetal tissue may be considered medically necessary:

- 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)
- In all cases of pregnancy loss after 20 weeks of gestation

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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<tbody>
<tr>
<td>CPT</td>
<td></td>
</tr>
<tr>
<td>81229</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>
</tr>
</tbody>
</table>

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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.

Genetics Nomenclature Update

The Human Genome Variation Society nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. It is being implemented for genetic testing medical evidence review updates starting in 2017 (see Table 1). The Society’s nomenclature is recommended by the Human Variome Project, the HUman Genome Organization, and by the Human Genome Variation Society itself.

The American College of Medical Genetics and Genomics and the Association for Molecular Pathology standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations, in addition to 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 2 shows the recommended standard terminology—“pathogenic,” “likely pathogenic,” “uncertain significance,” “likely benign,” and “benign”—to describe variants identified that cause Mendelian disorders.

Table 1. Nomenclature to Report on Variants Found in DNA

<table>
<thead>
<tr>
<th>Previous</th>
<th>Updated</th>
<th>Definition</th>
</tr>
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<tbody>
<tr>
<td>Mutation</td>
<td>Disease-associated variant</td>
<td>Disease-associated change in the DNA sequence</td>
</tr>
<tr>
<td>Variant</td>
<td>Change in the DNA sequence</td>
<td></td>
</tr>
<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>
Table 2. 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>Pathogenic</td>
<td>Disease-causing change in the DNA sequence</td>
</tr>
<tr>
<td>Likely pathogenic</td>
<td>Likely disease-causing change in the DNA sequence</td>
</tr>
<tr>
<td>Variant of uncertain significance</td>
<td>Change in DNA sequence with uncertain effects on disease</td>
</tr>
<tr>
<td>Likely benign</td>
<td>Likely benign change in the DNA sequence</td>
</tr>
<tr>
<td>Benign</td>
<td>Benign change in the DNA sequence</td>
</tr>
</tbody>
</table>

ACMG: American College of Medical Genetics and Genomics; AMP: Association for Molecular Pathology.

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.

Consideration of Age

The age stated in this policy for which chromosomal microarray analysis may be considered medically necessary in cases of pregnancy loss is 20 weeks. This age is based on recommendations from several reproductive health organizations and the American College of Obstetrics and Gynecology.
Description

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. 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. Pregnancy loss primarily 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 abnormalities are thought to be the predominant cause. When products of conception are examined, it has been estimated that 60% of early pregnancy losses are associated with chromosomal abnormalities, particularly trisomies and monosomy X.\textsuperscript{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 as 2 or more failed pregnancies, is less common, occurring in approximately 5% of women.\textsuperscript{3} 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.\textsuperscript{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 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 the reassurance that there was nothing 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 the 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; American Society for Reproductive Medicine (2012) guidelines on the management of recurrent pregnancy loss 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.4

**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 1,000 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), Korteweg et al (2012) reported a cytogenic abnormalities were detected in 11.9%.5

Reasons to evaluate 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 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.
**Chromosomal Microarray Testing**

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

**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 suggests that CMA 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 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 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 the products of conception 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.
Ongoing and Unpublished Clinical Trials

A search of ClinicalTrials.gov in July 2018 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 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 for 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 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

The American College of Obstetrics and Gynecologists and the Society for Maternal-Fetal Medicine (2013) 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

The American Society for Reproductive Medicine (2012) issued an opinion on the evaluation and treatment of recurrent pregnancy loss. The statement drew the following conclusions:

• 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:
  o Peripheral karyotype of the parents.
  o Screening for lupus anticoagulant, anticardiolipin antibodies, and anti-β<sub>2</sub> glycoprotein I.
  o Sonohysterogram, hysterosalpingogram, and/or hysteroscopy.
  o 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.

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.

Regulatory Status

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Act. Laboratories that offer laboratory-developed tests must be
licensed by Clinical Laboratory Improvement Act for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

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

References


<table>
<thead>
<tr>
<th>Date</th>
<th>Comments</th>
</tr>
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<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>
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<tr>
<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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<td>06/22/18</td>
<td>Minor edit for clarification, “AND” changed to “OR” in policy statement.</td>
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<tr>
<td>10/01/18</td>
<td>Annual Review, approved September 20, 2018. Re-added Consideration of Age Information, which was inadvertently deleted during a previous update. Policy updated with literature review through June 2018; no references added; reference 32 updated. Policy statement unchanged.</td>
</tr>
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</table>

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