PHP_2.04.122	Chromosomal Microarray Testing for the Evaluation of Pregnancy Loss		
Original Policy Date:	April 1, 2026	**Effective Date:**	June 1, 2026
Section:	2.0 Medicine	**Page:**	Page 1 of 19

State Guidelines

Applicable Medi-Cal guidelines as of the publication of this policy (this guideline supersedes the criteria in the Policy Statement section below):

I. Department of Managed Health Care (DMHC) All Plan Letter (APL) Guideline:
- N/A

II. Department of Health Care Services (DHCS) Provider Manual Guideline:
- Pathology: Molecular Pathology (path molec)

Below is an excerpt of the guideline language. Please refer to the specific Provider Manual in the link above for the complete guideline.

Requirements for CPT codes 81228 and 81229:
A Treatment Authorization Request (TAR) requires documentation of all of the following criteria:
For Prenatal Testing of Fetus:
1. Member has received pre-test genetic counseling and will receive post-test genetic counseling, and
2. One of the following criteria must be met (a thru c):
   a. Prenatal ultrasound identified one or more structural abnormalities in the fetus, or
   b. Member is undergoing invasive diagnostic fetal testing for a risk factor (for example, positive or inconclusive non-invasive prenatal screening test, advanced maternal age, family history of chromosomal or genetic abnormality, etc.), or
   c. Member has experienced intrauterine fetal death in the second or third trimester and testing of fetal cells/products of conception is needed to inform future pregnancies

III. Department of Health Care Services (DHCS) All Plan Letter (APL) Guideline:
- N/A

Policy Statement

Any criteria that are not specifically addressed in the above Provider Manual, please refer to the criteria below.

I. Chromosomal microarray testing of fetal tissue may be considered **medically necessary** for the evaluation of pregnancy loss in individuals with indications for genetic analysis of the embryo or fetus (see Policy Guidelines). ***(Per Medi-Cal guidelines and for Medi-Cal members only: please see additional criteria in the State Guidelines section above.)***

Policy Guidelines

Clinical guidelines and recommendations to address the management of cases of miscarriage or intrauterine fetal demise where genetic analysis of the embryo, fetus, or stillborn infant is indicated. These guidelines, which specifically address the use of karyotyping and/or microarray testing in miscarriage or intrauterine fetal demise, were developed by reproductive health associations, including the American Society for Reproductive Medicine and the American College of Obstetricians and Gynecologists. Genetic testing may be indicated (if desired by parents):

- In cases of pregnancy loss at 20 weeks of gestation or earlier when there is a maternal history of recurrent miscarriage (defined as a history of ≥2 failed pregnancies); OR
- In all cases of pregnancy loss after 20 weeks of gestation.

The decision to obtain genetic testing should be made jointly by the mother or parents and the treating clinician.

This policy does not address the use of chromosomal microarray testing for preimplantation genetic diagnosis or preimplantation genetic screening, or the evaluation of suspected chromosomal abnormalities in the postnatal period.

Plans may need to alter local coverage medical policy to conform to state law regarding coverage of biomarker testing.

Genetic Counseling

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

Definitions

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

Early pregnancy loss or miscarriage is considered to be a pregnancy loss that occurs at or before 20 weeks of gestational age.

Intrauterine fetal demise is defined as delivery of a non-live-born fetus after 20 weeks of gestational age.

Coding

See the Codes table for details.

Description

Chromosomal microarray (CMA) testing of fetal tissue or placental tissue derived from the fetal genotype has been proposed as a technique to evaluate the cause of isolated and recurrent early pregnancy loss (miscarriages) and later pregnancy loss (intrauterine fetal demise [IUFD]). The evaluation of both recurrent and isolated miscarriages and IUFD may involve genetic testing of the products of conception. Such testing has typically been carried out through cell culture and karyotyping of cells in metaphase. However, the analysis of fetal or placental tissue has been

inhibited by the following limitations: the need for fresh tissue, the potential for cell culture failure, and the potential for maternal cell contamination.

Summary of Evidence

For individuals who have pregnancy loss with indications for genetic analysis of the embryo or fetus who receive chromosomal microarray (CMA) testing of fetal tissue, the evidence includes prospective and retrospective cohort studies that report on the yield of CMA testing. Relevant outcomes are test accuracy and validity, other test performance measures, changes in reproductive decision making, morbid events, and quality of life. The available evidence has suggested that CMA testing has a high rate of concordance with standard karyotyping. For both early and late pregnancy loss, CMA is more likely to yield a result than karyotyping. Other studies have reported that CMA testing detects a substantial number of abnormalities in patients with normal karyotypes, although the precise yield is uncertain and likely varies based on gestational age. Rates of variants of uncertain significance in CMA testing of miscarriage samples are not well characterized. Potential benefits from identifying a genetic abnormality in a miscarriage or intrauterine fetal demise (IUFD) include reducing emotional distress for families, altering additional testing undertaken to assess for other causes of pregnancy loss, and changing reproductive decision making for future pregnancies. The potential for clinical utility with CMA testing of fetal tissue in pregnancy loss is parallel to that for obtaining a karyotype of fetal tissue in pregnancy loss, which is recommended by a number of organizations. None of the studies identified directly demonstrated whether (or how) patient management would change based on CMA testing of the products of conception from early or late pregnancy losses, nor did they demonstrate how patient outcomes would improve. However, the available evidence suggests that, for situations in which a genetic evaluation is indicated, CMA testing would be expected to perform as well as (or better) than standard karyotyping. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

Additional Information

Not applicable.

Related Policies

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

Benefit Application

Blue Shield of California Promise Health Plan is contracted with L.A. Care Health Plan for Los Angeles County and the Department of Health Care Services for San Diego County to provide Medi-Cal health benefits to its Medi-Cal recipients. In order to provide the best health care services and practices, Blue Shield of California Promise Health Plan has an extensive network of Medi-Cal primary care providers and specialists. Recognizing the rich diversity of its membership, our providers are given training and educational materials to assist in understanding the health needs of their patients as it could be affected by a member's cultural heritage.

The benefit designs associated with the Blue Shield of California Promise Medi-Cal plans are described in the Member Handbook (also called Evidence of Coverage).

Regulatory Status

Cal. Health & Safety Code §1367.667, Insurance Code Section 10123.209, and Welfare and Institutions Code 14132.09
California laws that require insurers to cover biomarker testing for the diagnosis, treatment, appropriate management, or ongoing monitoring of an enrollee's disease or condition to guide treatment decisions, as prescribed.

Clinical Laboratory Improvement Amendments (CLIA) and FDA Regulatory Overview
Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA). Laboratories that offer laboratory-developed tests must be licensed by the CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

Multiple laboratories offer chromosomal microarray tests for prenatal samples that are not specifically designed for testing the products of conception.

Health Equity Statement

Blue Shield of California Promise Health Plan's mission is to transform its health care delivery system into one that is worthy of families and friends. Blue Shield of California Promise Health Plan seeks to advance health equity in support of achieving Blue Shield of California Promise Health Plan's mission.

Blue Shield of California Promise Health Plan ensures all Covered Services are available and accessible to all members regardless of sex, race, color, religion, ancestry, national origin, ethnic group identification, age, mental disability, physical disability, medical condition, genetic information, marital status, gender, gender identity, or sexual orientation, or identification with any other persons or groups defined in Penal Code section 422.56, and that all Covered Services are provided in a culturally and linguistically appropriate manner.

Rationale

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 twentieth 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 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 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 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.

Chromosomal Microarray Testing

There is interest in using alternative genetic testing methods, particularly array comparative genomic hybridization, to detect chromosomal or other genetic abnormalities in the evaluation of miscarriages and IUFD.

Literature Review

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 PICO was 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 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 for the characterization of large numbers of genes, but with the downside that analysis may identify large numbers of CNVs of uncertain significance.

Chromosomal microarray 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. 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 Chromosomal Microarray Testing in Pregnancy Loss

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 testing 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 the 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 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%) 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 on rates of structural abnormalities detected with aCGH-based CMA testing in IUFD after 22 weeks of gestation.[31] From a cohort of 54 stillbirths, 29 were prospectively determined to be "unexplained" or 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 a statewide repository of data on IUFD cases, which included 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, 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, 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 Chromosomal Microarray 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 would suggest a way in which CMA testing of POC could be used in an algorithm to determine testing for recurrent pregnancy loss, it does not demonstrate that use of CMA testing improves outcomes. Further research evaluating the implementation of such a decision tool in practice is needed.

Improvement in Patient Outcomes Following Chromosomal Microarray Testing

Several potential health-related outcomes could result from CMA testing of POC in pregnancy loss. Knowledge of the cause of the loss might lead to reduced parent distress or anxiety. For couples with recurrent pregnancy loss, preimplantation genetic diagnosis with the 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.

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 idiosyncrasy 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.

Supplemental Information

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Clinical Input 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.

2015 Input

In response to requests, input was received from 3 academic medical centers, 1 of which provided 2 responses, and 3 physician specialty societies, 1 of which provided 3 responses, while this policy was under review in 2015. There was a consensus that chromosomal microarray (CMA) testing is medically necessary for the evaluation of intrauterine fetal demise (IUFD). 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 CMA testing yield 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

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

American College of Obstetrics and Gynecologists

In 2016, the American College of Obstetricians and Gynecologists' Committee on Genetics and the Society for Maternal-Fetal Medicine published an opinion on the use of advanced genetic diagnostic tools in obstetrics and gynecology; the document was reaffirmed in 2023.[34] The guidelines made the following recommendations and conclusions regarding the use of CMA:

- "Chromosomal microarray analysis [CMA] is a method of measuring gains and losses of DNA throughout the human genome. It can identify chromosomal aneuploidy and other large changes in the structure of chromosomes that would otherwise be identified by standard karyotype analysis, as well as submicroscopic abnormalities that are too small to be detected by traditional modalities."
- "Most genetic changes identified by CMA that typically are not identified on standard karyotype are not associated with increasing maternal age; therefore, the use of this test can be considered for all women, regardless of age, who undergo prenatal diagnostic testing."
- "Prenatal CMA is recommended for a patient with a fetus with 1 or more major structural abnormalities identified on ultrasonographic examination and who is undergoing invasive prenatal diagnosis. This test typically can replace the need for fetal karyotype."
- "In a patient with a structurally normal fetus who is undergoing invasive prenatal diagnostic testing, either fetal karyotyping or a CMA can be performed."
- "CMA of fetal tissue is recommended in the evaluation of IUFD or stillbirth when further cytogenetic analysis is desired because of the test's increased likelihood of obtaining results and improved detection of causative abnormalities."
- "Comprehensive patient pretest and posttest genetic counseling from an obstetrician-gynecologist or other health care provider with genetics expertise regarding the benefits, limitations, and results of CMA is essential. CMA should not be ordered without informed consent, which should include discussion of the potential to identify findings of uncertain significance, nonpaternity, consanguinity, and adult-onset disease."
- "Additional information is needed regarding the clinical use and cost-effectiveness in cases of recurrent miscarriage and structurally normal pregnancy losses at less than 20 weeks of gestation."

In 2020, the American College of Obstetricians and Gynecologists also published an obstetric care consensus on the management of stillbirth; reaffirmed in 2025.[6] The consensus states that microarray analysis, incorporated into the stillbirth evaluation, "improves the test success rate and the detection of genetic anomalies compared with conventional karyotyping [strong recommendation; high-quality evidence]." As such, the authors of the consensus recommend microarray as the preferred method of stillbirth evaluation; however, "due to cost and logistics concerns, karyotype may be the only method readily available for some patients."

American Society for Reproductive Medicine

In 2012, the American Society for Reproductive Medicine issued an opinion on the evaluation and treatment of recurrent pregnancy loss.[1] The statement drew the following conclusions:

- "Evaluation of recurrent pregnancy loss [RPL] can proceed after 2 consecutive clinical pregnancy losses."
- "Assessment of RPL focuses on screening for genetic factors and antiphospholipid syndrome, assessment of uterine anatomy, hormonal and metabolic factors, and lifestyle variables. These may include:
    - Peripheral karyotype of the parents.
    - Screening for lupus anticoagulant, anticardiolipin antibodies, and anti-β_2 glycoprotein I.
    - Sonohysterogram, hysterosalpingogram, and/or hysteroscopy.
    - Screening for thyroid and prolactin abnormalities."
- "Karyotypic analysis of products of conception may be useful in the setting of ongoing therapy for RPL."

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

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

Ongoing and Unpublished Clinical Trials

A search of ClinicalTrials.gov in June 2025 did not identify any ongoing or unpublished trials that would likely influence this review.

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Documentation for Clinical Review

Please provide the following documentation:

- History and physical and/or consultation notes including:
  - History of pregnancies
    - Isolated and recurrent early pregnancy loss (miscarriages)
    - Later pregnancy loss (intrauterine fetal demise [IUDF])
  - Previous treatment plan(s) and response(s)
  - Current treatment plan
  - Clinical justification for Chromosomal Microarray Analysis (CMA)
- Genetic counseling reports (if available)

Post Service (in addition to the above, please include the following):

- CMA of fetal tissue, if applicable
- Results/reports of tests performed

Coding

The list of codes in this Medical Policy is intended as a general reference and may not cover all codes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy.

Type	Code	Description
CPT®	81228	Cytogenomic constitutional (genome-wide) microarray analysis; interrogation of genomic regions for copy number variants (e.g.,

Type	Code	Description
		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
HCPCS	None	

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action
04/01/2026	New policy.
06/01/2026	Administrative update. Definitions of Decision Determinations section updated.

Definitions of Decision Determinations

Healthcare Services: For the purpose of this Medical Policy, Healthcare Services means procedures, treatments, supplies, devices, and equipment.

Medically Necessary or **Medical Necessity** means reasonable and necessary services to protect life, to prevent significant illness or significant disability, or alleviate severe pain through the diagnosis or treatment of disease, illness, or injury, as required under W&I section 14059.5(a) and 22 CCR section 51303(a). Medically Necessary services must include services necessary to achieve age-appropriate growth and development, and attain, maintain, or regain functional capacity.

For Members less than 21 years of age, a service is Medically Necessary if it meets the Early and Periodic Screening, Diagnostic, and Treatment (EPSDT) standard of Medical Necessity set forth in 42 USC section 1396d(r)(5), as required by W&I sections 14059.5(b) and 14132(v). Without limitation, Medically Necessary services for Members less than 21 years of age include all services necessary to achieve or maintain age-appropriate growth and development, attain, regain or maintain functional capacity, or improve, support, or maintain the Member's current health condition. Contractor must determine Medical Necessity on a case-by-case basis, taking into account the individual needs of the Child.

Criteria Determining Experimental/Investigational Status

Below is an excerpt of the language taken from California Children's Services Numbered Letter 05-1020.*

*Department of Healthcare Services Numbered Letter 05-1020. Accessed April 21, 2026, from https://www.dhcs.ca.gov/services/ccs/Documents/CCS-NL-05-1020-Experimental-and-Investigational-Services.pdf

Policy

A. The California Children's Services (CCS) Program and the Genetically Handicapped Persons Program (GHPP) will not provide coverage for experimental services unless specifically authorized by law.
B. The CCS Program and GHPP may provide coverage for an investigational service if:
    1. It is approved by the FDA under any Investigational New Drug (IND) Application; or
    2. It is authorized for use under the State of California's Right to Try Act; and

3. Its use is consistent with its FDA-approved IND Application or the State of California's Right to Try Act;

C. Additional criteria that will be considered in the adjudication process include:
1. Conventional therapy will not adequately treat the intended patient's condition;
2. Conventional therapy will not prevent progressive disability or premature death;
3. The provider of the proposed service has a record of safety and success with it or equivalent to that of other providers of the investigational services;
4. Other criteria (e.g., cost and availability) may be considered in the adjudication of a given request in cases in which more than one investigational service is available;
5. There is reasonable expectation that the investigational service will significantly prolong the patient's life or will maintain or restore a range of physical and social function suited to activities of daily living; and
6. The service is not being performed as part of a research study protocol. For a beneficiary with cancer who participates in a clinical trial for cancer, California Health and Safety Code (HSC) § 1370.6 requires that all routine patient care costs related to the clinical trial be covered if the beneficiary's CCS-paneled treating physician recommends participation in the clinical trial after determining that participation in the clinical trial has a meaningful potential to benefit the enrollee. The coverage does not include investigational services that have not been approved by the FDA and that are associated with the clinical trial.

Feedback

Blue Shield of California Promise Health Plan is interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration. Our medical policies are available to view or download at www.blueshieldca.com/en/bsp/providers.

For medical policy feedback, please send comments to: MedPolicy@blueshieldca.com

Questions regarding the applicability of this policy should be directed to the Blue Shield of California Promise Health Plan Prior Authorization Department at (800) 468-9935, or the Complex Case Management Department at (855) 699-5557 (TTY 711) for San Diego County and (800) 605-2556 (TTY 711) for Los Angeles County or visit the provider portal at www.blueshieldca.com/en/bsp/providers.

Disclaimer: Blue Shield of California Promise Health Plan may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as member health services contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member health services contracts may differ in their benefits. Blue Shield of California Promise Health Plan reserves the right to review and update policies as appropriate.