



Louisiana

Chromosomal Microarray Testing for the Evaluation of Pregnancy Loss

Policy # 00449

Original Effective Date: 10/15/2014

Current Effective Date: 07/13/2020

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Note: Invasive Prenatal (Fetal) Diagnostic Testing is addressed separately in medical policy 00690.

Note: Genetic Testing for Developmental Delay/Intellectual Disability, Autism Spectrum Disorder, and Congenital Anomalies is addressed separately in medical policy 00536.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider chromosomal microarray (CMA) testing of fetal tissue for the evaluation of pregnancy loss in patients with indications for genetic analysis of the embryo or fetus to be **eligible for coverage**** (see Policy Guidelines).

Patient Selection Criteria

Coverage eligibility for CMA testing of fetal tissue will be met (if desired by parents) with the following indications:

- 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.

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When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers chromosomal microarray (CMA) testing of fetal tissue for the evaluation of pregnancy loss when patient selection criteria are not met is considered to be **investigational**.*

Policy Guidelines

Clinical guidelines and recommendations to address the management of cases of miscarriage or intrauterine fetal demise where genetic analysis of the embryo, fetus, or stillborn infant is indicated. These guidelines, which specifically address the use of karyotyping and/or microarray testing in miscarriage or intrauterine fetal demise, were developed by several reproductive health associations, including the American Society for Reproductive Medicine (ASRM [2013]; ASRM [2012]), the National Society of Genetic Counselors (Laurino et al [2005]), and the American College of Obstetrics and Gynecology (ACOG [2009]). According to such guidelines, 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 failed pregnancies); OR
- In all cases of pregnancy loss after 20 weeks of gestation.

The decision to obtain genetic testing should be made jointly by 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.

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 PG1). The Society's

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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 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

Previous	Updated	Definition
Mutation	Disease-associated variant	Disease-associated change in the DNA sequence
	Variant	Change in the DNA sequence
	Familial variant	Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives

Table PG2. ACMG-AMP Standards and Guidelines for Variant Classification

Variant Classification	Definition
Pathogenic	Disease-causing change in the DNA sequence
Likely pathogenic	Likely disease-causing change in the DNA sequence
Variant of uncertain significance	Change in DNA sequence with uncertain effects on disease
Likely benign	Likely benign change in the DNA sequence
Benign	Benign change in the DNA sequence

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

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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.

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 occurs at or before 20 weeks of gestational age.

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

Background/Overview

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. 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. Recurrent pregnancy loss may be related to cytogenetic abnormalities, particularly balanced translocations, uterine abnormalities, thrombophilias, including antiphospholipid syndrome, and metabolic or

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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 the reassurance 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, aneuploidy, 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.

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), Korteweg et al (2012) reported a cytogenetic abnormality rate of 11.9%.

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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 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.

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.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

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 the 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.

Rationale/Source

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

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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 IUD 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.

Input obtained in 2015 strongly supported CMA testing as medically necessary for the evaluation of IUD and likely offered 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 commentators noted 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 but

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not determinative or unable to be performed (ie, in case of cell culture failure or maternal cell overgrowth).

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 a 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 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

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 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."

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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:
 - Peripheral karyotype of the parents.
 - Screening for lupus anticoagulant, anticardiolipin antibodies, and anti- β 2 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."

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 July 2018 did not identify any ongoing or unpublished trials that would likely influence this review.

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|------------|---|
| 10/02/2014 | Medical Policy Committee review |
| 10/15/2014 | Medical Policy Implementation Committee approval. New policy. |
| 01/01/2015 | Coding Update |
| 07/01/2015 | Coding Update |
| 08/03/2015 | Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed. |
| 10/08/2015 | Medical Policy Committee review |
| 10/21/2015 | Medical Policy Implementation Committee approval. Policy updated to now include CMA testing for intrauterine fetal demise, title change and new policy statement added. |
| 04/07/2016 | Medical Policy Committee review |
| 04/20/2016 | Medical Policy Implementation Committee approval. Title change. Coverage statement revised to cover testing for loss at any stage meeting criteria. |
| 01/01/2017 | Coding update: Removing ICD-9 Diagnosis Codes and CPT coding update |
| 04/06/2017 | Medical Policy Committee review |
| 04/19/2017 | Medical Policy Implementation Committee approval. Coverage eligibility unchanged. |

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02/19/2018 Coding update
06/07/2018 Medical Policy Committee review
06/20/2018 Medical Policy Implementation Committee approval. Title changed from “Chromosomal Microarray Analysis for the Evaluation of Pregnancy Loss” to “Chromosomal Microarray Testing for the Evaluation of Pregnancy Loss”. Policy statements changed from “analysis” to “testing”. Removed the “Note” from our coverage section and moved it to the Policy Guidelines section to include all of BCBSA’s Policy Guidelines. Coverage eligibility unchanged.
06/06/2019 Medical Policy Committee review
06/19/2019 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
06/04/2020 Medical Policy Committee review
06/10/2020 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

Next Scheduled Review Date: 06/2021

Coding

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Chromosomal Microarray Testing for the Evaluation of Pregnancy Loss

Policy # 00449

Original Effective Date: 10/15/2014

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contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.

CPT is a registered trademark of the American Medical Association.

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	81228, 81229, 81479
HCPCS	No codes
ICD-10 Diagnosis	N96, O26.20-O26.23, Z31.441

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

- A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
- B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
 - 1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
 - 2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
 - 3. Reference to federal regulations.

**Medically Necessary (or “Medical Necessity”) - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment,

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would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

- A. In accordance with nationally accepted standards of medical practice;
- B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
- C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

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