
Medical Policy



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***Current Policy Effective Date: 5/1/26**
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Title: Invasive Prenatal (Fetal) Diagnostic Testing

Description

Invasive prenatal (fetal) diagnostic testing may be used to identify pathogenic genetic alterations in fetuses at increased risk based on prenatal screening or in women who choose to undergo diagnostic testing due to other risk factors. This evidence review only addresses the use of chromosomal microarray (CMA) testing, molecular diagnosis of single-gene disorders, and next-generation sequencing.

Medical Policy Statement

For individuals who are undergoing invasive diagnostic prenatal (fetal) testing, chromosome microarray analysis is **established** when criteria are met.

For individuals who are undergoing invasive diagnostic prenatal (fetal) testing, molecular analysis for single-gene disorders is **established** when criteria are met.

The use of next-generation sequencing in the setting of invasive prenatal testing is considered **experimental/investigational**. The evidence is insufficient to determine that the technology results in an improvement in net health outcomes.

Inclusionary and Exclusionary Guidelines

Inclusions:

Chromosomal Microarray

In individuals who are undergoing invasive diagnostic prenatal (fetal) testing as an alternative to karyotyping.

Single-Gene Disorders

Invasive diagnostic prenatal (fetal) testing for molecular analysis for single-gene disorders when a pregnancy has been identified as being at high risk by **one** of the following:

- For autosomal dominant conditions, at least one of the parents has a known pathogenic variant.
- For autosomal recessive conditions:
 - Both parents are suspected to be carriers or are known to be carriers, OR
 - One parent is clinically affected and the other parent is suspected to be or is a known carrier.
- For X-linked conditions: a parent is suspected to be or is a known carrier.

AND all of the following are met:

- The natural history of the disease is well understood, and there is a reasonable likelihood that the disease is one with high morbidity in the homozygous or compound heterozygous state, AND
- Any variants that have a high penetrance, AND
- The genetic test has adequate sensitivity and specificity to guide clinical decision making and residual risk is understood, AND
- An association of the marker with the disorder has been established.

Exclusions:

- Invasive diagnostic prenatal (fetal) testing when above criteria are not met.
- The use of next-generation sequencing in the setting of invasive prenatal testing.

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

Established codes:

81228	81229	81349	81405	88271	88272
88274	88275	59000	59012	59015	

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

81479	0335U	0336U	0469U
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Background

Fetal Malformations

Fetal malformations identified by ultrasound, characterized as major or minor malformations, whether isolated or multiple, may be part of a genetic syndrome, despite a normal fetal karyotype.

Major malformations are structural defects that have a significant effect on function or social acceptability. They may be lethal or associated with possible survival with severe or moderate immediate or long-term morbidity. Examples by organ system include genitourinary: renal agenesis (unilateral or bilateral), hypoplastic/cystic kidney; cardiovascular: complex heart malformations; musculoskeletal: osteochondrodysplasia/osteogenesis imperfecta, clubfoot, craniosynostosis; central nervous system: anencephaly, hydrocephalus, myelomeningocele; facial clefts; body wall: omphalocele/gastroschisis; and respiratory: cystic adenomatoid lung malformation.

Single-Gene Disorders

An individual may be suspected of being a carrier if there is a family history of or ethnic predilection for a disease. Carrier screening is not recommended if the carrier rate is less than 1% in the general population.

In most cases, before a prenatal diagnosis using molecular genetic testing can be offered, the familial variant must be identified, either in an affected relative or carrier parent(s). Therefore, panel testing in this setting would not be considered appropriate.

In some cases, the father may not be available for testing, and the risk assessment of the fetus will need to be estimated without knowing the father's genetic status.

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.

PRENATAL GENETIC TESTING METHODOLOGIES

The focus of this evidence review is the use of certain invasive prenatal genetic testing methodologies in the prenatal (fetal) setting to provide a framework for evaluating the clinical utility of diagnosing monogenic disorders in this setting. The purpose of prenatal genetic testing is to identify conditions that might affect the fetus, newborn, or mother to inform pregnancy management e.g., prenatal treatment, decisions about delivery location and personnel, or pregnancy termination.

Invasive fetal diagnostic testing can include obtaining fetal tissue for karyotyping, fluorescence in situ hybridization (FISH), chromosomal microarray analysis (CMA) testing, quantitative polymerase chain reaction (qPCR), next-generation sequencing (NGS), and multiplex ligation-dependent probe amplification (MLPA).

This evidence review will only address the following:

- The diagnosis of copy number variants using CMA technology
- The diagnosis of single-gene disorders, most of which are due to single nucleotide variants (SNVs) or very small deletions and use molecular methods to diagnose (mainly PCR, but also MLPA)
- NGS

This evidence review applies only if there is not a separate evidence review that outlines specific criteria for diagnostic testing. If a separate evidence review exists, then the criteria in it supersede the guidelines herein. This evidence review does NOT cover the use of:

- prenatal carrier testing
- preimplantation genetic diagnosis or screening
- noninvasive prenatal testing
- testing in the setting of fetal demise

Genetic disorders are generally categorized into three main groups: chromosomal, single gene, and multifactorial. Single-gene disorders (also known as monogenic) result from errors in a specific gene, whereas those that are chromosomal include larger aberrations that are numerical or structural.

Invasive prenatal testing refers to the direct testing of fetal tissue, typically by chorionic villus sampling (CVS) or amniocentesis. Both procedures increase the risk of miscarriage. Chorionic villus sampling utilizes placental cells that are derived from the same fertilized egg as the fetus. The chorionic villi are collected for genetic evaluation under ultrasound guidance without entering the amniotic sac. During amniocentesis, a small sample of the fluid that surrounds the fetus is removed. This fluid contains cells that are shed primarily from the fetal skin, bladder, gastrointestinal tract, and amnion. Typically, CVS is done at earlier gestation than amniocentesis. Most times only one procedure is done; however, sometimes CVS has ambiguous results from maternal cell contamination or placental mosaicism such that amniocentesis might additionally be needed for clarification. Invasive prenatal procedures are typically performed in pregnancies of women who have been identified as having a fetus at increased risk for a chromosomal abnormality, or if there is a family history of a single-gene disorder. For confirming positive cell-free DNA results, amniocentesis might be preferred over CVS to avoid potential false-positive results due to confined placental mosaicism^{[1,2](#)}.

Chromosomal Microarray Analysis (CMA)

CMA technology 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. However, there are disadvantages to CMA, including the detection of variants of unknown clinical significance and the fact that it cannot detect certain types of chromosomal abnormalities, including balanced rearrangements.

CMA analyzes abnormalities at the level of the chromosome and measures gains and losses of DNA (known as copy number variants [CNVs] throughout the genome. CMA analysis detects CNVs by comparing a reference genomic sequence ("normal") with the corresponding patient sequence. Each sample has a different fluorescent label so that they can be distinguished, and both are cohybridized to a sample of a specific reference (also normal) DNA fragment of the known genomic locus. If the patient sequence is missing part of the normal sequence (deletion) or has the normal sequence plus additional genomic material within that genomic location (e.g., a duplication of the same sequence), the sequence imbalance is detected as a difference in fluorescence intensity. For this reason, standard CMA (non-single nucleotide polymorphisms [SNPs]) cannot detect balanced CNVs (equal exchange of material between chromosomes) or sequence inversions (same sequence is present in reverse base pair order) because the fluorescence intensity would not change.

CMA analysis uses thousands of cloned or synthesized DNA fragments of known genomic locus immobilized on a glass slide (microarray) to conduct thousands of comparative reactions at the same time. The prepared sample and control DNA are hybridized to the fragments on the slide, and CNVs are determined by computer analysis of the array patterns and intensities of the hybridization signals. Array resolution is limited only by the average size of the fragment used and by the chromosomal distance between loci represented by the reference DNA fragments on the slide. High-resolution oligonucleotide arrays are capable of detecting changes at a resolution of up to 50 to 100 Kb.

Types of CMA Technologies

There are differences in CMA technology, most notably in the various types of microarrays. They can differ first by construction; earliest versions were used of DNA fragments cloned from bacterial artificial chromosome. They have been largely replaced by oligonucleotide (oligos; short, synthesized DNA) arrays, which offer better reproducibility. Finally, arrays that detect hundreds of thousands of SNPs across the genome have some advantages as well. A SNP is a DNA variation in which a single nucleotide in the genomic sequence is altered. This variation can occur between two different individuals or between paired chromosomes from the same individual and may or may not cause disease. Oligo/SNP hybrid arrays have been constructed to merge the advantages of each.

The 2 types of microarrays both detect CNVs, but they identify different types of genetic variation. The oligo arrays detect CNVs for relatively large deletions or duplications, including whole chromosome duplications (trisomies), but cannot detect triploidy. SNP arrays provide a genome-wide copy number analysis, and can detect consanguinity, as well as triploidy and uniparental disomy.

Microarrays may be prepared by the laboratory using the technology, or more commonly by commercial manufacturers, and sold to laboratories that must qualify and validate the product for use in their assay, in conjunction with computerized software for interpretation. The proliferation of in-house developed and commercially available platforms prompted the American College of Medical Genetics (ACMG) to publish guidelines for the design and performance expectations for clinical microarrays and associated software in the postnatal setting.

At this time, no guidelines indicate whether targeted or genome-wide arrays should be used or what regions of the genome should be covered. Both targeted and genome-wide arrays

search the entire genome for CNVs, however, targeted arrays are designed to cover only clinically significant areas of the genome. The ACMG guideline for designing microarrays recommends probe enrichment in clinically significant areas of the genome to maximize detection of known abnormalities. Depending on the laboratory that develops a targeted array, it can include as many or as few microdeletions and microduplication syndromes as thought to be needed. The advantage, and purpose, of targeted arrays is to minimize the number of variants of unknown significance (VUS).

Whole genome CMA analysis has allowed the characterization of several new genetic syndromes with other potential candidates currently under study. However, the whole genome arrays also have the disadvantage of potentially high numbers of apparent false-positive results, because benign CNVs are also found in phenotypically normal populations; both benign and pathogenic CNVs are continuously cataloged and, to some extent, made available in public reference databases to aid in clinical interpretation relevance.

Clinical Relevance of CMA Findings and VUS

CNVs are generally classified as pathogenic (known to be disease causing), benign, or a VUS.

A VUS is defined as a CNV that:

- Has not been previously identified in a laboratory's patient population, or
- Has not been reported in the medical literature, or
- Is not found in publicly available databases, or
- Does not involve any known disease-causing genes

To determine clinical relevance (consistent association with a disease) of CNV findings, the following actions are taken:

- CNVs are confirmed by another method (e.g., FISH, MLPA, PCR).
- CNVs detected are checked against public databases and, if available, against private databases maintained by the laboratory. Known pathogenic CNVs associated with the same or similar phenotype as the patient are assumed to explain the etiology of the case; known benign CNVs are assumed to be nonpathogenic.
- A pathogenic etiology is additionally supported when a CNV includes a gene known to cause the phenotype when inactivated (microdeletion) or overexpressed (microduplication).
- The laboratory may establish a size cutoff; potentially pathogenic CNVs are likely to be larger than benign polymorphic CNVs; cutoffs for CNVs not previously reported typically range from 300 kb to 1 Mb
- Parental studies are indicated when CNVs of appropriate size are detected and not found in available databases; CNVs inherited from a clinically normal parent are assumed to be benign variants whereas those appearing de novo are likely pathogenic; etiology may become more certain as other similar cases accrue.

The International Standards for Cytogenomic Arrays (ISCA) Consortium was organized (available at <https://www.iscaconsortium.org/index.php>); it established a public database containing deidentified whole genome microarray data from a subset of the ISCA Consortium member clinical diagnostic laboratories. Array analysis was carried out on subjects with phenotypes including intellectual disability, autism, and developmental delay. As of July 2018, nearly 10,500 "expert reviewed" variants are listed in the database. Data are currently hosted on ClinGen.³

Use of the database includes an intra-laboratory curation process; whereby laboratories are alerted to any inconsistencies among their own reported CNVs or other variants, as well as any not consistent with the ISCA “known” pathogenic and “known” benign lists. The intra-laboratory conflict rate was initially about 3% overall, following release of the first ISCA curated track, the intra-laboratory conflict rate decreased to about 1.5%. A planned interlaboratory curation process, whereby a group of experts curates reported CNVs/variants across laboratories, is currently in progress.

The consortium proposed “an evidence-based approach to guide the development of content on chromosomal microarrays and to support interpretation of clinically significant copy number variation.” The proposal defines levels of evidence (from the literature and/or ISCA and other public databases) that describe how well or how poorly detected variants or CNVs correlate with phenotypes.

ISCA is also developing vendor-neutral recommendations for standards for the design, resolution, and content of cytogenomic arrays using an evidence-based process and an international panel of experts in clinical genetics, clinical laboratory genetics, genomics, and bioinformatics.

Single-Gene (Mendelian) Disorders

Mendelian or single-gene disorders include those with an inheritance mode of autosomal dominant or recessive, X-linked dominant or recessive. Women may be identified as being at increased risk for having a fetus with an inherited genetic condition because of previously affected pregnancies, a family history in a suggestive pattern of inheritance, or being a member of a subpopulation with elevated frequencies of certain autosomal recessive conditions.

Most Mendelian disorders are caused by point variant or very small deletions or duplications. Monogenic variants are diagnosed by molecular methods, mainly PCR for SNVs, but also other methods like MLPA for very small deletions and duplications. There are approximately 5000 known disorders that are inherited in this fashion. Diagnostic tests are currently available for most of the common monogenic disorders, as well as for a number of rarer disorders. For most single-gene disorders, testing in the prenatal setting requires knowledge of the familial variants.

Next-Generation Sequencing

NGS has been used to identify pathogenic variants in disease-associated genes in many Mendelian disorders. Approximately 85% of known disease-causing variants occur within the 1% of the genome that encodes for proteins (exome). Therefore, whole exome sequencing could rapidly and cost-effectively capture the majority of protein-coding regions. However, although whole exome and whole genome sequencing have significant potential, there remain concerns of technical complexity, difficulties with bioinformatic interpretation and VUS, as well as ethical issues.⁴

Commercially Available Tests

Many academic and commercial laboratories offer CMA testing and single-gene disorder testing. The following is not inclusive; it is only an example of some laboratories that offer CMA

testing. The test should be cleared or approved by the Food and Drug Administration or performed in a Clinical Laboratory Improvement Amendment-certified laboratory.

SUMMARY OF EVIDENCE

For individuals who are undergoing invasive diagnostic prenatal (fetal) testing who receive chromosomal microarray analysis, the evidence includes a systematic review and meta-analysis and prospective cohort and retrospective analyses comparing the diagnostic yield of CMA testing with that of karyotyping. Relevant outcomes are test accuracy, test validity, and changes in reproductive decision-making. CMA testing has a higher detection rate of pathogenic chromosomal alterations than karyotyping. CMA testing can yield results that have variants of uncertain clinical significance; however, such results can be minimized by the use of targeted arrays, testing phenotypically normal parents for the copy number variant and the continued accumulation of pathogenic variants in international databases. The highest yield of pathogenic copy number variants by CMA testing has been found in fetuses with malformations identified by ultrasound. Changes in reproductive decision making could include decisions regarding continuation of the pregnancy, enabling for timely treatment of a condition that could be treated medically or surgically either in utero or immediately after birth and birthing decisions. The American College of Obstetricians and Gynecologists recommend CMA testing in women who are undergoing an invasive diagnostic procedure. The evidence is sufficient to determine that the technology results in an improvement in the net health outcomes.

For individuals who are undergoing invasive diagnostic prenatal (fetal) testing who receive molecular testing for single-gene disorders, the evidence includes case series that may report disorders detected and test validity. Relevant outcomes are test accuracy and validity and changes in reproductive decision-making. In general, it is necessary to identify the particular variant(s) in the affected parent(s) so that the particular variant(s) can be sought for prenatal diagnosis. When a familial variant is known, the analytic validity of testing for this variant is expected to be high, approaching 100% accuracy. For clinical validity, when there is a known pathogenic familial variant, the sensitivity and specificity for testing for the variant in other family members is expected to be very high. Changes in reproductive decision making could include decisions regarding continuation of the pregnancy, facilitating timely treatment of a condition medically or surgically either in utero or immediately after birth, decisions concerning the place of delivery (i.e., tertiary care center), and route of delivery. The evidence is sufficient to determine that the technology results in an improvement in the net health outcomes.

For individuals who are undergoing invasive diagnostic prenatal (fetal) testing who receive next-generation sequencing (NGS), the evidence is limited to systematic reviews of small observational studies. Relevant outcomes are test accuracy, test validity, and changes in reproductive decision-making. NGS can include multigene panel testing, as well as whole exome and whole genome sequencing. While the use of NGS has been accepted in certain noninvasive prenatal testing settings, its use in the setting of invasive prenatal testing for detecting CNVs and single-gene variants still includes concerns about interpretation of the data generated and the data's clinical relevance and data about pregnancy outcomes with use of NGS is lacking. The clinical utility of NGS in the prenatal setting is unknown. The evidence is insufficient to determine that the technology results in an improvement in the net health outcomes.

Rationale

Evidence reviews assess clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function including benefits and harms. Every clinical condition has specific outcomes that are important to individuals and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms. The following is a summary of the key literature to date.

CHROMOSOMAL MICROARRAY TESTING

Clinical Context and Test Purpose

The purpose of CMA testing (copy number variants [CNVs]) in individuals who are undergoing invasive prenatal testing is to inform reproductive decisions.

Most of the literature on CMA testing in the prenatal (fetal) setting consists of prospective and retrospective analyses of CMA findings compared to conventional karyotyping, either in patients with known karyotype results or in patients with concurrently performed karyotyping and CMA. CMA analysis has been proposed as being used as either a first-tier test (in place of or in conjunction with karyotype) or as a second-tier test (after a negative karyotype).

Review of Evidence

Systematic Reviews

Sun et al (2021) conducted a meta-analysis on the incidence of chromosomal abnormalities and additional diagnostic gain of CMA compared with standard karyotyping in the detection of cases of fetal ventriculomegaly (VM). Twenty-three articles involving 1635 patients were included based on a literature search through April 2020. Meta-analysis determined that the incidence of chromosomal abnormalities in VM was 9% (95% confidence interval [CI], 5% to 12%) and incremental yield of CMA in VM was 11% (95% CI, 7% to 16%), demonstrating an improvement in the detection rate of abnormalities. The incidences of chromosomal abnormalities in mild, severe, isolated, and non-isolated VM were 9% (95% CI, 4% to 16%), 5% (95% CI, 1% to 11%), 3% (95% CI, 1% to 6%), and 13% (95% CI, 4% to 25%) respectively.

Jansen et al (2015) conducted a systematic review and meta-analysis of the additional diagnostic gain of array comparative genomic hybridization (CGH) compared with standard karyotyping and 22q11 by fluorescence in situ hybridization (FISH) in prenatally diagnosed cardiac malformations. Thirteen studies with 1131 cases of congenital heart disease (CHD) were included. A meta-analysis identified an incremental yield of 7.0% (95% confidence interval [CI], 5.3% to 8.6%) for the detection of copy number variants using CGH, excluding aneuploidy and 22q11 microdeletion cases. A subgroup analysis showed a 3.4% (95% CI, 0.3% to 6.6%) incremental yield in isolated CHD cases, and 9.3% (95% CI, 6.6% to 12%) when extracardiac malformations were present. Overall, an incremental yield of 12% (95% CI,

7.6% to 16%) was found when 22q11 deletion cases were included. The rate of variants of unknown significance (VOUS) was 3.4% (95% CI, 2.1% to 4.6%).

A review by Wapner et al (2014) summarized the existing literature of the largest studies that reported the estimates of detectable pathogenic CNVs according to the indication for CMA testing. For studies that included only high-risk pregnancies (which were primarily because of abnormal ultrasound abnormalities), the range of pathogenic CNV detection was 2.6% to 7.8%, with a combination of all studies (n=1800) being 5.0%. For pregnancies in which CMA was performed for only low-risk indications (advanced maternal age [AMA], abnormal Down syndrome screening test, parental anxiety), the range of pathogenic CNV detection was 0.5% to 1.6%, with a combination of all studies (n=10099) being 0.9%.

Hillman et al (2013) conducted a prospective cohort study and systematic review and meta-analysis. The cohort study involved 243 women undergoing CMA and karyotyping for a structural abnormality detected on prenatal ultrasound. There was an excess detection rate of abnormalities by CMA of 4.1% over conventional karyotyping, with a VOUS rate of 2.1% (95% CI, 1.3% to 3.3%). The meta-analysis was 10% (95% CI, 8% to 13%). The VOUS rate was 1.4% (95% CI, 0.5% to 3.7%) when any indication for prenatal CMA was meta-analyzed and 2.1% (95% CI, 1.3 to 3.3) when the indication for the CMA was an abnormal ultrasound finding.

Prospective and Retrospective Studies

Various prospective and retrospective cohort studies have compared CMA and karyotype testing.⁹⁻²² Studies have consistently found CMA testing to have a higher rate of detection (diagnostic yield) of pathogenic chromosomal abnormalities than karyotyping, but results have varied by indication. A sampling of the largest studies is discussed below.

Xiang et al (2021) retrospectively evaluated a cohort to compare the diagnostic yield of CMA testing using a SNP-array compared to G-banded karyotyping. There were 4022 women who were evaluated that had chosen to receive CMA and karyotyping simultaneously in their pregnancy. Of these, 151 cases of aneuploidy and 2 cases of triploidy (69,XXX) were identified with both CMA testing and karyotyping. Among 3665 cases with normal results on karyotyping, CMA testing yielded an additional 286 abnormal results (286/3665, 7.8%) including 2 cases of mosaic 45,X, 19 cases of loss of heterozygosity, and 265 cases of microduplication/microdeletion.

Robson et al (2017) reported on results of the U.K. Evaluation of Array Comparative genomic Hybridisation (EACH) study, a multicenter cohort study including an economic and qualitative substudy. Enrolled women underwent quantitative fluorescent polymerase chain reaction and conventional karyotyping after chorionic villus sampling (CVS; 55.8%), amniocentesis (40.8%), or fetal blood sampling (2.7%). Testing indications included an isolated nuchal translucency (≥ 3.5 mm) or any structural anomaly detected on ultrasound at 11 to 14 weeks. Nine laboratories performed testing with an identical oligonucleotide-CGH array. Between March 2012 and May 2014, 1718 women were recruited and the results from 1123 were analyzed. Irrespective of indication for testing, results were observed as shown in Table 1.

Table 1. Comparison of Karyotype and Chromosomal Microarray Testing Results (EACH Study)

Karyotyping	Chromosomal Microarray Testing	n (%)
Pathogenic alteration	Benign alteration	15 (1.3)
Pathogenic alteration	Pathogenic alteration	58 (5.2)
Benign alteration	Pathogenic alteration	42 (3.7)
Benign alteration	Variant of uncertain significance	38 (3.4)

Adapted from Robson et al (2017)

Similar to other studies discussed below, results varied by indication for testing. The authors concluded: "The results suggest that CMA is a robust, acceptable and probably cost-effective diagnostic test and should replace karyotyping in care pathways when the indication for fetal testing is one or more structural anomalies or an isolated NT [nuchal translucency] of ≥ 3.5 mm on an ultrasound scan after a normal QF-PCR result."

Lovrecic et al (2016) evaluated the clinical usefulness of prenatal CMA testing for small (submicroscopic) imbalances (CNV) in 218 fetuses across a range of indications for testing. In fetuses with ultrasound findings, the diagnostic yield of CMA testing was 10% or 7.7% more than was obtained with karyotyping. Similar to other studies, diagnostic yield varied by indication for testing. For example, a pathogenic CNV rate was found in 6.3% of fetuses with intrauterine growth retardation and 16.7% of fetuses with multiple anomalies. The results support an increase in the diagnostic yield with CMA testing over conventional karyotyping.

Papoulidis et al (2015) compared the diagnostic yield of conventional karyotyping with a CGH in 1763 prenatal samples. Samples of trophoblastic tissue (n=458) and amniotic fluid (n=1305) were examined. Pathogenic alterations were identified in 125 (7.1%) and a VUS in 13(0.7%). The incremental diagnostic yield from a CGH was 0.9%. Incremental improvements were greatest when test indications were second-trimester ultrasound markers (incremental improvement, 1.5%) or structural anomalies (1.3%), but lower with increased nuchal translucency (0.5%). The authors concluded: "The present study indicates that routine implementation of aCGH offers an incremental yield over conventional karyotype analysis, which is also present in cases with 'milder' indications, further supporting its use as a first-tier test."

Armengol et al (2012) conducted a comparative study of available technologies, including karyotyping and CMA, for the detection of chromosomal abnormalities after invasive prenatal sampling. Multiple testing techniques were performed on the same sample. The study included 900 women with the main indications for testing being abnormal ultrasound findings, altered biochemical screening, family history of a chromosomal disorder or other genetic condition, and AMA. A total of 57 (6.3%) clinically relevant chromosomal aberrations were found, with CMA testing having the highest detection rate, 32% above other methods. Most VUSs could be classified as likely benign after proving they were inherited. Cross-validation was provided by the simultaneous use of multiple techniques, and additional molecular techniques were performed in the follow-up of some of the alterations identified by CMA.

Table 2 reports the data on karyotyping and CMA testing. The diagnostic accuracy was 98.2% (97.1% to 99.0%) for karyotyping and 99.7% (99.0% to 99.9%) CMA testing.

Table 2. Clinical Validity of Karyotyping vs. CMA Testing

Study	Initial N	Final N	Clinical Validity (95% Confidence Interval), %			
			Sensitivity	Specificity	PPV	NPV
Armengol et al (2012)	906 ^a	57 ^a				
Karyotyping			76.4 (63.0 to 87.0)	99.9 (99.2 to 99.9)	97.7 (87.7 to 99.9)	98.3 (97.1 to 99.1)
CMA Testing			98.2 (90.4 to 99.9)	99.7 (99.1 to 99.9)	96.5 (87.9 to 99.5)	99.9 (99.3 to 100)

CMA: chromosomal microarray; NPV: negative predictive value; PPV: positive predictive value.

^a Fifty-seven variants detected from 906 fetal samples from 900 women.

Shaffer et al (2012) reported on the results of microarray testing for prenatal diagnosis in over 5000 prospectively collected prenatal samples received from 2004 to 2011 for a variety of indications.¹³ They used a CGH microarrays targeted to known chromosomal syndromes, with later versions providing backbone coverage of the entire genome. Cases were stratified by test results (normal, VUS, abnormal) and indication for the study and compared with karyotyping results. Of 5003 prenatal specimens, 56% were referred with normal karyotypes, 13% had known abnormal karyotypes, 16% had karyotypes performed concurrently with microarray testing, and 15% had unknown karyotype status. Indications for microarray testing included a known abnormal karyotype (n=648), family history of a parent known to carry a chromosomal rearrangement or imbalance (n=62), fetal demise (n=417), abnormal ultrasound (n=2858) (detailed in another study by the same group)¹⁴, abnormal first- or second-trimester screen (n=77), other family history of a genetic condition (n=487), AMA (n=346), parental anxiety (n=95), or other/not specified (n=13). The overall detection rate of clinically significant results with microarray testing was 5.3%. The detection rate of clinically significant CNVs was 5.5% among cases with known normal karyotypes. After excluding the cases of fetal demise, the VUS rate was 4.2%, but if only de novo CNVs were considered (the rate was 0.39%).

In the other study, Shaffer et al (2012) retrospectively analyzed 2858 pregnancies with abnormal ultrasound findings (as stratified by organ system).¹⁴ Most cases had previously normal karyotypes (n=2052 [72%]). The remaining had karyotyping performed concurrently with microarray testing (n=465 [16%]) or had unknown or failed karyotypes (n=341 [12%]). Ultrasound anomalies were categorized in several ways: multiple structural anomalies, structural anomalies involving a single-organ system, isolated abnormalities of growth, isolated abnormal amniotic fluid volume, single or multiple soft marker(s), or multiple nonstructural anomalies (e.g., intrauterine growth restriction). Soft markers included choroid plexus cysts, echogenic foci in the heart or bowel, isolated short, long bones, absent nasal bones, sandal gap between the first and second toes, fifth finger clinodactyly, single umbilical artery, and persistent right umbilical vein. The average maternal age at the time of testing was 31.8 years. Most tests were whole genome, oligoarrays (n=2161 [76%]), and the remaining were bacterial artificial chromosome-based arrays, either with coverage of the whole genome (n=506 [18%]) or targeted coverage (n=191 [7%]). Overall, with microarray testing, 6.5% showed clinically significant results, and 4.8% had VUS. For the cases with a previously normal karyotype, the detection rate for significant CNVs was similar (6.2%). Clinically significant genomic alterations were identified in cases with a single ultrasound anomaly (n=99/1773 [5.6%]), anomalies in 2 or more organ systems (n=77/808 [9.5%]), isolated growth abnormalities (n=2/76 [2.6%]), and soft markers (n=2/77 [2.6%]). Certain anomalies, either in isolation or with additional

anomalies, had higher detection rates: holoprosencephaly (n=9/85 [10.6%]), posterior fossa defects (n=21/144 [14.6%]), skeletal anomalies (n=15/140 [10.7%]), ventricular septal defect (n=14/132 [10.6%]), hypoplastic left heart (n=11/68 [16.2%]), and cleft lip/palate (n=14/136 [10.3%]).

Wapner et al (2012) conducted a prospective study to compare the accuracy, efficacy, and incremental yield of CMA testing with karyotyping for routine prenatal diagnosis.¹⁵ A total of 4406 women undergoing routine prenatal diagnosis in 1 of 29 diagnostic centers by either CVS or amniocentesis had a sample split in 2 for standard karyotyping and CMA testing. Indications for prenatal diagnosis included AMA (46.6%), a positive aneuploidy screening result (18.8%), structural anomalies detected by ultrasound (25.2%), and other indications (9.4%). CMA analysis was successful in 98.8% of the fetal samples. A total of 4282 samples were included in the primary analysis. Of these, common autosomal aneuploidies were identified in 317 (7.4%) and sex chromosome aneuploidies were identified in 57 (1.3%) by standard karyotyping. CMA testing identified all of these aneuploidies. None of the balanced rearrangements identified on karyotyping was identified with CMA, nor did CMA identify any of the triploid samples (0.4%). Of the 3822 cases with a normal karyotype, on the microarray, 1399 samples were identified as having CNVs; of these, 88.2% were classified as common benign and 0.9% were on the predetermined list of pathogenic CNVs. The cases of uncertain clinical significance were adjudicated by a clinical advisory committee, which reclassified them as likely to be benign (1.8% of all 1399 samples) or of potential clinical significance (1.6% of all 1399 samples). Overall, 96 (2.5%; 95% CI, 2.1% to 3.1%) of the 3822 fetal samples with normal karyotypes had a microdeletion or duplication of clinical significance.

In a subgroup analysis of 755 women with normal karyotypes and fetuses with suspected growth or structural anomalies, 45 (6.0%; 95% CI, 4.5% to 7.9%) had clinically relevant findings on the microarray. These included CNVs that were predetermined as known pathogenic, as well as those classified by the clinical advisory committee as clinically relevant. In this population with structural abnormalities identified on ultrasound, CNVs of uncertain clinical significance, but likely benign, were found in 16 (2.1%) patients. Of the women tested for AMA, 1.7% (95% CI, 1.2% to 2.4%) had a clinically relevant finding on the microarray, as did 1.6% (95% CI, 0.9% to 2.9%) of women who tested positive on Down syndrome screening. Recurrent CNVs associated with autism and neurocognitive alterations were detected in 1.3% of karyotypically normal pregnancies-3.6% with, and 0.8% without structural anomalies. In summary, Wapner et al (2012) study included 3822 individuals with normal karyotype and the following indications for prenatal diagnosis: advanced maternal age (n=1966), positive Down syndrome screen (n=729), an anomaly on ultrasound (n=755), and other (n=372).

Breman et al (2012) evaluated the prenatal CMA results of more than 1000 fetal samples sent for testing at the medical genetics laboratories of an academic institution between 2005 and 2011.¹⁶ A total of 1124 specimens were received, of which reportable results were obtained in 1115. Maternal blood samples were required with every fetal sample (and paternal if possible) to exclude maternal cell contamination and to assist with interpretation of CNVs. In 881 (79%) of the 1115 samples, no deletions or duplications were observed using prenatal CMA analysis. Copy number changes were detected in 234 (21%) cases. Of these, 131 (11.7%) were classified as likely benign. Eighty-five (7.6%) cases were found to have clinically significant genomic imbalances. Twenty-seven microdeletion or microduplication findings (2.4% of total cases; 32% of abnormal cases) were small gains or losses below the resolution of prenatal karyotype analysis and would not have been detected by conventional chromosome studies

alone. Of these, family history was the indication for testing in 8 cases, an abnormal fluorescence in situ hybridization result was the indication for 1 case, and the remaining 18 abnormal findings were unanticipated. Eighteen (1.6%) of the 1115 specimens had results of uncertain clinical significance. An additional 17 cases were found to have multiple inherited CNVs interpreted as likely benign familial variants. The indications yielding the greatest number of clinically significant findings by microarray analysis were abnormal karyotype/fluorescence in situ hybridization (42.6%), a family history of a chromosomal abnormality (9.5%), all abnormal prenatal ultrasound findings (9.3%), abnormal serum screening (5.4%), and advanced maternal age (1.3%). In summary, the overall detection rate in the Berman et al (2012) study for clinically significant CNVs was 7.6%; the detection rate was 4.2% when the abnormal cases that had a previously identified chromosome abnormality or a known familial genomic imbalance were excluded. In 1.7% of the cases, abnormal results were obtained that were neither anticipated before microarray analysis nor detectable by conventional prenatal chromosome analysis. The clinical significance of the microarray results could not be determined in 1.7% of cases.

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.

No randomized trials were identified on the use of CMA testing for this indication.

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.

The premise of undergoing an invasive prenatal procedure and its attendant risks is that a test result will inform pregnancy decisions. Accordingly, evidence in addition to clinical validity is not required to support clinical utility.

SINGLE-GENE DISORDERS

Clinical Context and Test Purpose

The purpose of testing for single-gene disorders in individuals who are undergoing invasive prenatal testing is to inform reproductive decisions.

Review of Evidence

When there is a known pathogenic family-specific variant, the sensitivity and specificity for testing for the variant in other family members is expected to be very high. That a prenatal diagnosis established from fetal tissue is accurate is broadly accepted. For example, in a case series of spinal muscular atrophy, Kocheva et al (2008) tested Macedonian families.²³ Using restriction fragment length polymorphism (RFLP) analysis of 12 prenatal diagnostic CVS samples, 4 fetuses were determined to be homozygous for exons 7 and 8 of the *SMN1* gene and 8 fetuses were normal. The 8 fetuses were carried to term and their unaffected state confirmed; 4 pregnancies were terminated and the deletions subsequently confirmed. Also relying on RFLP analysis, Chen et al (2007) reported agreement between invasive prenatal testing results in 4 Chinese aborted fetuses homozygous for *SMN1* variants and 7 (3 normal, 4 carrier) live births.²⁴

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.

No randomized trials were identified on testing for single-gene disorders for this indication.

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.

As with CMA testing, the premise of undergoing an invasive prenatal procedure and its attendant risks is that a test result will inform pregnancy decisions. Accordingly, evidence in addition to clinical validity is not required to support clinical utility.

NEXT-GENERATION SEQUENCING

Clinical Context and Test Purpose

The purpose of next-generation sequencing (NGS) in individuals who are undergoing invasive prenatal testing is to inform reproductive decisions.

Review of Evidence

Systematic Reviews

Marchionni et al (2024) performed a systematic review and meta-analysis that compared the incremental diagnostic rate of exome sequencing over karyotype and CMA in fetuses with central nervous system anomalies.²⁵ Twelve studies were included in the analysis. The pooled incremental diagnostic yield for exome sequencing and genome sequencing over karyotype/CMA was 36% (95% CI, 28% to 45%; I²=65%).

Moradi et al (2023) conducted a systematic review and meta-analysis that compared the diagnostic yield of exome sequencing compared to CMA in fetuses with brain anomalies detected with ultrasound or magnetic resonance imaging.²⁶ The authors included 11 studies (N=779). Heterogeneity among the studies included was low. Using a random effects model, the overall diagnostic yield (weighted mean) of exome sequencing was 26.53% compared to 3.46% for CMA. The risk difference between exome sequencing and CMA in detecting complex brain anomalies was 0.36 (95% CI, 0.24 to 0.47) and 0.22 (95% CI, 0.18 to 0.25) for detecting single brain anomalies.

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.

It is not possible to construct an indirect chain of evidence for clinical utility due to the lack of clinical validity.

Ongoing and Unpublished Clinical Trials

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

SUPPLEMENTAL INFORMATION

PRACTICE GUIDELINES AND POSITION STATEMENTS

American College of Obstetricians and Gynecologists / Society for Maternal Fetal Medicine

The American College of Obstetricians and Gynecologists Committee on Genetics and the Society for Maternal Fetal Medicine have offered recommendations in 2016 on the use of chromosomal microarray testing and next-generation sequencing in prenatal diagnosis (Committee Opinion Number 682):²⁷

- “Chromosomal microarray analysis 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 karyotypes analysis, as well as submicroscopic abnormalities that are too small to be detected by traditional modalities.
- Most genetic changes identified by chromosomal microarray analysis that typically are not identified on standard karyotypes 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 chromosomal microarray analysis is recommended for a patient with a fetus with one 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 chromosomal microarray analysis can be performed.
- 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 chromosomal microarray analysis is essential.
- Chromosomal microarray analysis 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.
- The routine use of whole-genome or whole-exome sequencing for prenatal diagnosis is not recommended outside of the context of clinical trials until sufficient peer-reviewed data and validation studies are published.

The Committee Opinion was reaffirmed in 2023.

International Society for Prenatal Diagnosis, et al.

In 2018, the International Society for Prenatal Diagnosis, the Society for Maternal-Fetal Medicine, and the Perinatal Quality Foundation released a joint position statement on the use of prenatal exome and genome-wide sequencing for fetal diagnosis.²⁸ This initial position statement was replaced in 2022.²⁹ The 2022 position statement provides suggestions for clinical use, as described in the clinical indications below:

1. "The current existing data support that prenatal sequencing is beneficial for the following indications:
 - a. A current pregnancy with a fetus having a major single anomaly or multiple organ system anomalies:
 - i. For which no genetic diagnosis was found after CMA and a clinical genetic expert review considers the phenotype suggestive of a possible genetic etiology.
 - ii. For which the multiple anomaly 'pattern' strongly suggests a single gene disorder with no prior genetic testing. As pES [prenatal exome sequencing] is not currently validated to detect all CNVs [copy number variants], CMA should be run before or in parallel with pES in this scenario.
 - b. A personal (maternal or paternal) history of a prior undiagnosed fetus (or child) affected with a major single or multiple anomalies:
 - i. With a recurrence of similar anomalies in the current pregnancy without a genetic diagnosis after karyotype or CMA for the current or prior undiagnosed pregnancy. Point a.i. above also applies in these circumstances.
 - ii. When such parents present for preconception counseling and no sample is available from the affected proband, or if a fetal sample cannot be obtained in an ongoing pregnancy, it is considered appropriate to offer sequencing for both biological parents to look for shared carrier status for autosomal recessive variants that might explain the fetal phenotype. However, where possible, obtaining tissue from a previous abnormal fetus or child for pES is preferable.
 2. There is currently no evidence that supports routine testing (including upon parental request) on fetal tissue obtained from an invasive prenatal procedure (amniocentesis, CVS, cordocentesis, other) for indications other than fetal anomalies.
 - a. There may be special settings when prenatal sequencing in the absence of a fetal phenotype visible on prenatal imaging can be considered, such as with a strong family history of a recurrent childhood-onset severe genetic condition with no prenatal phenotype in previous children for whom no genetic evaluation was done and is not possible. Such scenarios should be reviewed by an expert multidisciplinary team preferentially in the context of a research protocol. If sequencing is done for this indication, it must be done as trio sequencing, using an appropriate analytical approach."
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Regulatory Status

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

Government Regulations

National:

NCD, publication number 100-3, Manual Section 190.3. Cytogenetic Studies, effective 7/16/98.

Indications and Limitations of Coverage

Medicare covers these tests when they are reasonable and necessary for the diagnosis or treatment of the following conditions:

- Genetic disorders (e.g., mongolism) in a fetus; (See the Medicare Benefit Policy Chapter 15, "Covered Medical and Other Health Services," §20.1)
- Failure of sexual development;
- Chronic myelogenous leukemia;
- Acute leukemias lymphoid (FAB L1-L3), myeloid (FAB M0-M7), and unclassified; or
- Myelodysplasia

Local:

WPS Local Coverage Decision, L34655, for services performed on or after 10/1/15, retired 9/1/15.

Indications

Cytogenetic studies may be undertaken to rule out a constitutional or acquired chromosomal abnormality. For most laboratories cytogenetic analyses now include standard G-banded chromosome analyses and/or molecular cytogenetic studies utilizing the method of fluorescence-in-situ-hybridization.

The term cytogenetic studies are used to describe the microscopic examination of the physical appearance of human chromosomes.

Medicare covers these tests when they are reasonable and necessary for the diagnosis or treatment of the following conditions:

- Genetic disorders (e.g., mongolism) in a fetus; (See the Medicare Benefit Policy Chapter 15, "Covered Medical and Other Health Services," §20.1)
- Failure of sexual development;
- Chronic myelogenous leukemia;
- Acute leukemias lymphoid (FAB L1-L3), myeloid (FAB M0-M7), and unclassified; or myelodysplasia

Constitutional chromosome abnormalities refer to those present at birth. Constitutional studies may be undertaken **PRENATALLY** or postnatally:

PRENATAL cytogenetic studies are indicated:

1. To rule out the presence of an abnormality in the fetus. Reasons for referral may include advanced maternal age (associated with an increased risk for trisomy), abnormalities observed on ultrasound, family history of a chromosome abnormality that increases risk for the current pregnancy). Cytogenetic studies are also performed on products of conception, to determine whether a chromosome abnormality was responsible for a fetal loss.

POSTNATAL cytogenetic studies are indicated:

1. To rule out a constitutional chromosome abnormality (present at birth) that may be associated with congenital anomalies, developmental delays, and/or mental retardation, and/or problems in sexual maturation or reproduction. The chromosome abnormalities involved in these disorders may be of number (gain or loss of a chromosome) or structure (e.g., deletions, duplications, derivative chromosomes resulting in both partial losses and gains of chromosomal material, inversions). Recently, with the advent of high-resolution cytogenetics and supplemental studies by fluorescence-in-situ-hybridization (FISH) it has been possible to identify very subtle abnormalities that may be associated with neurologic and developmental issues (e.g., autism) rather than the multiple congenital anomalies. Many of these abnormalities represent so-called "microduplications or microdeletions". Specific FISH probes that can evaluate the presence or loss or duplication of specific gene regions involved in these duplications and deletions are now a part of routine cytogenetic practice (e.g., probes for Prader-Willi syndrome, DiGeorge syndrome, Williams's syndrome.)
2. To rule out the presence of a balanced chromosomal rearrangement (e.g., translocation) that puts the individual at risk for having a child with multiple congenital anomalies or for risk of recurrent miscarriage.
3. To rule out the presence of a chromosome instability syndrome that predisposes to development of malignancy (e.g., Fanconi anemia, Bloom syndrome, ataxia telangiectasia)

Acquired chromosome abnormalities refer to those that are typically acquired after birth, by a subpopulation of cells that is involved in a premalignant or malignant condition.

1. It is now recognized that the majority of hematologic malignancies are associated with clonal chromosomal abnormalities. Identifying the specific chromosome abnormality is now required for differential diagnosis of many of the lymphoid and myeloid leukemias and myelodysplastic syndromes. Additionally, as many of these chromosome abnormalities have been shown to have independent prognostic significance, identification of these abnormalities has become important for determining therapeutic regimens. For certain abnormalities (e.g., the Philadelphia chromosome and the 15; 17 translocation) there are specific therapies targeted to the specific abnormalities.
2. Chromosome abnormalities for diagnosis and therapy decisions have also been identified in solid tumors including lymphomas, the small round blue cell tumors of childhood, and adult solid tumors such as breast and prostate, urinary bladder, lung and brain.
3. As with the constitutional studies, FISH studies targeted at identifying the specific gene rearrangement associated with the recurring chromosomal abnormality have become routine (e.g., the BCR/ABL fusion generated by the Philadelphia chromosome in CML and acute lymphoblastic leukemia, the PML/RARA fusion of the 15;17 translocation in APL)

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are

Related Policies

- Genetic Testing for FMR1 variants (including Fragile X Syndrome)
 - Genetic Testing, Including Chromosomal Microarray (CMA) Analysis and Next-Generation Sequencing Panels, for the Evaluation of Children with Developmental Delay/Intellectual Disability or Autism Spectrum Disorder
 - Genetic Testing-Noninvasive Prenatal Screening for Fetal Aneuploidies, microdeletions, single-gene disorders, and twin zygosity using Cell-Free DNA Genetic Testing-Preimplantation
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The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through January 2026, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
3/1/17	12/13/16	12/13/16	Joint policy established
1/1/18	10/19/17	10/19/17	Routine policy maintenance. Rationale updated, reference # 1, 11, 12, 13-16, and 18 were added. No change in policy statement.
1/1/19	10/16/18	10/16/18	Routine policy maintenance, removed Medicaid section under government section. No change in policy status.
1/1/20	10/15/19		Rationale reorganized, no references added/removed. No change in policy status.
1/1/21	10/20/20		Routine policy maintenance, no change in policy status.
1/1/22	10/19/21		Routine policy maintenance, added reference #16. No change in policy status.
5/1/22	2/15/22		Added code 81349 effective 1/1/22, codes 81228, 81229 and 81405 nomenclature revised.
5/1/23	2/21/23		Rationale updated, added references 5, 26 and 27. Added codes 0335U and 0336U as E/I. No change in policy status. (ds)
5/1/24	2/20/24		Routine policy maintenance, no change in policy status. Vendor managed: N/A (ds)
5/1/25	2/18/25		Code 0469U added as E/I. MPS separated, inclusion/exclusion section updated. Rationale updated with reference 25 & 26 added. Vendor managed: N/A (ds)
5/1/26	2/17/26		Routine policy maintenance, no change in status. Formatting changes made. Vendor managed: N/A (ds)

Next Review Date: 1st Qtr. 2027

Pre-Consolidation Medical Policy History

Original Policy Date	Comments
BCN:	Revised:
BCBSM:	Revised:

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: INVASIVE PRENATAL (FETAL) DIAGNOSTIC TESTING

I. Coverage Determination:

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

II. Administrative Guidelines:

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