Protocol

Chromosomal Microarray Testing for the Evaluation of Pregnancy Loss

(204122)

Medical Benefit		**Effective Date**: 04/01/16	**Next Review Date**: 11/19
Preauthorization	No	**Review Dates**: 09/14, 05/15, 11/15, 01/16, 11/16, 11/17, 11/18	

Preauthorization is not required.

The following protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient's contract at the time the services are rendered.

Populations	Interventions	Comparators	Outcomes
Individuals: • With pregnancy loss with indications for genetic analysis of the embryo or fetus	Interventions of interest are: • Chromosomal microarray testing of fetal tissue	Comparators of interest are: • Karyotype of fetal tissue	Relevant outcomes include: • Test accuracy • Test validity • Other test performance measures • Changes in reproductive decision making • Morbid events • Quality of life

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.

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 has suggested that CMA testing has a high rate of concordance with standard karyotyping. For both early and late pregnancy loss, CMA is more likely to yield a result than karyotyping. Other studies have reported that CMA testing detects a substantial number of abnormalities in patients with normal karyotypes, although the precise yield is uncertain and likely varies based on gestational age. Rates of variants of uncertain significance in CMA testing of miscarriage samples are not well characterized. Potential benefits from identifying a genetic abnormality in a miscarriage or IUFD include reducing emotional distress for families, altering additional testing undertaken to

assess for other causes of pregnancy loss, and changing reproductive decision making for future pregnancies. The potential for clinical utility with CMA testing of fetal tissue in pregnancy loss is parallel to that for obtaining a karyotype of fetal tissue in pregnancy loss, which is recommended by a number of organizations. None of the studies identified directly demonstrated whether (or how) patient management would change based on CMA testing of 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.

POLICY

Chromosomal microarray testing 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 (see Policy Guidelines).

POLICY GUIDELINES

Clinical guidelines and recommendations exist to address the management of cases of miscarriage or IUFD 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 IUFD, 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 two 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 by the mother or parents and the treating clinician.

This protocol 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 (HGVS) 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 protocol updates starting in 2017 (see Table PG1). The Society's nomenclature is recommended by the Human Variome Project, the HUman Genome Organization (HUGO) and HGVS 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 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 occurred at or before 20 weeks gestational age.

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

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.[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 two 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 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.[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 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."[1] 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 (e.g., 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 abnormality rate of 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 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.

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). Laboratories that offer LDTs must be licensed by the 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.

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

RELATED PROTOCOLS

Carrier Testing for Genetic Diseases

Genetic Testing for Developmental Delay and Autism Spectrum Disorder

Invasive Prenatal (Fetal) Diagnostic Testing

Preimplantation Genetic Testing

Services that are the subject of a clinical trial do not meet our Technology Assessment Protocol criteria and are considered investigational. *For explanation of experimental and investigational, please refer to the Technology Assessment Protocol.*

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. **Some of this protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.**

REFERENCES

We are not responsible for the continuing viability of web site addresses that may be listed in any references below.

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