BlueCross BlueShield Federal Employee Program.

FEP 2.04.122 Chromosomal Microarray Testing for the Evaluation of Pregnancy Loss

Effective Date: January 15, 2019

Related Policies:
2.04.59 Genetic Testing Developmental Delay/Intellectual Disability, Autism Spectrum Disorder, and/or Congenital Anomalies

Chromosomal Microarray Testing for the Evaluation of Pregnancy Loss

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.

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 patients 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 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 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 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.

FEP 2.04.122 Chromosomal Microarray Testing for the Evaluation of Pregnancy Loss

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).

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. 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

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.

SUPPLEMENTAL INFORMATION

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.[31] 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."

American Society for Reproductive Medicine

The American Society for Reproductive Medicine (2012) issued an opinion on the evaluation and treatment of recurrent pregnancy loss.[1] 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 (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

REFERENCES

1. Practice Committee of the American Society for Reproductive Medicine. Evaluation and treatment of recurrent pregnancy loss: a committee opinion. *Fertil Steril.* Nov 2012;98(5):1103-1111. PMID 22835448
2. Laurino MY, Bennett RL, Saraiya DS, et al. Genetic evaluation and counseling of couples with recurrent miscarriage: recommendations of the National Society of Genetic Counselors. *J Genet Couns.* Jun 2005;14(3):165-181. PMID 15959648
3. Practice Committee of American Society for Reproductive Medicine. Definitions of infertility and recurrent pregnancy loss: a committee opinion. *Fertil Steril.* Jan 2013;99(1):63. PMID 23095139
4. Christiansen OB. Evidence-based investigations and treatments of recurrent pregnancy loss. *Curr Opin Obstet Gynecol.* Jun 2006;18(3):304-312. PMID 16735831

5. Korteweg FJ, Erwich JJ, Timmer A, et al. Evaluation of 1025 fetal deaths: proposed diagnostic workup. *Am J Obstet Gynecol.* Jan 2012;206(1):53 e51-53 e12. PMID 22196684
6. Silver RM, Varner MW, Reddy U, et al. Work-up of stillbirth: a review of the evidence. *Am J Obstet Gynecol.* May 2007;196(5):433-444. PMID 17466694
7. Robberecht C, Schuddinck V, Fryns JP, et al. Diagnosis of miscarriages by molecular karyotyping: benefits and pitfalls. *Genet Med.* Sep 2009;11(9):646-654. PMID 19617844
8. Kearney HM, Thorland EC, Brown KK, et al. American College of Medical Genetics standards and guidelines for interpretation and reporting of postnatal constitutional copy number variants. *Genet Med.* Jul 2011;13(7):680-685. PMID 21681106
9. Dhillon RK, Hillman SC, Morris RK, et al. Additional information from chromosomal microarray analysis (CMA) over conventional karyotyping when diagnosing chromosomal abnormalities in miscarriage: a systematic review and meta-analysis. *BJOG.* Jan 2014;121(1):11-21. PMID 23859082
10. Lathi RB, Massie JA, Loring M, et al. Informatics enhanced SNP microarray analysis of 30 miscarriage samples compared to routine cytogenetics. *PLoS One.* Mar 2012;7(3):e31282. PMID 22403611
11. Menten B, Swerts K, Delle Chiaie B, et al. Array comparative genomic hybridization and flow cytometry analysis of spontaneous abortions and mors in utero samples. *BMC Med Genet.* Sep 14 2009;10:89. PMID 19751515
12. Hu Y, Chen X, Chen LL, et al. Comparative genomic hybridization analysis of spontaneous abortion. *Int J Gynaecol Obstet.* Jan 2006;92(1):52-57. PMID 16263126
13. Viaggi CD, Cavani S, Malacarne M, et al. First-trimester euploid miscarriages analysed by array-CGH. *J Appl Genet.* Aug 2013;54(3):353-359. PMID 23780398
14. Centre for Applied Genomics. Database of Genomic Variants. n.d.; http://dgv.tcag.ca/dgv/app/home. Accessed July 19, 2018.
15. Wellcome Trust Sanger Institute. DECIPHER GRCh37. Version 9.24. 2018; https://decipher.sanger.ac.uk/. Accessed July 19, 2018.
16. Benkhalifa M, Kasakyan S, Clement P, et al. Array comparative genomic hybridization profiling of first-trimester spontaneous abortions that fail to grow in vitro. *Prenat Diagn.* Oct 2005;25(10):894-900. PMID 16088865
17. Doria S, Carvalho F, Ramalho C, et al. An efficient protocol for the detection of chromosomal abnormalities in spontaneous miscarriages or foetal deaths. *Eur J Obstet Gynecol Reprod Biol.* Dec 2009;147(2):144-150. PMID 19740589
18. Barrett IJ, Lomax BL, Loukianova T, et al. Comparative genomic hybridization: a new tool for reproductive pathology. *Arch Pathol Lab Med.* Jan 2001;125(1):81-84. PMID 11151058
19. Lathi RB, Gustin SL, Keller J, et al. Reliability of 46,XX results on miscarriage specimens: a review of 1,222 first-trimester miscarriage specimens. *Fertil Steril.* Jan 2014;101(1):178-182. PMID 24182409
20. Levy B, Sigurjonsson S, Pettersen B, et al. Genomic imbalance in products of conception: single-nucleotide polymorphism chromosomal microarray analysis. *Obstet Gynecol.* Aug 2014;124(2 Pt 1):202-209. PMID 25004334
21. Maslow BS, Budinetz T, Sueldo C, et al. Single-nucleotide polymorphism-microarray ploidy analysis of paraffin-embedded products of conception in recurrent pregnancy loss evaluations. *Obstet Gynecol.* Jul 2015;126(1):175-181. PMID 26241271
22. Romero ST, Geiersbach KB, Paxton CN, et al. Differentiation of genetic abnormalities in early pregnancy loss. *Ultrasound Obstet Gynecol.* Jan 2015;45(1):89-94. PMID 25358469
23. Mathur N, Triplett L, Stephenson MD. Miscarriage chromosome testing: utility of comparative genomic hybridization with reflex microsatellite analysis in preserved miscarriage tissue. *Fertil Steril.* May 2014;101(5):1349-1352. PMID 24636399
24. Warren JE, Turok DK, Maxwell TM, et al. Array comparative genomic hybridization for genetic evaluation of fetal loss between 10 and 20 weeks of gestation. *Obstet Gynecol.* Nov 2009;114(5):1093-1102. PMID 20168112
25. Azmanov DN, Milachich TV, Zaharieva BM, et al. Profile of chromosomal aberrations in different gestational age spontaneous abortions detected by comparative genomic hybridization. *Eur J Obstet Gynecol Reprod Biol.* Apr 2007;131(2):127-131. PMID 16759788
26. Sahlin E, Gustavsson P, Lieden A, et al. Molecular and cytogenetic analysis in stillbirth: results from 481 consecutive cases. *Fetal Diagn Ther.* Jul 19 2014;36(4):326-332. PMID 25059832
27. Reddy UM, Page GP, Saade GR, et al. Karyotype versus microarray testing for genetic abnormalities after stillbirth. *N Engl J Med.* Dec 06 2012;367(23):2185-2193. PMID 23215556
28. Harris RA, Ferrari F, Ben-Shachar S, et al. Genome-wide array-based copy number profiling in human placentas from unexplained stillbirths. *Prenat Diagn.* Oct 2011;31(10):932-944. PMID 21732394

29. Raca G, Artzer A, Thorson L, et al. Array-based comparative genomic hybridization (aCGH) in the genetic evaluation of stillbirth. *Am J Med Genet A.* Nov 2009;149A(11):2437-2443. PMID 19876905
30. Bernardi LA, Plunkett BA, Stephenson MD. Is chromosome testing of the second miscarriage cost saving? A decision analysis of selective versus universal recurrent pregnancy loss evaluation. *Fertil Steril.* Jul 2012;98(1):156-161. PMID 22516510
31. American College of Obstetricians Gynecologists Committee on Genetics. Committee Opinion No. 581: the use of chromosomal microarray analysis in prenatal diagnosis. *Obstet Gynecol.* Dec 2013;122(6):1374-1377. PMID 24264715
32. Regan L, Backos M, Rai R. *The Investigation andTreatment of Couples with Recurrent First-trimester and Second-trimester Miscarriage. Green Top Guideline No. 17.* London, UK: Royal College of Obstetricians and Gynaecologists; 2011.

POLICY HISTORY

Date	Action	Description
September 2014	New Policy	
March 2015	Updated 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	Updated 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	Updated Policy	Policy updated with literature review through June 22, 2018; no references added; reference 32 updated. Policy statement unchanged.