

## ***Genetic Testing for the Evaluation of Products of Conception and Pregnancy Loss***

**Effective:** July 1, 2021

**Next Review:** April 2022

**Last Review:** May 2021

### **IMPORTANT REMINDER**

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

### **DESCRIPTION**

Aneuploidy testing of products of conception, including fetal tissue or placental tissue, using chromosomal microarray (CMA) or next-generation sequencing (NGS) may be performed to evaluate the cause of isolated and recurrent early pregnancy loss (miscarriages) and later pregnancy loss (intrauterine fetal demise [IUFD]).

### **MEDICAL POLICY CRITERIA**

**Note:** Please refer to the Cross References section below for genetic testing not addressed in this policy, including but not limited to, whole exome or genome sequencing, preimplantation diagnosis or screening, carrier screening, and single-gene testing.

- I. Chromosomal microarray (CMA) testing of fetal tissue, a formed fetus, or placental tissue derived from the fetus may be considered **medically necessary** when any of the following criteria are met:
  - A. In cases of pregnancy loss at less than or equal to 20 weeks of gestation when there is a maternal history of recurrent pregnancy loss, defined as having two or more consecutive clinical pregnancy losses; or

- B. In all cases of pregnancy loss after 20 weeks of gestation.
- II. The use of CMA testing for products of conception or for pregnancy loss is considered **investigational** when Criterion I. above is not met.
- III. The use of next-generation sequencing (NGS) aneuploidy testing for products of conception or for pregnancy loss is considered **investigational**.

*NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.*

## POLICY GUIDELINES

### DEFINITIONS

Fetal tissue may consist of fetal tissue, a formed fetus, or placental tissue derived from the fetus, depending on the stage of pregnancy at the time of the fetal loss.

Early pregnancy loss or miscarriage is considered to be a pregnancy loss that occurred at or before 20 weeks of gestational age.<sup>[1, 2]</sup>

## LIST OF INFORMATION NEEDED FOR REVIEW

In order to determine the clinical utility of gene test(s), all of the following information must be submitted for review. If any of these items are not submitted, it could impact our review and decision outcome:

1. Name of the genetic test(s) or panel test
2. Name of the performing laboratory and/or genetic testing organization (more than one may be listed)
3. The exact gene(s) and/or variant(s) being tested
4. Relevant billing codes
5. Brief description of how the genetic test results will guide clinical decisions that would not otherwise be made in the absence testing
6. Medical records related to this genetic test:
  - History and physical exam including any relevant diagnoses related to the genetic testing
  - Conventional testing and outcomes
  - Conservative treatments, if any

## CROSS REFERENCES

1. [Preimplantation Genetic Testing of Embryos](#), Genetic Testing, Policy No. 18
2. [Genetic and Molecular Diagnostic Testing](#), Genetic Testing, Policy No. 20
3. [Noninvasive Prenatal Testing to Determine Fetal Aneuploidies and Microdeletions using Cell-Free DNA](#), Genetic Testing, Policy No 44
4. [Chromosomal Microarray Analysis \(CMA\) or Copy Number Analysis for the Genetic Evaluation of Patients with Developmental Delay, Intellectual Disability, Autism Spectrum Disorder, or Congenital Anomalies](#), Genetic Testing, Pol. No. 58
5. [Evaluating the Utility of Genetic Panels](#), Genetic Testing, Policy No. 64
6. [Whole Exome and Whole Genome Sequencing](#), Genetic Testing, Policy No. 76
7. [Invasive Prenatal \(Fetal\) Diagnostic Testing Using Chromosomal Microarray Analysis \(CMA\)](#), Genetic Testing, Policy No. 78
8. [Reproductive Carrier Screening for Genetic Diseases](#), Genetic Testing, Policy No. 81

### PREGNANCY LOSS: ETIOLOGY AND EVALUATION

#### Early Pregnancy Loss

Pregnancy loss is common, occurring in at least 15% to 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. 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 (POC) are examined, it is estimated that 60% of early pregnancy losses are associated with chromosomal abnormalities, particularly trisomies and monosomy X.<sup>[2, 3]</sup> 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.<sup>[1]</sup> 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% to 6% for cytogenetic abnormalities, 8% to 42% for antiphospholipid antibody syndrome, and 1.8% to 37.6% for uterine abnormalities.<sup>[2]</sup> 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 undertake an evaluation 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 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 ASRM state 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.” Finally, among patients FA who are found to have a potential nongenetic 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.<sup>[4]</sup>

Genetic testing of POC, if possible, is recommended by several reproductive health organizations. A committee opinion from ASRM recommends that the assessment of recurrent pregnancy loss include peripheral karyotyping of the parents and states that karyotypic analysis of POC may be useful in the setting of ongoing therapy for recurrent pregnancy loss.<sup>[2]</sup> The National Society of Genetic Counselors convened a multidisciplinary Inherited Pregnancy Loss Working Group. It recommended that, for the genetic evaluation of couples with recurrent pregnancy loss, when possible, chromosomal analysis on fetal tissue from POC should be pursued.<sup>[3]</sup>

## 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 1,000 births in the United States, representing about 60% of perinatal mortality. IUFD 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, although, in many cases, the precise cause is unidentifiable. Chromosomal or genetic abnormalities can be found in 8% to 13% of IUFD, most commonly aneuploidies. In one large series of IUFD (n=1,025), cytogenic abnormalities were detected in 11.9%.<sup>[5]</sup>

The American College of Obstetrics and Gynecology recommends that evaluation after an IUFD includes examination of the stillborn fetus, along with examination of the placenta and umbilical cord and genetic testing for all IUFD (after parental permission is obtained). Other evaluation should be based on maternal history and may include evaluation for thyroid disorders, systemic lupus erythematosus, and infections.<sup>[6]</sup>

Some motivations for evaluation for a cause of IUFD are similar to those for earlier pregnancy loss. Although both early and later pregnancy losses may cause grief for the mother and her family, IUFD can be particularly devastating. Information about the cause of the pregnancy loss may be important in counseling women about their recurrence risk. In low-risk women with an unexplained IUFD, the risk of recurrence is 7.8 to 10.5 of 1,000 live births, but this increases to 21.8 per 1,000 live births in women with a history of fetal growth restriction. Identification of a heritable genetic variant in a fetus may prompt testing in the parents; if a heritable variant is identified, parents may pursue preimplantation genetic diagnosis in future pregnancies.

## GENETIC ABNORMALITIES IN MISCARRIAGE AND IUFD

Genetic disorders are generally categorized into three main groups: single gene, chromosomal, and multifactorial. Single-gene disorders (also known as monogenic disorders) result from errors in a specific gene, whereas those that are chromosomal include larger aberrations that are numerical or structural. Evidence about 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 12% of IUFD.<sup>[7]</sup> Rates of single-gene disorders in IUFD are less well-quantified. However, of stillborn fetuses who undergo 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.

Traditionally, genetic evaluation of the POC after a miscarriage is conducted by karyotyping of metaphase cells after 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 Mb), so smaller genetic variants may not be detected. In addition, karyotype requires culturing the target cells, which may fail or be infeasible, particularly for formalin-preserved samples. In addition, 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 one study that included 103 first trimester miscarriages, culture failure occurred in 25% of cases.<sup>[8]</sup>

## **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.

### **Types of Chromosomal Microarray Analysis Technologies**

Several types of microarray technology are in current clinical use, primarily aCGH and single-nucleotide polymorphism (SNP) microarrays. Comparative genomic hybridization (CGH) chromosomal microarray analysis (CMA) analysis 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. The reference DNA and the unknown sample are labelled with different fluorescent tags, and both samples are cohybridized 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.

In SNP-based CMA testing, a microarray of SNPs, which may include hundreds of thousands of SNPs, 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 specific 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 included. 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 the characterization of large numbers of genes, but with the downside that analysis may identify large numbers of CNVs of undetermined significance.

### **CMA Compared with Karyotyping**

CMA 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. SNP-based CMA, in addition to detecting deletions and duplications, can detect runs of homozygosity, which suggests consanguinity, triploidy, and uniparental disomy.

CMA also has the advantage of not requiring 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 of 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.

CMA has the disadvantage of higher rates of detection of variants of uncertain significance. The American College of Medical Genetics (ACMG) has published guidelines on the interpretation and reporting of CNVs in the postnatal setting. ACMG recommends that laboratories performing array-based assessment of CNVs track their experience with CNVs and document pathogenic CNVs, CNVs of uncertain significance, and CNVs determined to represent benign variation based on comparisons with internal and external databases.<sup>[9]</sup>

## **NEXT-GENERATION SEQUENCING**

Next-generation sequencing (NGS) is a method that uses massively parallel sequencing of small fragments of DNA to allow the rapid sequencing of large stretches of DNA. NGS assays have been developed to detect aneuploidies.

## **COMMERCIALLY AVAILABLE TESTS**

Natera Inc. (San Carlos, CA) offers the Anora<sup>®</sup> miscarriage test, which uses a SNP-based array system for testing of POC. 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 POC 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,<sup>[10]</sup> 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 "is clinically validated to detect whole chromosome aneuploidy, triploidy, tetraploidy, uniparental disomy, and deletions and duplications greater than 5 Mb. Terminal deletions or duplications and clinically significant deletions and duplications down to 1 Mb are also reported."<sup>[11]</sup>

Invitae offers the Invitae Pregnancy Loss Chromosomal Microarray Analysis, Arup Laboratories offers the Genomic SNP Microarray, Products of Conception, and the Mayo Clinic offers the Chromosomal Microarray, Autopsy/Products of Conception/Stillbirth, Tissue.<sup>[12-14]</sup>

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

Igenomix offers a product-of-conception test that uses NGS technology for aneuploidy testing.

## **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). The Anora<sup>®</sup> miscarriage test, the CombiSNP<sup>™</sup> Array for Pregnancy Loss, the CombiBAC<sup>™</sup> Array, and the GeneDx Whole Genome Chromosomal Microarray for Products of Conception, along with other chromosomal microarray analysis testing platforms currently available are LDTs available under the auspices of 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 these tests.

## EVIDENCE SUMMARY

Human Genome Variation Society (HGVS) nomenclature<sup>[15]</sup> is used to describe variants found in DNA and serves as an international standard. It is being implemented for genetic testing medical evidence review updates starting in 2017. According to this nomenclature, the term “variant” is used to describe a change in a DNA or protein sequence, replacing previously-used terms, such as “mutation.” Pathogenic variants are variants associated with disease, while benign variants are not. The majority of genetic changes have unknown effects on human health, and these are referred to as variants of uncertain significance.

### CHROMOSOMAL MICROARRAY ANALYSIS

The use of chromosomal microarray analysis (CMA) for the evaluation of products of conception and pregnancy loss has been established as standard of care primarily due to clinical consensus for the following situations:

- pregnancy loss after 20 weeks of gestation
- pregnancy loss less than or equal to 20 weeks of gestation when there is a maternal history of recurrent pregnancy loss

Therefore, evidence for the above indications with medical necessity criteria will no longer be reviewed. Only situations considered investigational will be reviewed for evidence.

Although the clinical validity of most diagnostic genetic tests are evaluated based on their ability to diagnosing clinically defined disease, for the purposes of assessment of POC, the diagnosis of a known chromosomal or genetic abnormality in the setting of pregnancy loss may serve as a surrogate end point. The results of CMA 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.

### Diagnostic Accuracy of CMA

Martinez-Portilla (2019) published results from a systematic review and meta-analysis of seven studies assessing the added value of CMA over conventional karyotyping during a stillbirth work-up (i.e., fetal loss after 20 weeks of gestation).<sup>[16]</sup> The studies included 1,443 fetal losses, of which 903 (63%) were stillbirths with a normal karyotype. A total of 1,057 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 two of the studies to have a high risk of bias - one 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.

In a 2017 systematic review, Pauta evaluated the added value of CMA analysis over karyotyping in early pregnancy loss.<sup>[17]</sup> Twenty-three studies were published between January 2000 and April 2017 that met the inclusion criteria. This included 5,520 pregnancy losses up to 20 weeks. When CMA and karyotyping were performed concurrently, informative results were provided by CMA in 95% (95% CI 94 to 96%) of cases and by karyotyping in 67% (95% CI 64 to 70%) of cases. The incremental yield of pathogenic CNV by CMA over karyotyping was 2%.

In 2014, Dhillon reported results from a systematic review and meta-analysis of studies that compared CMA with conventional karyotyping in the evaluation of miscarriage.<sup>[18]</sup> The authors included nine studies that reported results from CMA on POC following miscarriage alongside conventional karyotyping. Overall, there were 314 miscarriage samples in the included studies. One study was included that assessed 41 cases of spontaneous pregnancy loss <20 weeks of gestation, and two studies assessed first-trimester spontaneous miscarriage (n=14, 86). These studies were not analyzed separately for the others. In 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 (Cochrane Q, I<sup>2</sup>=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 variants of uncertain significance [VOUS or VUS]). Conventional karyotyping detected 3% (95% CI 1.0% to 10.0%) additional abnormalities not detected by CMA. Among five studies that reported VOUS, the pooled chance of having a VOUS was 2% (95% CI 1.0% to 10.0%). This systematic review demonstrated good overall agreement between CMA and karyotype in the analysis of miscarriage specimens. However, the CI around the estimate of VOUS rate was large, indicating uncertainty regarding the true rate. Further research is required to determine whether CNVs found in POC are pathogenic or benign.

A number of additional studies not included in the above systematic reviews have compared CMA with karyotyping.

Popescu (2018) reported on a single-center prospective cohort study of 100 patients.<sup>[19]</sup> The study compared the percent of patients that learned a cause of recurrent pregnancy loss from the standard American Society for Reproductive Medicine (ASRM) evaluation, which included karyotyping, for recurrent miscarriage versus from ASRM evaluation plus CMA evaluation. Patients with two or more pregnancy losses. A definite or probable cause of pregnancy loss was identified in 95% of patients with ASRM plus CMA evaluation. The ASRM workup alone identified probable cause of pregnancy loss in 45% of patients whereas the CMA evaluation alone identified probable cause of pregnancy loss in 67% of patients. The final 5% of patients did not have a probable or definitive cause of pregnancy loss identified.

In 2014, Lathi reported results from a comparison of a SNP-based array with informatics assistance ("Parental Support" algorithm previously described) with conventional karyotyping in 30 first-trimester miscarriage samples.<sup>[20]</sup> CMA was conducted using a single-nucleotide polymerase (SNP)-based microarray, which measures about 300,000 SNPs across the



genome (approximately one SNP every 10 Kb). The “Parental Support” technique compares 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 karyotype were confirmed to be from fetal tissue on microarray analysis. Four samples were discordant between CMA and karyotype, including one case of whole genome duplication and one balanced translocation, both of which would not be expected to be detected on microarray, and two additional discrepancies that were attributed to sampling error, tissue mosaicism, or culture artifact.

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

## **Yield of CMA in Pregnancy Loss**

### CMA in Early Pregnancy Loss

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

In 2014, Lathi reported results of a retrospective analysis of the use of CMA in detecting maternal cell contamination on conventional karyotyping in 1,222 POC samples from first-trimester miscarriages that were evaluated at the Natera laboratory from January 2010 to August 2011.<sup>[10]</sup> The POC samples, along with maternal peripheral blood samples, were evaluated with a SNP-based CMA. When CMA results for the POC were 46 XX, a comparison with the maternal genotype fingerprint allowed investigators to determine if 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 may improve accurate detection of fetal chromosomal abnormalities.

Viaggi (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.<sup>[22]</sup> Frozen samples were evaluated with aCGH with a resolution of 100 Kb. CNVs were compared with those present in the Database of Genomic Variants (<http://projects.tcag.ca/variation>), Decipher (<http://decipher.sanger.ac.uk>), and the Database of Human CNVs (<http://gvarianti.homelinux.net/gvarianti/index.php>) 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 of the 45 CNVs identified (68%) were defined as common CNVs. When the CNVs were compared with control CNVs

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

Doria (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.<sup>[23]</sup> Tissue culture and karyotype was attempted on all specimens; samples that could not be karyotyped were tested with aCGH, followed by additional confirmation with fluorescence in situ hybridization (FISH) confirmation. Culture failure occurred in 25.4% of the cases. Of the 173 (74.6%) with valid karyotypes, 66 of 173 (38.2%) were abnormal: 62 of 66 with numerical abnormalities (single, double, or triple trisomies, monosomy X, polyploidy, or mosaicism), and five of 66 with structural abnormalities. Array CGH was performed in 58 of 59 cases with culture failure (1 case with insufficient DNA for CGH). Fifteen of the 58 cases were abnormal, with three cases of monosomy X, one case of XY with gain for X, seven cases of trisomy 15, two cases of trisomy 16, and one case each of trisomy 18 and 21. With the addition of FISH testing, four new cases of triploidy were detected. This study suggests that the use of aCGH increases the yield of testing of genetic testing of POC beyond that of standard karyotyping.

Benkhalifa (2005) evaluated 26 samples from first-trimester miscarriages that failed to divide in routine cytogenetic studies with array used CMA methods with array CGH.<sup>[24]</sup> 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 instance of monosomy 16 and two instances of monosomy X.

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

Gou (2020) evaluated POC using CMA in 222 specimens. There was a 40.54% overall detection rate for clinically significant chromosomal anomalies.<sup>[25]</sup> Of these, 53 (23.87%) were autosomal aneuploidy, 16 (7.21%) were sex chromosome aneuploidy, 5 (2.25%) were multiple aneuploidy, 4 (1.80%) were triploidy, and 12 (5.41%) were pathogenic copy number variants (pCNVs). Total chromosomal abnormality, autosomal aneuploidy, sex chromosome aneuploidy, multiple aneuploidy, and triploidy detection rates were higher in early versus late pregnancy loss, whereas the reverse was true for pCNV detection rate.

In 2016, Wang reported on a prospective study assessing the clinical application of CMA testing for first-trimester pregnancy loss, successfully analyzing 551 fresh miscarriage specimens using single-nucleotide polymorphism (SNP) array.<sup>[26]</sup> Among the specimens, 2.9% (16/551) had significant maternal cell contamination and were excluded from the study. Clinically significant chromosomal abnormalities were identified in 295 (55.1%) cases, including 214 (40%) with aneuploidy, 40 (7.5%) with polyploidy, 19 (3.6%) with partial aneuploidy, 12 (2.2%) with pathogenic microdeletion/microduplication, and 10 (1.9%) with uniparental isodisomy (isoUPD). Variants of uncertain significance were obtained in 15 cases (2.8%). The authors concluded that SNP array is a reliable, robust, and high-resolution technology for genetic diagnosis of miscarriage in clinical practice.

In 2016, Wou reported on a three-year retrospective study that analyzed tissue from products of conception and perinatal losses using QF-PCR and microarray. CMA was performed mostly in samples with normal QF-PCR results.<sup>[27]</sup> Of the 1071 informative specimens analyzed, 30.8% (n=330) were positive for chromosomal abnormalities, with 57.6% (n 190) of the abnormalities being detected by QF-PCR and 42.4% (n=140) by aCGH. In addition high-resolution aCGH enabled an additional diagnostic yield of 36 cases of microdeletions and/or microduplications (10.9%) in specimens found to be abnormal by QF-PCR and 3.4% of all successfully analyzed specimens. Gestational age was known in 940 specimens. The study reported that the highest rate of chromosomal abnormalities (a combined analysis of QF-PCR and aCGH abnormalities) was observed in the first trimester (<12 weeks) with 67.6% being considered pathogenic. The difference in proportions of pathogenic findings across trimesters was statistically significant ( $p < 0.001$ ) with the greater proportion of findings being in the first trimester.

In 2015, Maslow evaluated the yield of SNP-based array for determining chromosome number in paraffin-fixed POC compared with a standard evaluation for couples with recurrent first-trimester pregnancy losses.<sup>[28]</sup> Eligible patients previously had analysis of chromosome number and screening tests recommended by the American Society for Reproductive Medicine (ASRM) 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. SNP-based microarray was able to determine a fetal chromosome number in 44 of 62 (71%) of samples, 25 (57%) of which were noneuploid. Recurrent pregnancy loss screening was normal in 35 of 42 (83%) participants. The detection rate for any cause of pregnancy loss was significantly higher with SNP microarray (0.50; 95% CI 0.36 to 0.64) than with the ASRM-recommended recurrent pregnancy loss evaluation (0.17; 95% CI 0.08 to 0.31,  $p=0.002$ ).

Also in 2015, Romero reported on types of genetic abnormalities found on CMA in early pregnancy losses (<20 weeks of gestation) among 86 women.<sup>[29]</sup> Thirteen (14.9%) of POC samples were excluded because placental villi or fetal tissue could not be identified with certainty and nine were excluded due to complete maternal cell contamination, leaving a sample of 64 for analysis. The overall prevalence of aneuploidy and pathogenic CNV or VOUS was 43.8% (28/64). Excluding the two cases with VOUS, 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 ( $p<0.01$ ). Aneuploidy was the most common abnormality, occurring in 37.5% (24/64) cases.

Levy (2014) reported results of SNP microarray analysis of 2447 consecutively received POC samples, of which 2400 were fresh samples.<sup>[30]</sup> 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 the 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 VOUS.

In 2014, Mathur reported 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.<sup>[31]</sup> All women had a history of recurrent pregnancy loss, defined as two or more

ultrasound-documented miscarriages at less than 10 weeks of gestation. Samples were evaluated with CGH; if results were 46 XX, the genotype of the POC was compared with the maternal genotype at several highly polymorphic loci through microsatellite analysis (MSA) to determine if the 46 XX results were consistent with maternal cell contamination. Sixteen samples (21%) yielded uninformative results due to minimal pregnancy tissue (n=9), poor quality DNA (n=2), or confirmed maternal cell contamination (n=2). CGH was considered informative in 61 cases (79%), with 22 noneuploid and 39 euploid. Thirty-three of the euploid specimens were 46 XX, 11 of which were not sent for reflex MSA. The author concluded that CMA testing of preserved POC is technically feasible, including in cases where karyotyping had failed due to cell growth failure, which had occurred in eight samples evaluated.

Warren (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).<sup>[32]</sup> 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 against 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 CGH 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 Kb for more accurate characterization. DNA was successfully isolated in 30 cases (all from the fresh tissue samples). De novo CNVs were detected in six of the 30 (20%) cases using the bacterial artificial chromosome array and confirmed in four of 30 (13%) cases using the oligonucleotide array.

### CMA in IUFD

The use of CMA for evaluating products of conception for IUFD is documented in a number of large nonrandomized studies. In studies that used CMA on samples that had been previously found to have normal karyotypes, approximately 13% were found to have pathogenic results via CMA testing.<sup>[33, 34]</sup>

In a large study that compared CMA with karyotype in the evaluation of 532 cases of IUFD.<sup>[35]</sup> Of the karyotypes attempted, 375 (70.5%) yielded a result. Of those, 31 of 375 (8.3%) 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 yielded results in 465 (87.4%) of samples, significantly more than were successfully karyotyped (p<0.001). Of those, 32 (6.9%) were aneuploidy, 12 (2.6%) were considered a pathogenic variant, and 25 (5.4%) were considered a VOUS. Nine pathogenic variants on CMA were detected in stillbirths with normal karyotypes. CMA detected aneuploidy in seven cases of the 157 in which karyotyping was unsuccessful.

### Section Summary

The evidence related to the validity of CMA testing of products of conception comes primarily from studies that compared genetic testing results from CMA with conventional karyotype, and from several studies that evaluated the yield of CMA in patients with a normal or unsuccessful karyotype. These studies suggest 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 yield of testing in early pregnancy losses suggests that aneuploidies are the most common abnormality detected, CMA may detect abnormalities not detected on karyotype. Relatively few studies have reported CMA outcomes in late pregnancy losses, but they suggest that CMA is more likely to yield a result than conventional karyotyping.

### **Changes in Patient Management and Outcomes Following CMA**

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.

One argument for genetic evaluation (karyotype or CMA) in POC in cases of recurrent pregnancy loss is that an abnormal genetic evaluation would potentially 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. In the study by Maslow (described above), the yield of testing using a SNP microarray in recurrent pregnancy loss was higher than the yield of other recommended testing (some of which are potentially invasive).<sup>[28]</sup>

Several potential health-related outcomes result from CMA testing POC in pregnancy loss. These outcomes are the same for both early and late 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 identified reported whether the use of CMA is associated with changes in parental mental health outcomes or management of future successful pregnancies.

### **Section Summary**

Although there are several ways in which CMA of fetal tissue in early pregnancy loss may change management and outcomes, including leading to changes in diagnostic testing, reduced parental distress, or preimplantation genetic diagnosis, no studies identified directly demonstrated changes in outcomes.

### **NEXT-GENERATION SEQUENCING ANEUPLOIDY TESTING**

Tamura (2021) evaluated 279 cases of spontaneous abortion for aneuploidy using NGS.<sup>[36]</sup> Chorionic villi were separated from the POC for analysis. Seven samples were also analyzed with G-banding karyotyping. Of these, five were analyzed (one was excluded for culture failure and one for maternal cell contamination) and all were consistent with G-banding. Of the 279 cases analyzed with NGS, 61 (21.9%) were normal karyotype, 186 (66.7%) showed chromosomal abnormality, and 32 (11.5%) did not show distinct chorionic villi in POC specimens. Of the cases with abnormal findings, there were 172 (61.6%) cases of aneuploidy (autosomal trisomy and sex chromosome aneuploidy), 8 (2.9%) cases of segmental aneuploidy (duplication and deletion), and 6 (2.2%) cases of mosaicism, indicating that more than half of the cases in this study were chromosomally abnormal.

Xu (2020) compared the performance of traditional G-banding karyotyping with NGS for detecting common trisomies in POC.<sup>[37]</sup> A total of 28 miscarriage samples were tested via high-resolution G-banding karyotyping and NGS, while 20 samples were analyzed with NGS alone. Multiplex PCR was also used to monitor maternal cell contamination (MCC), chromosomal status, and sex. NGS identified all 21 abnormalities which were found in karyotype examination. Specificity and sensitivity of NGS combined with multiplex PCR was 100% for both normal (7/7) and abnormal (21/21) results.

Fan (2020) evaluated 1,010 POC from first-trimester pregnancy loss with NGS for chromosomal abnormalities.<sup>[38]</sup> Four samples were excluded to due maternal cell contamination. Benign CNVs were considered to be normal chromosomal variants. Chromosomal variants were detected in 634 cases. Of these, 383 were aneuploidy (60.4%), 44 were polyploidy (6.9%), 35 were mosaicisms (5.5%), 19 were benign CNVs (3.0%), 52 were pathogenic CNVs (8.2%), and 101 were VOUS CNVs (16%). Advanced maternal age was associated with a sharp increase in frequency of aneuploidy, both for sporadic abortion (with 71 of 121 age  $\geq 35$  presenting with aneuploidy vs. 155 of 432 for under 35) and for recurrent miscarriage (with 49 of 104 age  $\geq 35$  presenting with aneuploidy vs. 108 of 349 for under 35).

## **SUMMARY OF EVIDENCE**

The evidence for the use of chromosomal microarray analysis (CMA) testing of fetal tissue in individuals who have pregnancy loss 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, although the precise yield is uncertain and likely varies based on gestational age. Rates of variants of unknown 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 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 pregnancy loss at 20 weeks gestation or less in recurrent pregnancy loss, and after 20 weeks gestation in pregnancy loss, CMA would be expected to perform as well as or better than standard karyotyping.

The evidence for the use of next-generation sequencing (NGS) aneuploidy testing of fetal tissue in individuals who have pregnancy loss is limited. While there is some research to suggest that it performs similarly to karyotyping, sample sizes are small and more research is needed to know for sure.

## **PRACTICE GUIDELINE SUMMARY**

### **AMERICAN COLLEGE OF OBSTETRICS AND GYNECOLOGISTS**

In 2016 (and reaffirmed in 2020), the American College of Obstetrics and Gynecologists Committee (ACOG) on Genetics and the Society for Maternal-Fetal Medicine published a joint

committee opinion (No. 682) on the use of CMA testing in obstetrics and gynecology, stating the following:<sup>[39]</sup>

“Chromosomal microarray analysis of fetal tissue (ie, amniotic fluid, placenta, or products of conception) is recommended in the evaluation of intrauterine fetal death or stillbirth when further cytogenetic analysis is desired because of the test’s increased likelihood of obtaining results and improved detection of causative abnormalities.”

In 2020, ACOG also published an obstetric care consensus on the management of stillbirth.<sup>[40]</sup> 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.<sup>[2]</sup> The statement makes the following conclusions about the evaluation of recurrent pregnancy loss:

- “Evaluation of recurrent pregnancy loss can proceed after two consecutive clinical pregnancy losses.”
- Assessment of recurrent pregnancy loss focuses on screening for genetic factors, which may include peripheral karyotype of the parents.
- “Karyotypic analysis of products of conception may be useful in the setting of ongoing therapy for recurrent pregnancy loss.”

### **ROYAL COLLEGE OF OBSTETRICIANS AND GYNAECOLOGISTS**

In 2011, the Royal College of Obstetricians and Gynaecologists issued guidelines on the evaluation and treatment of couples with recurrent first-trimester and second-trimester miscarriage.<sup>[41]</sup> 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 [nonanalytical studies, eg, case reports, case series]).

## **SUMMARY**

The research on chromosomal microarray analysis (CMA) testing of fetal tissue is limited. However, practice guidelines recommend CMA testing for pregnancy loss for certain individuals. Therefore, CMA testing may be considered medically necessary in cases of

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pregnancy loss at less than or equal to 20 weeks of gestation when there is recurrent pregnancy loss or pregnancy loss after 20 weeks of gestation.

There is not enough research to show that chromosomal microarray analysis (CMA) testing of fetal tissue is helpful for individuals that do not meet the policy criteria. Clinical guidelines only recommend testing for pregnancy loss at less than or equal to 20 weeks of gestation when there is recurrent pregnancy loss, or if there is pregnancy loss after 20 weeks of gestation. Therefore, this testing is considered investigational when policy criteria are not met.

There is not enough research to show that the use of next-generation sequencing (NGS) aneuploidy testing of fetal tissue for pregnancy loss improves health outcomes. No clinical guidelines based on research recommend this method of testing for pregnancy loss. Therefore, this testing is considered investigational.

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## REFERENCES

1. M Practice Committee of American Society for Reproductive. Definitions of infertility and recurrent pregnancy loss: a committee opinion. *Fertility and sterility*. 2013;99(1):63. PMID: 23095139
2. M Practice Committee of the American Society for Reproductive. Evaluation and treatment of recurrent pregnancy loss: a committee opinion. *Fertility and sterility*. 2012;98(5):1103-11. PMID: 22835448
3. MY Laurino, RL Bennett, DS Saraiya, et al. Genetic evaluation and counseling of couples with recurrent miscarriage: recommendations of the National Society of Genetic Counselors. *Journal of genetic counseling*. 2005;14(3):165-81. PMID: 15959648
4. OB Christiansen. Evidence-based investigations and treatments of recurrent pregnancy loss. *Current opinion in obstetrics & gynecology*. 2006;18(3):304-12. PMID: 16735831
5. FJ Korteweg, JJHM Erwich, A Timmer, et al. Evaluation of 1025 fetal deaths: proposed diagnostic workup. *American Journal of Obstetrics and Gynecology*. 2012;206(1):53.e1-53.e12. PMID:
6. ACOG Practice Bulletin No. 102: management of stillbirth. *Obstetrics and gynecology*. 2009;113(3):748-61. PMID: 19300347
7. RM Silver, MW Varner, U Reddy, et al. Work-up of stillbirth: a review of the evidence. *American Journal of Obstetrics and Gynecology*. 2007;196(5):433-44. PMID:
8. C Robberecht, V Schuddinck, JP Fryns, JR Vermeesch. Diagnosis of miscarriages by molecular karyotyping: benefits and pitfalls. *Genetics in medicine : official journal of the American College of Medical Genetics*. 2009;11(9):646-54. PMID: 19617844
9. HM Kearney, EC Thorland, KK Brown, F Quintero-Rivera, ST South. American College of Medical Genetics standards and guidelines for interpretation and reporting of postnatal constitutional copy number variants. *Genetics in medicine : official journal of the American College of Medical Genetics*. 2011;13(7):680-85. PMID:
10. RB Lathi, SL Gustin, J Keller, et al. Reliability of 46,XX results on miscarriage specimens: a review of 1,222 first-trimester miscarriage specimens. *Fertility and sterility*. 2014;101(1):178-82. PMID: 24182409
11. Natera. Anora Health Provider Information. [cited 4/27/2021]. Available from: <https://www.natera.com/womens-health/anora-miscarriage-test/>.
12. Invitae Pregnancy Loss Chromosomal Microarray Analysis. [cited 4/27/2021]. Available from: <https://www.invitae.com/en/pregnancy-loss-analysis/>.



13. Arup Laboratories Genomic SNP Microarray, Products of Conception. [cited 4/27/2021]. Available from: <https://ltd.aruplab.com/Tests/Pub/2005633>.
14. Mayo Clinic Laboratories Chromosomal Microarray, Autopsy/Products of Conception/Stillbirth, Tissue. [cited 4/27/2021]. Available from: <https://www.mayocliniclabs.com/test-catalog/Overview/62667>.
15. JT den Dunnen, R Dalgleish, DR Maglott, et al. HGVS Recommendations for the Description of Sequence Variants: 2016 Update. *Human mutation*. 2016;37(6):564-9. PMID: 26931183
16. RJ Martinez-Portilla, M Pauta, A Hawkins-Villarreal, et al. Added value of chromosomal microarray analysis over conventional karyotyping in stillbirth work-up: systematic review and meta-analysis. *Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology*. 2019;53(5):590-97. PMID: 30549343
17. M Pauta, M Grande, L Rodriguez-Revenga, E Kolomietz, A Borrell. Added value of Chromosomal Microarray Analysis (CMA) over karyotyping in Early Pregnancy Loss - a Systematic Review and Meta-Analysis. *Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology*. 2017. PMID: 29055063
18. RK Dhillon, SC Hillman, RK Morris, 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 : an international journal of obstetrics and gynaecology*. 2014;121(1):11-21. PMID: 23859082
19. F Popescu, CR Jaslow, WH Kutteh. Recurrent pregnancy loss evaluation combined with 24-chromosome microarray of miscarriage tissue provides a probable or definite cause of pregnancy loss in over 90% of patients. *Hum Reprod*. 2018;33(4):579-87. PMID: 29538673
20. RB Lathi, JA Massie, M Loring, et al. Informatics enhanced SNP microarray analysis of 30 miscarriage samples compared to routine cytogenetics. *PloS one*. 2012;7(3):e31282. PMID: 22403611
21. Y Hu, X Chen, LL Chen, ZF Xu, X Wang, H Cui. Comparative genomic hybridization analysis of spontaneous abortion. *International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics*. 2006;92(1):52-7. PMID: 16263126
22. CD Viaggi, S Cavani, M Malacarne, et al. First-trimester euploid miscarriages analysed by array-CGH. *Journal of applied genetics*. 2013;54(3):353-9. PMID: 23780398
23. S Doria, F Carvalho, C Ramalho, et al. An efficient protocol for the detection of chromosomal abnormalities in spontaneous miscarriages or foetal deaths. *European journal of obstetrics, gynecology, and reproductive biology*. 2009;147(2):144-50. PMID: 19740589
24. M Benkhalifa, S Kasakyan, P Clement, et al. Array comparative genomic hybridization profiling of first-trimester spontaneous abortions that fail to grow in vitro. *Prenatal diagnosis*. 2005;25(10):894-900. PMID: 16088865
25. L Gou, T Liu, Y Wang, et al. Clinical utilization of chromosomal microarray analysis for the genetic analysis in subgroups of pregnancy loss. *J Matern Fetal Neonatal Med*. 2020:1-8. PMID: 33228446
26. Y Wang, Q Cheng, L Meng, et al. Clinical application of SNP array analysis in first-trimester pregnancy loss: a prospective study. *Clinical genetics*. 2016. PMID: 27883173

27. K Wou, Y Hyun, D Chitayat, et al. Analysis of tissue from products of conception and perinatal losses using QF-PCR and microarray: A three-year retrospective study resulting in an efficient protocol. *European journal of medical genetics*. 2016;59(8):417-24. PMID: 27233578
28. BS Maslow, T Budinetz, C Sueldo, et al. Single-nucleotide polymorphism-microarray ploidy analysis of paraffin-embedded products of conception in recurrent pregnancy loss evaluations. *Obstetrics and gynecology*. 2015;126(1):175-81. PMID: 26241271
29. ST Romero, KB Geiersbach, CN Paxton, et al. Differentiation of genetic abnormalities in early pregnancy loss. *Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology*. 2015;45(1):89-94. PMID: 25358469
30. B Levy, S Sigurjonsson, B Pettersen, et al. Genomic imbalance in products of conception: single-nucleotide polymorphism chromosomal microarray analysis. *Obstetrics and gynecology*. 2014;124(2 Pt 1):202-9. PMID: 25004334
31. N Mathur, L Triplett, MD Stephenson. Miscarriage chromosome testing: utility of comparative genomic hybridization with reflex microsatellite analysis in preserved miscarriage tissue. *Fertility and sterility*. 2014;101(5):1349-52. PMID: 24636399
32. JE Warren, DK Turok, TM Maxwell, AR Brothman, RM Silver. Array comparative genomic hybridization for genetic evaluation of fetal loss between 10 and 20 weeks of gestation. *Obstetrics and gynecology*. 2009;114(5):1093-102. PMID: 20168112
33. JA Rosenfeld, ME Tucker, LF Escobar, et al. Diagnostic utility of microarray testing in pregnancy loss. *Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology*. 2015;46(4):478-86. PMID: 25846569
34. G Raca, A Artzer, L Thorson, et al. Array-based comparative genomic hybridization (aCGH) in the genetic evaluation of stillbirth. *American journal of medical genetics Part A*. 2009;149A(11):2437-43. PMID: 19876905
35. UM Reddy, GP Page, GR Saade, et al. Karyotype versus microarray testing for genetic abnormalities after stillbirth. *New England Journal of Medicine*. 2012;367(23):2185-93. PMID: 23215556
36. Y Tamura, M Santo, Y Araki, et al. Chromosomal copy number analysis of products of conception by conventional karyotyping and next-generation sequencing. *Reprod Med Biol*. 2021;20(1):71-75. PMID: 33488285
37. J Xu, M Chen, QY Liu, et al. Detecting trisomy in products of conception from first-trimester spontaneous miscarriages by next-generation sequencing (NGS). *Medicine (Baltimore)*. 2020;99(5):e18731. PMID: 32000376
38. L Fan, J Wu, Y Wu, et al. Analysis of Chromosomal Copy Number in First-Trimester Pregnancy Loss Using Next-Generation Sequencing. *Front Genet*. 2020;11:545856. PMID: 33193619
39. American College of Obstetricians, Gynecologists Committee on Genetics. Committee Opinion No. 682: Microarrays and Next-Generation Sequencing Technology: The Use of Advanced Genetic Diagnostic Tools in Obstetrics and Gynecology. Dec [cited 4/27/2021]. Available from: <https://www.acog.org/clinical/clinical-guidance/committee-opinion/articles/2016/12/microarrays-and-next-generation-sequencing-technology-the-use-of-advanced-genetic-diagnostic-tools-in-obstetrics-and-gynecology>.
40. TD Metz, RS Berry, RC Fretts, UM Reddy, MA Turrentine. Obstetric Care Consensus #10: Management of Stillbirth: (Replaces Practice Bulletin Number 102, March 2009). *Am J Obstet Gynecol*. 2020;222(3):B2-b20. PMID: 32004519

41. RCoOa Gynaecologists. Green Top Guideline No. 17: The Investigation and Treatment of Couples with Recurrent First-trimester and Second-trimester Miscarriage. [cited 4/27/2021]. Available from: [https://www.rcog.org.uk/globalassets/documents/guidelines/gtg\\_17.pdf](https://www.rcog.org.uk/globalassets/documents/guidelines/gtg_17.pdf).
42. BlueCross BlueShield Association Medical Policy Reference Manual "Chromosomal Microarray Analysis for the Evaluation of Pregnancy Loss." Policy No. 2.04.122

## CODES

**NOTE:** The appropriate codes for reporting CMA are 81228 for CMA alone, and 81229 for CMA testing that includes single nucleotide polymorphism (SNP) analysis. It is not appropriate to report code 81422 for CMA.

Codes	Number	Description
CPT	0252U	Fetal aneuploidy short tandem-repeat comparative analysis, fetal DNA from products of conception, reported as normal (euploidy), monosomy, trisomy, or partial deletion/duplications, mosaicism, and segmental aneuploidy
	81228	Cytogenomic constitutional (genome-wide) microarray analysis; interrogation of genomic regions for copy number variants (eg, bacterial artificial chromosome [BAC] or oligo-based comparative genomic hybridization [CGH] microarray analysis)
	81229	Cytogenomic constitutional (genome-wide) microarray analysis; interrogation of genomic regions for copy number and single nucleotide polymorphism (SNP) variants for chromosomal abnormalities
	81479	Unlisted molecular pathology procedure
	88271	Molecular cytogenetics; DNA probe, each (eg, FISH)
	88299	Unlisted cytogenetic study
HCPCS	None	

**Date of Origin:** April 2017