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FEP Medical Policy Manual

FEP 2.04.122 Chromosomal Microarray Testing for the Evaluation of Pregnancy Loss

Effective Policy Date: January 1, 2023

Original Policy Date: September 2014

Related Policies:

2.04.59 - Genetic Testing for Developmental Delay/Intellectual Disability, Autism Spectrum Disorder, and Congenital Anomalies

Chromosomal Microarray Testing for the Evaluation of Pregnancy Loss

Description

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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.

OBJECTIVE

The objective of this evidence review is to determine whether chromosomal microarray testing for fetal tissue improves the net health outcome in individuals who have experienced pregnancy loss and would be candidates for genetic analysis of their embryo or fetus.

POLICY STATEMENT

Chromosomal microarray testing of fetal tissue may be considered **medically necessary** for the evaluation of pregnancy loss in individuals with indications for genetic analysis of the embryo or fetus (see Policy Guidelines).

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 reproductive health associations, including the American Society for Reproductive Medicine and the American College of Obstetricians and Gynecologists. 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.

Genetic Counseling

Genetic counseling is primarily aimed at individuals who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual's family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. 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.

BENEFIT APPLICATION

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

Some Plans may have contract or benefit exclusions for genetic testing.

FDA 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 (CLIA). Laboratories that offer laboratory-developed tests 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 chromosomal microarray tests for prenatal samples that are not specifically designed for testing the products of conception.

RATIONALE

Summary of Evidence

For individuals who have pregnancy loss with indications for genetic analysis of the embryo or fetus who receive chromosomal microarray (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 intrauterine fetal demise (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 an improvement in the net health outcome.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information" if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American College of Obstetrics and Gynecologists

In 2016, the American College of Obstetricians and Gynecologists' Committee on Genetics and the Society for Maternal-Fetal Medicine published an opinion on the use of advanced genetic diagnostic tools in obstetrics and gynecology; the document was reaffirmed in 2020.[33,] The guidelines made the following recommendations and conclusions regarding the use of CMA:

- "Chromosomal microarray analysis [CMA] is a method of measuring gains and losses of DNA throughout the human genome. It can identify chromosomal aneuploidy and other large changes in the structure of chromosomes that would otherwise be identified by standard karyotype analysis, as well as submicroscopic abnormalities that are too small to be detected by traditional modalities."
- "Most genetic changes identified by CMA that typically are not identified on standard karyotype are not associated with increasing maternal age; therefore, the use of this test can be considered for all women, regardless of age, who undergo prenatal diagnostic testing."
- "Prenatal CMA is recommended for a patient with a fetus with 1 or more major structural abnormalities identified on ultrasonographic examination and who is undergoing invasive prenatal diagnosis. This test typically can replace the need for fetal karyotype."

- "In a patient with a structurally normal fetus who is undergoing invasive prenatal diagnostic testing, either fetal karyotyping or a CMA can be performed."
- "CMA of fetal tissue is recommended in the evaluation of IUFD or stillbirth when further cytogenetic analysis is desired because of the test's increased likelihood of obtaining results and improved detection of causative abnormalities."
- "Comprehensive patient pretest and posttest genetic counseling from an obstetrician-gynecologist or other health care provider with genetics expertise regarding the benefits, limitations, and results of CMA is essential. CMA should not be ordered without informed consent, which should include discussion of the potential to identify findings of uncertain significance, nonpaternity, consanguinity, and adult-onset disease."
- "Additional information is needed regarding the clinical use and cost-effectiveness in cases of recurrent miscarriage and structurally normal pregnancy losses at less than 20 weeks of gestation."

In 2020, the American College of Obstetricians and Gynecologists also published an obstetric care consensus on the management of stillbirth; reaffirmed in 2021.[6,] The consensus states that microarray analysis, incorporated into the stillbirth evaluation, "improves the test success rate and the detection of genetic anomalies compared with conventional karyotyping [strong recommendation; high-quality evidence]." As such, the authors of the consensus recommend microarray as the preferred method of stillbirth evaluation; however, "due to cost and logistics concerns, karyotype may be the only method readily available for some patients."

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.[1,] The statement drew the following conclusions:

- "Evaluation of recurrent pregnancy loss [RPL] can proceed after 2 consecutive clinical pregnancy losses."
- "Assessment of RPL 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 RPL."

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.

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POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:

Date	Action	Description
September 2014	New policy	
March 2015	Replace policy	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€
December 2017	Replace policy	Policy updated with literature review through June 22, 2017; references 19-20 and 33 added. Policy title and statement changed from "analysis€ to "testing€ . Policy statement otherwise unchanged.
December 2018	Replace policy	Policy updated with literature review through June 22, 2018; no references added; reference 32 updated. Policy statement unchanged.
December 2019	Replace policy	Policy updated with literature review through July 11, 2019; no references added; Policy statement unchanged.
December 2020	Replace policy	Policy updated with literature review through July 2, 2020; references added; Policy statement unchanged.
December 2021	Replace policy	Policy updated with literature review through June 21, 2021; references added; Policy statement unchanged.
December 2022	Replace policy	Policy updated with literature review through June 13, 2022; no references added. Minor editorial refinements to policy statements; intent unchanged.