Medical Policy

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Title: Genetic Testing-Chromosomal Microarray Testing for the Evaluation of Early Pregnancy Loss and Intrauterine Fetal Demise

Description/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 2 or more failed pregnancies, is less common, occurring in approximately 5% of women.[3,4,] 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 1 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 also be considered for couples with recurrent pregnancy loss without evidence of a structural genetic abnormality in 1 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.[5,]

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 2013, IUFD occurred in 5.96 of 1000 births in the United States[6,], 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%.[7,]

Reasons to evaluate for a cause of IUFD are the same as 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 mutation in a fetus may prompt testing in the parents; if a heritable mutation is identified, parents may pursue preimplantation genetic diagnosis in future pregnancies.

CHROMOSOMAL MICROARRAY ANALYSIS TESTING

There has been interest in using alternative genetic testing methods, particularly array comparative genomic hybridization (aCGH), 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 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 testing for prenatal sample that is not specifically designed for testing of POC.

Medical Policy Statement

The safety and effectiveness of chromosomal microarray analysis of fetal tissue have been established. It is a useful diagnostic option for the evaluation of pregnancy loss and intrauterine fetal demise when indicated.

Inclusionary and Exclusionary Guidelines

Inclusions:

- 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.

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)*

Established codes:

81228 81229 81349 88261 88262 88263 88271

Other codes (investigational, not medically necessary, etc.):

81277 0156U 0252U

Rationale

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

PREGNANCY LOSS WITH INDICATIONS FOR EMBRYONIC OR FETAL GENETIC ANALYSIS

Clinical Context and Test Purpose

The purpose of chromosomal microarray (CMA) testing in individuals who have early spontaneous pregnancy loss or intrauterine fetal demise (IUFD) is to inform decisions regarding risk for subsequent pregnancies and whether to implement relevant clinical evaluation and management.

The following **PICOs** were used to select literature to inform this review.

Populations

The relevant populations of interest are women who have experienced single or recurrent early spontaneous pregnancy loss or an IUFD. Evidence on specific abnormalities in miscarriages and IUFD is somewhat limited; however, it is estimated that 60% of early pregnancy losses are associated with chromosomal abnormalities, particularly trisomies and monosomy X. For later pregnancy losses, aneuploidies are most common in the 8% to 13% of tested IUFD that have an identified chromosomal or genetic abnormality. Karyotypic abnormalities are identified in 6% to 13% of IUFD.[6.] Rates of single-gene disorders in IUFD are less well quantified. However, of stillborn fetuses who undergo an autopsy, 25% to 35% are identified to have single or multiple malformations or deformations; of these, 25% have an abnormal karyotype, but other single-gene disorders are suspected to occur in a high proportion of stillborn fetuses with malformations.

Interventions

The test being considered is CMA testing. Several types of microarray technology are in current clinical use, primarily array comparative genomic hybridization (aCGH) and single nucleotide variant (SNV) microarrays. Array CGH CMA testing detects copy number variants (CNVs) by comparing a reference genomic sequence with the patient ("unknown") sequence in terms of binding to a microarray of cloned (from bacterial artificial chromosomes) or synthesized DNA fragments with known sequences. In SNV-based CMA testing, a microarray of SNVs, which may include hundreds of thousands of SNVs, is used for hybridization. In contrast with aCGH, a reference genomic sequence is not used. Instead, only the "unknown" sample is hybridized to the array platform, and the presence or absence of specifically known DNA sequence variants is evaluated by signal intensity to provide information about copy numbers. In some cases, laboratories confirm CNVs detected on CMA with an alternative technique, such as fluorescence in situ hybridization or flow cytometry.

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

CMA testing would be performed in any of the trimesters of pregnancy when there is an indication for genetic evaluation of a spontaneous pregnancy loss or IUFD. CMA testing would be provided in an obstetrics or perinatal care setting. Genetic counseling may also be provided.

Comparators

The following tools are currently being used to make decisions about the presence of genetic abnormalities as the cause of early pregnancy loss or IUFD. Traditionally, genetic evaluation of the products of conception (POC) after a miscarriage is conducted by karyotyping of metaphase cells after the cells are cultured in tissue. Karyotyping can identify whole-chromosome aneuploidies and large structural rearrangements; however, only visible rearrangements are likely to be identified using this method (down to a resolution of 5 to 10 megabases [Mb]), so smaller genetic variants may not be detected. In addition, karyotyping requires culturing the target cells, which may fail or be infeasible, particularly for formalin-preserved samples. Further still, there is the potential for maternal cell contamination, which may occur if the POC tissue is not separated from the maternal decidua before culturing, or if there is poor growth of noneuploid cells from the POC 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 result is due to a normal fetal karyotype or a maternal karyotype. In a 2009 study that included 103 first trimester miscarriages, Robberecht et al (2009) reported a culture failure rate in 25% of cases.[8,] The results of CMA testing can be compared directly with karyotyping, but there is no independent reference standard that can be used to determine the performance characteristics of each test.

Outcomes

The general outcomes of interest are test accuracy and validity, other test performance measures, changes in reproductive decision making, morbid events, and quality of life.

CMA testing has several advantages over karyotyping, including improved resolution (detection of smaller chromosomal variants that are undetectable using standard karyotyping), and therefore can result in potentially higher rates of detection of pathogenic chromosomal abnormalities. Array CGH can detect CNVs for larger deletions and duplications, including trisomies. However, CMA based on aCGH cannot detect balanced translocations or diploid, triploid, and tetraploid states, or sequence inversions because they are not associated with fluorescence intensity change. SNV-based CMA, in addition to detecting deletions and duplications, can detect runs of homozygosity, which suggests consanguinity, triploidy, and uniparental disomy.

Another advantage of CMA is that it does not require successful cell culture, so it may be more likely to yield a result in cases where karyotyping is technically unsuccessful due to failed culture. In the case of testing specimens from early miscarriage, CMA may also be used to rule out maternal cell contamination, if a fetal sample is compared with a maternal sample.

One distinct disadvantage of CMA is its higher rates of detection of variants of uncertain significance (VUS). In 2011, the American College of Medical Genetics initially published guidelines on the interpretation and reporting of CNVs in the postnatal setting.[9,] The College recommended that laboratories performing an array-based assessment of CNVs track their experience with CNVs and document pathogenic CNVs, CNVs of uncertain significance, and CNVs determined to represent benign variations based on comparisons with internal and external databases. In 2020, the American College of Medical Genetics and Genomics and the Clinical Genome Resource published an updated joint consensus recommendation regarding technical standards for the interpretation and reporting of constitutional CNVs.[10,] Major updates from the 2011 document included:

- "CNV classification categories will change to the 5-tier classification system recommended in the American College of Medical Genetics/Association for Molecular Pathology sequence variant interpretation guideline;
- Variants should be classified consistently between patients; while patient presentation and/or reason for referral may be used as evidence to support a particular classification, this information should not be used to justify disparate classifications of the same variant. Variant classifications should be based on evidence; at a given point in time, evidence supporting/refuting a given variant's pathogenicity should be the same. Therefore, the classification of that variant should be the same regardless of patient-specific factors such as reason for referral, sex, age, etc.;
- Laboratories should consider utilizing headers or subsections in the clinical report to clearly communicate primary versus incidental or secondary findings, such as carrier status for autosomal recessive conditions, pathogenic variants unrelated to the stated reason for referral, etc.;
- Explicit new guidance for interpreting CNVs occurring within individual genes;
- And points-based rubrics to guide laboratories toward more consistent CNV interpretations."

Study Selection Criteria
For the evaluation of clinical validity of CMA testing, studies that meet the following eligibility criteria were considered:

- Patient/sample clinical characteristics were described and
- Patient/sample selection criteria were described.

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Review of Evidence

Systematic Reviews
Martinez-Portilla et al (2019) published results from a systematic review and meta-analysis of 7 studies assessing the added value of CMA over conventional karyotyping during a stillbirth work-up (i.e., fetal loss after 20 weeks of gestation).[11,] The studies included 1443 fetal losses, of which 903 (63%) were stillbirths with a normal karyotype. A total of 1057 karyotyping and 701 CMA tests were performed. Results revealed a test success rate (i.e., rate of informative results) of 75% for conventional karyotyping versus 90% for CMA. The incremental yield of CMA over karyotyping was 4% (95% confidence interval [CI], 3% to 5%) for pathogenic CNVs and 8% (95% CI, 4% to 17%) for VUS. In a subgroup analysis, the incremental yield of CMA for pathogenic CNVs was 6% (95% CI, 4% to 10%) in structurally abnormal fetuses and was 3% (95% CI, 1% to 5%) for structurally normal fetuses. The authors concluded that CMA improves both test success rate and genetic abnormality detection when incorporated into a stillbirth workup as compared with conventional karyotyping. The risk of bias assessment judged 2 of the studies to have a high risk of bias - 1 in patient selection and the other in flow and timing. One other study had an unclear risk of bias for patient selection and in the reference standard.

Dhillon et al (2014) reported on the results of a systematic review and meta-analysis of studies that compared CMA testing with conventional karyotyping in the evaluation of

miscarriage.[12] Reviewers included 9 studies that reported results from CMA on POC following miscarriage alongside conventional karyotyping. There were 314 miscarriage samples in the included studies. In the pooled analysis, the overall agreement between karyotype and CMA results was 86.0% (95% CI, 77.0% to 96.0%), with high homogeneity across the studies (I^2=0.2%). CMA detected 13% (95% CI, 8.0% to 21.0%) additional chromosomal abnormalities not detected by karyotyping (including both likely pathogenic variants and VUS). Conventional karyotyping detected 3% (95% CI, 1.0% to 10.0%) additional abnormalities not detected by CMA. Among 5 studies that reported VUS, the pooled chance of having a VUS was 2% (95% CI, 1.0% to 10.0%). This systematic review demonstrated good overall agreement between CMA and karyotype testing in the analysis of miscarriage specimens. However, the CI around the estimate of the VUS rate was large, indicating uncertainty in the true rate. Further research is required to determine whether CNVs found in POC are pathogenic or benign.

Prospective Study

One prospective study by Lee et al (2021) compared the performance of karyotyping with CMA using both aCGH and SNV microarray to identify genetic abnormalities in miscarriage specimens.[13] Using a total of 63 specimens, genetic abnormalities were detected by at least 1 method in 49.2% of samples; the most common abnormality was single autosomal trisomy (71.0%). Using data from these 31 cases, the detection rate of genetic abnormalities was higher with SNV microarray compared with aCGH (93.5% vs. 77.4%; p=.045), and was lowest with karyotyping (76.0%).

Schilit et al (2022) reported on the efficacy of CMA testing in the evaluation of POC compared to available karyotype data.[14] There were 323 POC samples collected over a 42-month period. CMA analysis was performed using 2 different platforms: Affymetrix Cytoscan HD assay or Affymetrix Oncoscan assay. CMA was able to identify cytogenetic abnormalities in 47.4% (109/203) of first trimester losses and 10.9% (10/92) of second and third trimester losses. A total of 133 cases were evaluated by both CMA and karyotype. There was a 20% (9/45) discordance with CMA findings in samples with available karyotype data. Maternal cell overgrowth in the female karyotypes may have limited results. The most prevalent abnormalities reported overall were autosomal trisomies.

Retrospective Studies

A number of additional studies not included in the Dhillon systematic review have compared CMA with karyotyping. For example, CMA testing was conducted using an SNV-based microarray, which measures about 300,000 SNVs across the genome (»1 every 10 kilobase pairs).[15] A "Parental Support" technique was used to compare results from the POC sample with parental samples to determine the number and origin of each chromosome in the POC sample. On conventional karyotype, 63% of samples were chromosomally abnormal, with autosomal trisomies as the most common abnormality. All 46 XX samples on karyotyping were confirmed to be from fetal tissue on microarray analysis. Four samples were discordant between CMA and karyotype, including a case of whole-genome duplication and a balanced translocation, both of which would not be expected to be detected on the microarray; and 2 additional discrepancies were attributed to sampling error, tissue mosaicism, or culture artifact.

Menten et al (2009) reported on the results of an evaluation of 100 pregnancy losses with conventional karyotyping, flow cytometry, and aCGH.[16] Array CGH was performed using an investigator-developed bacterial artificial CMA at a resolution of approximately 1 Mb. On conventional karyotyping, normal karyotypes were found in 11 male and 44 female cases. In

28 cases, karyotyping was not possible due to culture failure. Chromosomal abnormalities were found in 17 cases (9 autosomal trisomies, 2 cases of monosomy X, 3 triploidy cases, 1 balanced and 1 unbalanced translocation). On aCGH, 23 abnormal results were found: 15 autosomal trisomies, 5 cases of monosomy X, and 3 structural abnormalities. Ten of the abnormalities on aCGH were not detected with conventional karyotyping. In 1 case, balanced translocation was not detected on aCGH. In 2 additional cases, a triploidy was suspected due to aberrant ratios for the sex chromosomes. Due to poor DNA quality, no result could be obtained for 2 samples.

Hu et al (2006) conducted a genetic analysis by both CGH and karyotyping in 38 POC from early pregnancy losses.[17,] The culture of chorionic villi and examination of metaphase chromosomes were attempted in all samples, but the cytogenic analysis was technically successful in only 31 samples. Of the 31 samples successfully karyotyped, 14 were diagnosed to be aneuploidies, including 4 with trisomy 21, 2 each with trisomies 13 and 16, 2 with monosomy X, and 1 each with trisomies 3, 7, 18, and 20. An additional 2 cases of triploidy were detected. On CGH analysis, 17 aneuploidies were identified (14 of those found on the karyotyped samples, along with 3 cases in samples for which cell culture failed), along with 1 structural chromosomal abnormality. For the 31 samples that had both tests conducted, there was generally good concordance between the approaches, with the exception that CGH did not detect the 2 cases of triploidy.

Yield of CMA in Pregnancy Loss

Early Pregnancy Loss

Several studies have evaluated the use of CMA analysis in the evaluation of early pregnancy loss when standard karyotyping is unsuccessful, or have evaluated the incremental benefit of CMA analysis in the detection of maternal cell contamination.

Lathi et al (2014) reported on the results of a retrospective analysis of CMA testing to detect maternal cell contamination of conventional karyotyping in 1222 POC samples from first trimester miscarriages evaluated at a Natera laboratory from January 2010 to August 2011.[18,] The POC samples, along with maternal peripheral blood samples, were evaluated with a SNV-based CMA. When CMA results for the POC were 46 XX, a comparison with the maternal genotype fingerprint allowed investigators to determine whether results were due to maternal cell contamination. On initial analysis, before comparison with the maternal genotype fingerprint, 48% of POC specimens were chromosomally abnormal, 37% were 46 XX, and 14% were 46 XY. Comparison with maternal bloody genotype indicated that 59% of the 46 XX results were due to maternal cell contamination. The authors suggested that the use of CMA testing might improve accurate detection of fetal chromosomal abnormalities.

Viaggi et al (2013) used a whole-genome aCGH to evaluate 40 POC samples from first trimester miscarriages that had normal karyotypes to assess for the presence and prevalence of CNVs.[19,] Frozen samples were evaluated with aCGH at a resolution of 100 kilobases. CNVs were compared with those present in the Database of Genomic Variants,[20,] Decipher,[21,] and the Database of Human CNVs to differentiate between benign CNVs and possibly pathogenic CNVs. Forty-five CNVs, corresponding to 22 different CNVs, were identified in 31 samples (31/40 [77.5%]). Thirty-one (68%) of the 45 CNVs identified were defined as common CNVs. When the CNVs were compared with control CNVs reported in the

Database of Genomic Variants, 7 CNV frequencies were considered statistically different from the control population.

Doria et al (2009) evaluated aCGH as part of a sequential protocol in the genetic evaluation of 232 spontaneous miscarriages or fetal deaths, 186 of which were from the first trimester, 24 from the second trimester, and 22 from the third trimester.[22] Tissue culture and karyotyping were attempted on all specimens; samples that could not be karyotyped were tested with aCGH, followed by additional confirmation with fluorescence in situ hybridization. Culture failure occurred in 25.4% of the cases. Of the 173 (74.6%) with valid karyotypes, 66 (38.2%) of 173 were abnormal: 62 of 66 with numerical abnormalities (single, double, or triple trisomies, monosomy X, polyploidy, or mosaicism), and 5 of 66 with structural abnormalities. Array CGH was performed in 58 of 59 cases with culture failure (1 case had insufficient DNA for aCGH). Fifteen of the 58 cases were abnormal, with 3 cases of monosomy X, 1 case of XY with gain for X, 7 cases of trisomy 15, 2 cases of trisomy 16, and 1 case each of trisomies 18 and 21. With the addition of fluorescence in situ hybridization testing, 4 new cases of triploidy were detected. This study suggested that the use of aCGH increases the yield of testing of genetic testing of POC beyond that of standard karyotyping.

Benkhalifa et al (2005) evaluated 26 samples from first trimester miscarriages that failed to divide in routine cytogenetic studies with the aCGH technique.[23] The aCGH method used involved human genomic microarrays containing 2600 cloned areas spanning chromosome subtelomeric regions and critical areas spaced about 1 Mb along each chromosome. Of the 26 samples that failed to divide in routine cytogenetics, 15 had an abnormal genetic profile on aCGH. Abnormalities that are highly prevalent on routine karyotyping (trisomy 16, monosomy X, triploidy, which are estimated to account for >55% of cytogenetically abnormal findings in routine karyotyping) were relatively uncommon among the 15 abnormal samples, with an instance of monosomy 16 and 2 instances of monosomy X.

A number of studies have reported outcomes from CMA analysis of POC in various patient populations where karyotyping was not performed.

Maslow et al (2015) evaluated the yield of the SNV-based array for determining chromosome number in paraffin-fixed POC compared with a standard evaluation for couples with recurrent first trimester pregnancy losses.[24] Eligible patients had been previously analyzed for chromosome number and screening tests recommended by the American Society for Reproductive Medicine for recurrent pregnancy loss, including parental karyotypes, maternal serum testing for antiphospholipid antibodies, thyrotropin, and prolactin, and a uterine cavity evaluation via sonohysterogram or hysterosalpingogram. Forty-two women with a total of 178 first trimester losses were included, with 62 paraffin-embedded POC samples available. SNV-based microarray testing determined a fetal chromosome number in 44 (71%) of 62 samples, 25 (57%) of which were noneuploid. Recurrent pregnancy loss screening was normal in 35 (83%) of 42 participants. The detection rate for any cause of pregnancy loss was significantly higher with SNV microarray (0.50; 95% CI, 0.36 to 0.64) than with the American Society for Reproductive Medicine-recommended recurrent pregnancy loss evaluation (0.17; 95% CI, 0.08 to 0.31; p=.002).

Romero et al (2015) reported on types of genetic abnormalities found on CMA testing in early pregnancy losses (<20 weeks of gestation) among 86 women.[25] Thirteen (14.9%) of POC samples were excluded because placental villi or fetal tissue could not be identified with

certainty and 9 were excluded due to complete maternal cell contamination, leaving a sample of 64 for analysis. The overall prevalence of aneuploidy and pathogenic CNV or VUS was 43.8% (28/64). Excluding the 2 cases with VUS, rates of pathogenic CNV or aneuploidy differed by gestational age: 9.1%, 69.2%, and 28.0% of pre-embryonic, embryonic, and fetal samples, respectively (p<.01). Aneuploidy was the most common abnormality, occurring in 37.5% (24/64) of cases.
Levy et al (2014) reported on the results of SNV microarray analysis of 2447 consecutively received POC samples, of which 2400 were fresh samples.[26.] Of the fresh samples, 2392 (99.7%) were 20 weeks of gestation or less, and 1861 (77.6%) had no or negligible maternal cell contamination. The authors used a 10-Mb cutoff to estimate the threshold of detection for routine karyotyping in POC samples. At a resolution of conventional karyotyping, 1106 (59.4%) showed classical cytogenetic abnormalities. Of the remaining 755 samples considered normal at the karyotype level, 33 (4.4%) had a CNV (microdeletion or microduplication); 12 (36.4%) were considered clinically significant and the remaining were considered VUS.

Mathur et al (2014) reported on results from CMA testing in preserved POC samples from 58 women with 77 miscarriage specimens who were evaluated at a single recurrent pregnancy loss clinic.[27.] All women had a history of recurrent pregnancy loss, defined as 2 or more ultrasound-documented miscarriages at less than 10 weeks of gestation. Samples were evaluated with aCGH; if results were 46 XX, the genotype of the POC was compared with the maternal genotype at several highly polymorphic loci through microsatellite analysis to determine whether the 46 XX results were consistent with maternal cell contamination. Sixteen (21%) samples yielded uninformative results due to minimal pregnancy tissue (n=9), poor quality DNA (n=2), or confirmed maternal cell contamination (n=2). Array CGH was considered informative in 61 (79%) cases, with 22 noneuploid and 39 euploid. Thirty-three of the euploid specimens were 46 XX, 11 of which were not sent for reflex microsatellite analysis. The authors concluded that CMA testing of preserved POC is technically feasible, including cases where karyotyping has failed due to cell growth failure, which had occurred in 8 samples evaluated.

Warren et al (2009) conducted a prospective case series to evaluate results from aCGH in POC from 35 women who had pregnancy loss between 10 and 20 weeks of gestation with either normal karyotype (n=9) or no conventional cytogenetic testing (n=26).[28.] Thirty-five samples were from fresh tissue obtained at the time of pregnancy loss when dilatation and curettage was performed; the remainder was from paraffin-embedded tissue. Samples were assessed with a whole-genome bacterial artificial chromosome array chip. Clones that demonstrated copy number changes in the fetal tissue were compared with known copy number change regions in the Database of Genomic Variants and the internal database of apparently benign copy number changes maintained by the University of Utah aCGH laboratory. When CNVs were detected, parental samples were assessed with the same array chip, and CNVs present in fetal tissue but not parental DNA were defined as de novo CNVs. Samples with de novo CNVs on the bacterial artificial chromosome chip were further analyzed with an oligonucleotide microarray chip with an average resolution of 6.4 kilobases for more accurate characterization. DNA was successfully isolated in 30 cases (all from the fresh tissue samples). De novo CNVs were detected in 6 (20%) of the 30 cases using the bacterial artificial chromosome array and confirmed in 4 (13%) of 30 cases using the oligonucleotide array.

Intrauterine Fetal Demise

Relatively few studies have reported on the yield of CMA testing for IUFD, either in addition to or as an alternative to standard karyotyping. Sahlin et al (2014) evaluated CMA testing in a sample of 90 IUFD cases (after 22 weeks of gestation) with no known genetic diagnosis based on karyotype and quantitative fluorescence polymerase chain reaction.[29] CMA testing yielded results in all cases, 77% of which were benign or likely benign CNVs. Three variants were detected in genes known to be associated with IUFD or other disorders. Twenty-six VUS were identified in 21 cases of IUFD.

In the largest study identified, Reddy et al (2012) compared CMA testing with karyotyping in the evaluation of 532 cases of IUFD.[30] Of the karyotypes attempted, 375 (70.5%) yielded a result. Of those, 31 (8.3%) of 375 were classified as abnormal, with trisomy 21 (n=9), trisomy 18 (n=8), trisomy 13 (n=2), and monosomy X (n=5) representing the most common abnormalities. CMA testing yielded results in 465 (87.4%) of samples, significantly more than were successfully karyotyped (p<.001). Of those, 32 (6.9%) were aneuploidy, 12 (2.6%) were considered a pathogenic variant, and 25 (5.4%) were considered a VUS. Nine pathogenic variants on CMA testing were detected in stillbirths with normal karyotypes. CMA testing detected aneuploidy in 7 cases of the 157 in which karyotyping was unsuccessful.

Harris et al (2011) reported rates of structural abnormalities detected with array CGH-based CMA in IUFD after 22 weeks of gestation.[31] From a cohort of 54 stillbirths, 29 were prospectively determined to be “unexplained” and determined to have a normal conventional karyotype. Of those, 24 novel CNVs were detected.

Raca et al (2009) evaluated the yield of CMA testing in a sample of stillborn fetuses from the Wisconsin Stillbirth Service Program, a statewide repository of data on IUFD cases, which includes tissue samples for 573 cases from 1994 to 2002.[32] The authors identified 26 cases with tissue or cell samples available that met the following criteria: (1) the cause of death was thought to have been fetal, (2) the fetal phenotype suggested that a chromosomal imbalance might be present because of the presence of multiple congenital anomalies (at least 2 abnormalities of 2 different organs or parts of the body); and (3) cytogenetic results were either normal or were not obtained due to culture failure. In 15 cases with good-quality DNA available for analysis, aCGH detected 2 abnormalities (trisomy 21 and an unbalanced translocation between chromosomes 3 and 10).

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials.

Changes in management that could result from CMA testing include changes in additional testing to evaluate for causes of a pregnancy loss or changes in the management of future pregnancies, such as the decision to undertake preimplantation genetic testing. No empirical studies identified evaluated changes in management that occurred as a result of CMA testing in miscarriage or IUFD.

In addition, no studies identified addressed whether CMA testing of POC is associated with changes in management or future successful pregnancies.

Chain of Evidence
Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Changes in Patient Management Following CMA Testing
One argument for genetic evaluation (karyotype or CMA) in POC in cases of recurrent pregnancy loss is that an abnormal genetic evaluation could forestall an evaluation for other causes of recurrent pregnancy loss, which might include assessment of the uterine cavity, thyroid function testing, and testing for antiphospholipid antibodies. As described above in Maslow et al (2015), the testing yield using an SNV microarray in recurrent pregnancy loss was higher than the yield of other recommended testing (some of which are potentially invasive).[24.] Bernardi et al (2012) developed a decision analytic model to compare the cost of 2 strategies for recurrent pregnancy loss evaluation: (1) selective recurrent pregnancy loss evaluation, defined as an evaluation if the second miscarriage is euploid; or (2) universal recurrent pregnancy loss evaluation, defined as recurrent pregnancy loss evaluation after the second miscarriage of fewer than 10 weeks of size.[33.] Genetic analysis in the study's decision model in the "selected" recurrent pregnancy loss evaluation was stepwise, beginning with cytogenetic analysis. If the cytogenetic testing results were abnormal, no further evaluation would be needed. If the results were consistent with an unbalanced translocation, cytogenetic analysis of the parents would be indicated. If results on cytogenetics were consistent with 46 XX, microsatellite analysis would be indicated to evaluate for maternal cell contamination. If the 46 XX result was of maternal origin, CGH of stored miscarriage tissue would be indicated. Similarly, if there was no result from the cytogenetic analysis, CGH of stored miscarriage tissue would be indicated. If results on CGH were consistent with an unbalanced translocation, cytogenetic analysis of the parents would be indicated. If results were consistent with normal 46 XY on either karyotype or CGH or confirmed fetal normal 46 XX on karyotype or CGH, or an unbalanced translocation, further workup for recurrent pregnancy loss would be indicated.

Although this decision analysis suggests a way in which CMA of POC could be used in an algorithm to determine testing for recurrent pregnancy loss, it does not demonstrate that use of CMA analysis will improve outcomes. Further research evaluating the implementation of such a decision tool in practice is needed.

Improvement in Patient Outcomes Following CMA Testing
There are several potential health-related outcomes resulting from CMA testing POC in pregnancy loss. Knowledge of the cause of the loss may lead to reduced parent distress or anxiety. For couples with recurrent pregnancy loss, preimplantation genetic diagnosis with transfer of unaffected embryos or the use of donor gametes might be considered for therapy. No studies were identified that reported whether the use of CMA is associated with changes in parental mental health outcomes.

Section Summary: Pregnancy Loss with Indications for Embryonic or Fetal Genetic Analysis
The evidence on the clinical validity of CMA testing comes primarily from studies that have compared genetic testing results from CMA with conventional karyotype, and from several

studies that have evaluated the yield of CMA in patients with a normal or unsuccessful karyotype. These studies have suggested that CMA has good concordance with karyotype for detection of aneuploidy and is more likely to yield results than conventional karyotyping given the need for cell culture for karyotyping. Studies on the testing yield in early pregnancy losses have suggested that aneuploidies are the most common abnormality detected, and CMA may detect abnormalities not detected on karyotype. Relatively few studies have reported CMA outcomes in late pregnancy losses, but they do suggest that CMA testing is more likely to yield a result than conventional karyotyping. No studies identified have directly demonstrated how CMA testing would change management outcomes; however, based on a chain of evidence, there are several ways in which CMA testing of fetal tissue in pregnancy losses could have clinical utility, including leading to changes in diagnostic testing, reduced parental distress, or preimplantation genetic diagnosis.

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 suggests that CMA has a high rate of concordance with karyotyping. For both early and late pregnancy loss, CMA is more likely to yield a result than karyotyping. Other studies have reported that CMA detects a substantial number of abnormalities in patients with normal karyotypes, but most 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 a miscarriage or IUFD 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. The potential for clinical utility for 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. While no studies identified directly demonstrated whether or how patient management is changed based on CMA testing of POC from early or late pregnancy losses, or how patient outcomes are improved, the available evidence suggests that, for situations in which a genetic evaluation is indicated, CMA would be expected to perform as well as or better than standard karyotyping. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

ONGOING AND UNPUBLISHED CLINICAL TRIALS

A search of ClinicalTrials.gov did not identify any ongoing or unpublished trials that would likely influence this review.

SUPPLEMENTAL INFORMATION

CLINICAL INPUT RECEIVED 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, BCBSA received input on the policy 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 consensus that CMA testing is medically necessary in 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 yield of CMA testing 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

In 2016 (reaffirmed in 2023), 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.[34] The guidelines made the following recommendations and conclusions regarding the use of CMA:

- "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 a committee opinion on the evaluation and treatment of recurrent pregnancy loss.[1] The statement makes 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-β2 glycoprotein I.
  - Sonohysterogram, hysterosalpingogram, and/or hysteroscopy.
  - Screening for thyroid and prolactin abnormalities.
- Karyotypic analysis of POC may be useful in the setting of ongoing therapy for recurrent pregnancy loss.

Government Regulations

National:

There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

Local:

There is no local coverage determination (LCD).

Related Policies

Genetic Testing, Including Chromosomal Microarray and Next-Generation Sequencing Panels, for the Evaluation of Children With Developmental Delay/Intellectual Disability or Autism Spectrum Disorder, and/or Congenital Anomalies

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The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through November 2023, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
11/1/15	8/18/15	9/14/15	Joint policy established
7/1/16	4/19/16	4/19/16	Routine policy maintenance. Updated references and rationale sections. No change in policy status.
7/1/17	4/18/17	4/18/17	Routine maintenance. No change in policy status.
3/1/18	12/12/17	12/12/17	Routine policy maintenance, updated references. Medical policy statement changed to include coverage for testing in first and second trimesters.
3/1/19	12/11/18		Routine policy maintenance, No change in policy status.
3/1/20	12/17/19		Routine policy maintenance. No change in policy status.
3/1/21	12/15/20		Routine policy maintenance, References #3, 12, and 13 added. No change in policy status.
3/1/22	12/14/21		Updated rationale, added reference #15. Added code 0252U as E/I. No change in policy status.
3/1/23	12/20/22		Added codes 81228, 81229, 88261-88263, 88271, 81349, 81277 and 0156U. Routine policy maintenance, no change in policy status.
3/1/24	12/19/23		Rationale updated, reference #14 added. No change in policy status. Vendor managed: N/A (ds)

Next Review Date: 4th Qtr. 2024

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: GENETIC TESTING-CHROMOSOMAL MICROARRAY TESTING FOR THE EVALUATION OF EARLY PREGNANCY LOSS AND INTRAUTERINE FETAL DEMISE

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Covered; criteria apply
BCNA (Medicare Advantage)	See government section
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.