MEDICAL POLICY

POLICY TITLE	INVASIVE PRENATAL (FETAL) DIAGNOSTIC TESTING
POLICY NUMBER	MP-2.278

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I. POLICY

CHROMOSOMAL MICROARRAY

In patients who are undergoing invasive diagnostic prenatal (fetal) testing, chromosome microarray (CMA) testing may be considered **medically necessary**, as an alternative to karyotyping (see Policy Guidelines).

SINGLE-GENE DISORDERS

Invasive diagnostic prenatal (fetal) testing for molecular analysis for single-gene disorders may be considered **medically necessary** when a pregnancy has been identified as being at high risk:

1. For autosomal dominant conditions, at least one of the parents has a known pathogenic variant
2. 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.
3. For X-linked conditions: A parent is suspected to be or is a known carrier.

AND, ALL of the following are met:

a. 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
b. The disease has high penetrance, AND
c. The genetic test has adequate sensitivity and specificity to guide clinical decision making and residual risk is understood, AND
d. An association of the marker with the disorder has been established.

If the above criteria for molecular analysis for single-gene disorders are not met, invasive diagnostic prenatal (fetal) testing is considered **investigational**. There is insufficient evidence to support a conclusion concerning the health outcomes or benefits associated with this procedure.

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NEXT-GENERATION SEQUENCING

The use of next-generation sequencing in the setting of invasive prenatal testing is considered **investigational**. There is insufficient evidence to support a conclusion concerning the health outcomes or benefits associated with this procedure.

POLICY GUIDELINES

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; 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 ethic 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 family-specific mutation 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 to the fetus will need to be estimated without knowing the father's genetic status.

GENETICS NOMENCLATURE UPDATE

Human Genome Variation Society (HGVS) nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. It is being implemented for genetic testing medical evidence review updates starting in 2017 (see Table PG1). HGVS nomenclature is recommended by, the Human Variome Project, the Human Genome Organization and by the HUman Genome Variation Society itself.

The American College of Medical Genetics and Genomics (ACMG) and Association for Molecular Pathology (AMP) standards and guidelines for interpretation of sequence variants represent expert opinion from ACMG, AMP, and the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table PG2 shows the recommended

standard terminology— "pathogenic," "likely pathogenic," "uncertain significance," "likely benign," and "benign"—to describe variants identified that cause Mendelian disorders.

Table PG1. Nomenclature to Report on Variants Found in DNA

Previous	Updated	Definition
Mutation	Disease-associated variant	Disease-associated change in the DNA sequence
	Variant	Change in the DNA sequence
	Familial variant	Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives

Table PG2. ACMG-AMP Standards and Guidelines for Variant Classification

Variant Classification	Definition
Pathogenic	Disease-causing change in the DNA sequence
Likely pathogenic	Likely disease-causing change in the DNA sequence
Variant of uncertain significance	Change in DNA sequence with uncertain effects on disease
Likely benign	Likely benign change in the DNA sequence
Benign	Benign change in the DNA sequence

ACMG: American College of Medical Genetics and Genomics; AMP: Association for Molecular Pathology.

GENETIC COUNSELING

Experts recommend formal genetic counseling for patients who are at risk for inherited disorders and who wish to undergo genetic testing. Interpreting the results of genetic tests and understanding risk factors can be difficult for some patients; genetic counseling helps individuals understand the impact of genetic testing, including the possible effects the test results could have on the individual or their family members. It should be noted that genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing; further, genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

Cross-reference:

MP-2.242 Genetic Testing for Developmental Delay-Intellectual Disability, Autism Spectrum Disorder, and Congenital Anomalies

MP-2.258 Carrier Screening for Genetic Diseases

MP-2.324 Whole Exome and Whole Genome Sequencing for Diagnosis of Genetic Disorders
MP-7.009 Preimplantation Genetic Testing
MP-7.028 Chromosomal Microarray Testing for the Evaluation of Pregnancy Loss

II. PRODUCT VARIATIONS

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This policy is only applicable to certain programs and products administered by Capital BlueCross please see additional information below, and subject to benefit variations as discussed in Section VI below.

FEP PPO- Refer to FEP Benefit Brochure for information on Prenatal Diagnositc Testing
https://www.fepblue.org/benefit-plans/benefit-plans-brochures-and-forms
Note* - The Federal Employee Program (FEP) Service Benefit Plan does not have a medical policy related to these services. “

III. DESCRIPTION/BACKGROUND

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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 (CMA) testing, quantitative polymerase chain reaction (PCR), next-generation sequencing (NGS), and multiplex ligation–dependent probe amplification (MLPA).

This evidence review only addresses the following:

- the diagnosis of copy number variants (CNVs) 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 3 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. Invasive prenatal procedures are usually 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.

CMA Testing

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 higher rates of detection of pathogenic chromosomal abnormalities. However, there are disadvantages to CMA analysis, including the detection of variants of uncertain significance (VUS) and the fact that it cannot detect certain types of chromosomal abnormalities, including balanced rearrangements.

CMA analyzes abnormalities at the chromosomal level and measures gains and losses of DNA (known as 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 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 (eg, a duplication of the same sequence), the sequence imbalance is detected as a difference in fluorescence intensity. For this reason, standard CMA (non-SNVs, see the following) 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 loci 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.

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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 used 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 SNVs across the genome have some advantages as well. A SNV is a DNA variation in which a single nucleotide in the genomic sequence is altered. This variation can occur between 2 different individuals or between paired chromosomes from the same individual and may or may not cause disease. Oligo/SNV 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. SNV 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 and Genomics (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 have shown 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. ACMG guidelines for designing microarrays have recommended 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 VUS.

Whole genome CMA analysis has allowed for the characterization of several new genetic syndromes, with other potential candidates currently under study. However, 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 CNV that is considered a VUS:

- 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 (eg, 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 (2008) was organized; 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 10500 “expert reviewed” variants are listed in the ClinVar database. Data are currently hosted on ClinGen.[1]

Use of the database includes an intralaboratory curation process, whereby laboratories are alerted to any inconsistencies among their own reported CNVs or other variants, as well as any inconsistent with the ISCA “known” pathogenic and “known” benign lists. The intralaboratory conflict rate was initially about 3% overall; following release of the first ISCA curated track, the intralaboratory 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 phenotype.

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
Single-gene (Mendelian) 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 SNVs 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 the more rare 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 can cost-effectively capture the majority of protein-coding regions. However, there remain concerns about technical complexity, coverage, bioinformatics, interpretation, VUSs, as well as ethical issues.[2]

Commercially Available Tests
Many academic and commercial laboratories offer CMA testing and single-gene disorder testing. Many laboratories also offer reflex testing, which may be performed with microarray testing added if karyotyping is normal or unable to be performed (due to no growth of cells). The test should be cleared or approved by the Food and Drug Administration, or performed in a Clinical Laboratory Improvement Amendment–certified laboratory.

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 Amendments (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.

IV. RATIONALE

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SUMMARY OF EVIDENCE

For individuals who are undergoing invasive diagnostic prenatal (fetal) testing who receive CMA testing, 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 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 on continuation of a pregnancy, enabling 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 has recommended CMA testing in women who are undergoing an invasive diagnostic procedure. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

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, test validity, and changes in reproductive decision making. For clinical validity, when there is a known pathogenic familial variant, the sensitivity and specificity of testing for the variant in other family members is expected to be very high. Changes in reproductive decision making could include decisions on 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 (ie, tertiary care center), and route of delivery. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who are undergoing invasive diagnostic prenatal (fetal) testing who receive next-generation sequencing, the evidence is lacking. Relevant outcomes are test accuracy, test validity, and changes in reproductive decision making. There are concerns about the interpretation of data generated by next-generation sequencing and the data's clinical relevance. The clinical validity of next-generation sequencing in the prenatal setting is unknown. The evidence is insufficient to determine the effects of the technology on health outcomes.

V. DEFINITIONS

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Amniocentesis - A test that removes a small amount of fluid that surrounds the fetus and can be used for genetic testing of the fetus or the measurement of certain biochemical markers. Traditional amniocentesis is usually performed between weeks 15 and 20 of gestation.

Aneuploidy- A chromosomal abnormality in which the number of chromosomes is abnormal, either having more or less than the normal 46 chromosomes (44 autosomal, 2 sex chromosomes).

Autosomal -Any chromosome other than the sex-chromosomes (X and Y).

Chorionic Villus Sampling -CVS is generally performed after 9 weeks of gestation. It involves obtaining chorionic villi through transcervical or transabdominal access to the placenta. (Chorionic villi are of fetal origin, and are vascular processes that emerge from the outer sac that surrounds the developing fetus and provide for exchange between the fetal and maternal circulation).

Chromosomal Inversion -A chromosome inversion occurs when 2 breaks occur in the same chromosome and the intervening genetic material is inverted before the breaks are repaired. Even though no genetic material is lost or duplicated, and the person may not show abnormalities at the phenotypic level, gene function may be altered by the rearrangement, and carriers of inversions may have children with abnormalities.

Chromosomal Translocation/Rearrangement -A chromosomal translocation refers to an abnormal rearrangement of chromosomes. There are 2 main types: a reciprocal translocation, which occurs when 2 fragments break off from 2 different chromosomes, and they change places; and a Robertsonian translocation, in which 1 chromosome becomes attached to another. Approximately 1 in 500 people have a translocation. In reciprocal and Robertsonian translocations, no chromosome material is gained or lost (which is called a *balanced translocation*). Most people who carry a balanced translocation are phenotypically normal, but they are at risk of having a child with an *unbalanced translocation*. With an unbalanced translocation, there is either an extra piece of 1 chromosome and/or a missing piece of another chromosome, which can lead to a child with learning disabilities, developmental delay, and health problems.

Cytogenetics -The study of chromosomes.

Imprinted Genes-Usually, both copies of each gene (1 copy of each gene inherited from each parent) are active. Sometimes, only 1 copy is active, which depends on parent of origin; this is what is referred to as genomic imprinting. In genes that undergo genomic imprinting, certain segments of DNA undergo methylation. Imprinted genes tend to cluster in the same regions of chromosomes. Two major clusters of imprinted genes have been identified on chromosomes 11 and 15. Prader-Willi and Angelman syndrome are caused by UPD or other errors in imprinting involving genes on chromosome 15. Beckwith-Wiedemann syndrome is associated with abnormalities of imprinted genes on chromosome 11.

Karyotyping-A test that examines chromosomes in a sample of cells (i.e., from amniotic fluid and CVS), and can count the number of chromosomes and look for large structural changes in

chromosomes. A regular human cell has 46 chromosomes, 44 autosomes, and 2 sex chromosomes which specify gender (XX=female, XY=male).

Structural Chromosome Abnormality-There is a normal number of chromosomes (46), however, a segment(s) of chromosome(s) are missing (deleted), extra (inserted), or rearranged (trans located or inverted).

Subtelomeric Rearrangements -Subtelomeric regions (present on most chromosomes) are prone to rearrangements that have been suggested to represent a high proportion of abnormalities in individuals with idiopathic intellectual disability.

Triploidy -A chromosome number of 69 (3 copies of each chromosome).

Trisomy -The presence of an extra chromosome (e.g., trisomies 13, 18, 21 [Down syndrome]).

Uniparental Disomy-Normally, for each of the 23 pairs of chromosomes, 1 is inherited from the mother and the other from the father. UPD is an abnormal situation in which both chromosomes in a pair are inherited from 1 parent, and the other parent's chromosome from that pair is missing. UPD for most chromosomes is without consequence, but for some chromosomes, it can result in a genetic disorder. The most well-known conditions that result from UPD include Prader-Willi syndrome and Angelman syndrome.

VI. BENEFIT VARIATIONS TOP

The existence of this medical policy does not mean that this service is a covered benefit under the member's health benefit plan. Benefit determinations should be based in all cases on the applicable health benefit plan language. Medical policies do not constitute a description of benefits. A member's health benefit plan governs which services are covered, which are excluded, which are subject to benefit limits and which require preauthorization. There are different benefit plan designs in each product administered by Capital BlueCross. Members and providers should consult the member's health benefit plan for information or contact Capital BlueCross for benefit information.

VII. DISCLAIMER TOP

Capital BlueCross's medical policies are developed to assist in administering a member's benefits, do not constitute medical advice and are subject to change. Treating providers are solely responsible for medical advice and treatment of members. Members should discuss any medical policy related to their coverage or condition with their provider and consult their benefit information to determine if the service is covered. If there is a discrepancy between this medical policy and a member's benefit information, the benefit information will govern. If a provider or a member has a question concerning the application of this medical policy to a specific member's plan of benefits, please contact Capital BlueCross' Provider Services or Member Services.

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Capital BlueCross considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.

VIII. CODING INFORMATION

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Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

When used to bill for next-generation sequencing in the setting of invasive prenatal testing it is considered Investigational; therefore not covered:

CPT Codes®							
81470							

Covered when medically necessary:

CPT Codes®								
81228	81229	81405						

ICD-10-CM Diagnosis Code	Description
O09.891	Supervision of other high risk pregnancies, first trimester
O09.892	Supervision of other high risk pregnancies, second trimester
O09.893	Supervision of other high risk pregnancies, third trimester
O28.5	Abnormal chromosomal and genetic finding on antenatal screening of mother
O35.1XX1	Maternal care for (suspected) chromosomal abnormality in fetus, fetus 1
O35.1XX2	Maternal care for (suspected) chromosomal abnormality in fetus, fetus 2
O35.1XX3	Maternal care for (suspected) chromosomal abnormality in fetus, fetus 3
O35.1XX4	Maternal care for (suspected) chromosomal abnormality in fetus, fetus 4
O35.1XX5	Maternal care for (suspected) chromosomal abnormality in fetus, fetus 5
O35.1XX9	Maternal care for (suspected) chromosomal abnormality in fetus, other fetus
O35.2XX1	Maternal care for (suspected) hereditary disease in fetus, fetus 1
O35.2XX2	Maternal care for (suspected) hereditary disease in fetus, fetus 2
O35.2XX3	Maternal care for (suspected) hereditary disease in fetus, fetus 3
O35.2XX4	Maternal care for (suspected) hereditary disease in fetus, fetus 4
O35.2XX5	Maternal care for (suspected) hereditary disease in fetus, fetus 5
O35.2XX9	Maternal care for (suspected) hereditary disease in fetus, other fetus

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X. POLICY HISTORY

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MP-2.278	**CAC 3/24/15 New policy BCBSA adopted.** Invasive prenatal (fetal) diagnostic testing is medically necessary using CMA and for single-gene disorders when criteria for each category are met. NGS is considered investigational. Chromosomal microarray analysis for prenatal genetic testing was previously addressed in MP-2.242 Chromosomal Microarray (CMA) analysis for the Genetic Evaluation of Patients with Developmental Delay/Intellectual Disability or Autism Spectrum Disorder and was considered investigational. Policy coded.
	CAC 3/29/16 Consensus review. No change to the policy statements. References and rationale updated. Coding reviewed.
	11/15/16 Administrative update. Variation Reformatting. Added standard FEP variation.
	CAC 3/28/17 Consensus review. Policy statements unchanged. Policy Guidelines, Cross-Reference, Description/Background and Rationale sections updated. Appendix added. Coding Reviewed
	12/20/17 Consensus review. No change to policy statements. Rationale and references updated.
	11/13/18 Consensus review. No change to the policy statements. No references were added. Rationale revised**.** Appendix removed.
	8/16/2019 Consensus review. Policy statement unchanged. Tables reformatted. References updated.
	7/7/20 Consensus review. Policy statement unchanged. Genetic counseling information updated. References updated.

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