BLUE CROSS OF NORTHEASTERN PA "BCNEPA" MEDICAL POLICY BULLETIN	**MANUAL:** MEDICAL POLICY
	REFERENCE NO.: MPO-083-0036
EFFECTIVE DATE October 1, 2014	**SUBJECT:** Chromosomal Microarray Testing for the Evaluation of Early Pregnancy Loss

Blue Cross of Northeastern Pennsylvania ("BCNEPA") Medical Policy

Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical policy and claims payment policy are applied. Policies are provided for informational purposes only and are developed to assist in administering plan benefits and do not constitute medical advice.

Treating providers are solely responsible for medical advice and treatment. Policies are based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease.

Medical practices and information are constantly changing and BCNEPA may review and revise its medical policies periodically. Also, due to the rapid pace of changing technology and the advent of new medical procedures, BCNEPA may not have a policy to address every procedure.

In those cases, BCNEPA may review other sources of information including, but not limited to, current medical literature and other medical resources, such as Technology Evaluation Center Assessments (TEC) published by the Blue Cross Blue Shield Association. BCNEPA may also consult with health care providers possessing particular expertise in the services at issue.

DESCRIPTION:

Pregnancy loss occurring before the 20th week of gestation is common, and is typically thought to be related to a genetic abnormality. Chromosomal microarray analysis (CMA) of products of conception (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.

BENEFIT POLICY STATEMENT:

BCNEPA makes decisions on coverage based on Policy Bulletins, benefit plan documents, and the member's medical history and condition. Benefits may vary based on product line, group or contract, therefore, Member benefits must be verified. In the event of a conflict between the Member's benefit plan document and topics addressed in Medical Policy Bulletins (i.e., specific contract exclusions), the Member's benefit plan document always supersedes the information in the Medical Policy Bulletins. BCNEPA determines medical necessity only if the benefit exists and no contract exclusions are applicable.

Benefits are determined by the terms of the Member's specific benefit plan document [i.e., the Fully Insured policy, the Administrative Services Only (ASO) agreement applicable to the Self-Funded Plan Participant, or the Individual Policy] that is in effect at the time services are rendered.

BACKGROUND:

Early Pregnancy Loss – Etiology and Evaluation

Pregnancy loss is common, occurring in at least 15-25% of recognized pregnancies. Most pregnancy loss 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. Pregnancy loss that occurs later in the pregnancy is referred to as an intrauterine fetal demise. While a wide range of factors can lead to early pregnancy loss, genetic causes are thought to be the predominant cause: when products of conception are examined, it is 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 (ASRM) 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/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 2-6% for cytogenetic abnormalities, 8-42% for antiphospholipid antibody syndrome, and 1.8-37.6% 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.

There may be several motivations for clinicians and patients to undertake an evaluation for the cause of a single or recurrent early pregnancy loss. The knowledge that an early pregnancy loss is secondary to a sporadic genetic abnormality may provide parents with reassurance that there was nothing that 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 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; guidelines on the management of recurrent pregnancy loss from the ASRM state that “treatment options should be based on whether repeated miscarriages are euploid, aneuploidy, or due to an unbalanced structural rearrangement and no exclusively on the parental carrier status.” (1) Finally, among patients who are found to have a potential *non-genetic* underlying cause of recurrent pregnancy loss, such as antiphospholipid syndrome, cytogenetic analysis of pregnancy losses may provide evidence that the miscarriages were not due to treatment failure.(4)

Genetic testing of products of conception, if possible, is recommended by several reproductive health organizations. A committee opinion from the ASRM recommends that the assessment of recurrent pregnancy loss include peripheral karyotyping of the parents, and states that karyotypic analysis of products of conception may be useful in the setting of ongoing therapy for recurrent pregnancy loss.(1) The National Society of Genetic Counselors convened a multidisciplinary Inherited Pregnancy Loss Working Group which provided recommendations for the genetic evaluation of couples with recurrent pregnancy loss that stated that, when possible, chromosomal analysis on fetal tissue from products of conception should be pursued.(2)

Traditionally, genetic evaluation of the products of conception after a miscarriage is conducted by karyotyping of metaphase cells after cells are cultured in tissue. However, this approach is limited by the potential for cell culture failure and the fact that samples that have been preserved in formalin cannot be cultured. In addition, there is the potential for maternal cell contamination, which may occur if the products of conception tissue are not separated from the maternal decidua before culturing, or if there is poor

growth of non-euploid cells from the products of conception tissue, thereby allowing maternal cell overgrowth. The potential for maternal cell contamination makes it impossible to know if a normal female (46 XX) karyotype testing results is due to a normal fetal karyotype or a maternal karyotype. In one study that included 103 first trimester miscarriages, culture failure occurred in 25% of cases.(5)

Chromosomal Microarray Testing

Given the limitations of conventional karyotyping in the assessment of tissue samples from early pregnancy miscarriages, there has been interest in using alternative genetic testing methods, particularly array comparative genomic hybridization, to detect chromosomal or other genetic abnormalities in early pregnancy losses.

Several types of microarray technology are in current clinical use, primarily array comparative genomic hybridization (arrayCGH) and single nucleotide polymorphism (SNP) microarrays. Comparative genomic hybridization CMA analysis detects copy number variants (CNVs) by comparing a reference genomic sequence to the patient ("unknown") sequence in terms of binding to a microarray of cloned (from bacterial artificial chromosomes) or synthesized DNA fragments with known sequences. The reference DNA and the unknown sample are labelled with different fluorescent tags, and both samples are co-hybridized to the fragments of DNA on the microarray. Computer analysis is used to detect the array patterns and intensities of the hybridized samples. If the unknown sample contains a deletion or duplication of genetic material in a region contained on the reference microarray, the sequence imbalance is detected as a difference in fluorescence intensity. ArrayCGH can detect CNVs for larger deletions and duplications, including trisomies. However, arrayCGH cannot detect balanced translocations or diploid, triploid and tetraploid states.

In SNP-based CMA testing, a microarray of SNPs, which may include hundreds of thousands of SNPs, is used for hybridization. In contrast to arrayCGH, a reference genomic sequence is not used. Instead, only the "unknown" sample is hybridized to the array platform, and the presence or absence of specific known DNA sequence variants is evaluated by signal intensity to provide information about copy numbers. In addition to detecting deletions and duplications, SNP-based CMA analysis can detect runs of homozygosity, which suggests consanguinity, triploidy, and uniparental disomy. In some cases, laboratories confirm CNVs detected on CMA with an alternative technique, such as fluorescence in situ hybridization (FISH) or flow cytometry.

Microarrays also vary in breadth of coverage of the genome that they include. Targeted CMA analysis provides coverage of the genome with a concentration of sequences in areas with known, clinically significant CNVs. In contrast, whole-genome CMA allows the characterization of large numbers of genes, but with the downside that analysis may identify large numbers of CNVs of undetermined significance.

The American College of Medical Genetics has published guidelines regarding the interpretation and reporting of CNVs in the postnatal setting that recommend that laboratories that perform array-based assessment of CNVs track their experience with CNVs and document pathogenic CNVs, CNVs of uncertain significance, and CNVs that have been determined to represent benign variation based on comparisons to internal and external databases.(6)

Commercially Available Tests

Natera, Inc. (San Carlos, CA) offers the Anora™ miscarriage test, which uses a SNP-based array system for testing of products of conception. The test includes the company's proprietary "Parental Support Technology," which uses a DNA sample from one or both parents as a reference to the products of conception sample. This comparison can identify maternal cell contamination, uniparental disomy, and the parent of origin of a fetal chromosome abnormality. According to a description of the "Parental Support" algorithm (7), the algorithm uses the "SNP array data to calculate the relative amounts of each

of the two alleles at each SNP. At heterozygous loci, disomic chromosomes are expected to have SNP ratios of approximately 50%, trisomic chromosomes are expected to have SNP ratios of approximately 33% and 66%, and monosomic chromosomes are expected to have only homozygous loci. For each chromosome, the algorithm compares the observed SNP data to each of the expected alleles for the possible ploidy states and determines which is most likely."

According to the manufacturer's website, the test reports the following abnormalities, including the parent of origin of any anomaly when a parental sample has been submitted:(8)

- Any whole chromosome aneuploidy.
- Triploidy.
- Tetraploidy where one parent contributed one set of chromosomes and the other parent contributed the other three. Tetraploidy when parental contribution is equal cannot be detected.
- Uniparental disomy.
- Interstitial deletions and duplications greater than 5 Mb.
- Any terminal deletion or duplication, as it could be an indication for a balanced translocation.
- Deletions of 1 Mb or greater and duplications of 2 mB or greater are reviewed individually by a genetic counselor/geneticist and reported if the potential cause of a miscarriage or recurrence risk implications are identified.
- Any of the following deletions and duplications, when identified:
    - 1p36 deletion
    - 1q21.1 deletion (epilepsy)
    - 2q37 deletion
    - 3q29 terminal deletion
    - 4p16.3 deletion (Wolf-Hirschhorn syndrome)
    - 5p15.2 deletion (Cri du Chat)
    - 7q11.23 deletion (Williams syndrome)
    - 8q23.2-8q24.1 deletion (Langer-Giedon)
    - 9q34 deletion
    - 11p13-14 deletion (WAGR)
    - 11q24.1 deletion (Jacobsen syndrome)
    - 10p13-p14 deletion (DiGeorge 2)
    - 15q11-q13 deletion (Prader-Willi/Angelman region)
    - 16p11.2 deletion (epilepsy)
    - 17p11.2 deletion (Smith-Magenis)
    - 17p13.3 deletion (Miller-Dieker)
    - 17q21.31 deletion
    - 22q13 deletion (Phelan-McDermid syndrome)
    - 22q11.2 deletion (DiGeorge/VCFS)
    - 22q11.2 duplication
    - Xq28 deletion (MECP2 deletion)
    - Xq28 duplication (MECP2 duplication)

CombiMatrix (Irvine, CA) offers two SNP-based microarray systems for testing products of conception, the CombiSNP™ Array for Pregnancy Loss, which is used for testing fresh tissue samples, and the CombiBAC™ Array, which is used for testing formalin-fixed, paraffin-embedded tissue samples. According to the manufacturer's website, the CombiSNP Array is a high resolution SNP microarray that can detect triploidy, numeric chromosome abnormalities, unbalanced structural rearrangements, microdeletion/ duplication syndromes, long stretches of homozygosity, which can indicate shared ancestry or uniparental disomy (UPD) and maternal cell contamination. The CombiBAC Array is an

arrayCGH method that can detect numeric chromosome abnormalities, unbalanced structural rearrangements and microdeletion/microduplication syndromes. (9)

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

MEDICAL POLICY STATEMENT:

BCNEPA will not provide coverage for chromosomal microarray analysis of products of conception (fetal tissue or placental tissue derived from the fetal genotype) as this is considered investigational for the evaluation of early pregnancy loss.

GUIDELINES:

Early pregnancy loss is considered to be a pregnancy loss occurred at or before 20 weeks gestational age.

This policy does not address the use of chromosomal microarray testing (CMA) for preimplantation genetic diagnosis or preimplantation genetic screening, for the evaluation of genetic causes of late pregnancy losses (after 20 weeks gestational age), or the evaluation of suspected chromosomal abnormalities in the postnatal period.

RATIONALE:

The evaluation of both recurrent and isolated early pregnancy loss 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, this technique is limited by the need for fresh tissue, the potential for cell culture failure, and the potential for maternal cell contamination. Chromosomal microarray analysis (CMA) of products of conception has been proposed as a technique to evaluate the cause of isolated and recurrent early pregnancy loss. The evidence related to the use of CMA in the evaluation of products of conception is primarily from studies that compare CMA test results to conventional karyotyping; these studies suggest that CMA has a reasonably high rate of concordance with karyotyping. Other studies have reported that CMA detects a substantial number of abnormalities in patients with normal karyotypes, but these studies are small and the precise yield is uncertain. Rates of variants of unknown significance on CMA testing of miscarriage samples are not well characterized.

Potential benefits from identifying a genetic abnormality in an early pregnancy loss include reducing emotional distress for families, altering additional testing that is undertaken to assess for other causes of pregnancy loss, and changing reproductive decision-making for future pregnancies. No studies were identified that identify whether or how patient management is changed based on CMA testing of products of conception from early pregnancy losses, or how patient outcomes are improved. Therefore, CMA testing of products of conception is considered investigational for the evaluation of early pregnancy loss.

Practice Guidelines and Position Statements

In 2013, the American College of Obstetrics and Gynecologists Committee on Genetics and the Society for Maternal-Fetal Medicine published a committee opinion on the use of chromosomal microarray analysis in prenatal diagnosis.(19) The guidelines make 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.

In 2012, the American Society for Reproductive Medicine (ASRM) issued a committee opinion on the evaluation and treatment of recurrent pregnancy loss.(1) The statement makes the following conclusions about the evaluation of recurrent pregnancy loss:

- 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.

In 2011, the Royal College of Obstetricians and Gynaecologists issued guidelines on the investigation and treatment of couples with recurrent first-trimester and second-trimester miscarriage. (20) The guidelines make the following recommendations related to karyotyping in recurrent miscarriage:

- Cytogenetic analysis should be performed on products of conception of the third and subsequent consecutive miscarriage(s). (Grade of evidence D [evidence level 3 or 4; or extrapolated from studies rated as 2+]; Evidence level 4 [expert opinion]).
- Parental peripheral blood karyotyping of both partners should be performed in couples with recurrent miscarriage where testing of products of conception reports an unbalanced structural chromosomal abnormality. (Grade of evidence D; Evidence level 3 [non-analytical studies, e.g., case reports, case series]).

Medicare National Coverage

None

DEFINITIONS:

N/A

CODING:

- **The identification of a code in this section does not denote coverage or separate reimbursement.**
- Covered procedure codes are dependent upon meeting criteria of the policy and appropriate diagnosis code.
- The following list of codes may not be all-inclusive, and are subject to change at any time.
- Benefits are determined by the terms of the Member's specific benefit plan document [i.e., the Fully Insured policy, the Administrative Services Only (ASO) agreement applicable to the Self-Funded Plan Participant, or the Individual Policy] that is in effect at the time services are rendered.

PROCEDURE CODES

No Specific Code

SOURCES:

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APPROVALS:

Approved by Vice President, Clinical Operations & Chief Medical Officer:

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