MEDICAL POLICY

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

CLINICAL BENEFIT	☒ MINIMIZE SAFETY RISK OR CONCERN. ☒ MINIMIZE HARMFUL OR INEFFECTIVE INTERVENTIONS. ☐ ASSURE APPROPRIATE LEVEL OF CARE. ☐ ASSURE APPROPRIATE DURATION OF SERVICE FOR INTERVENTIONS. ☒ ASSURE THAT RECOMMENDED MEDICAL PREREQUISITES HAVE BEEN MET. ☐ ASSURE APPROPRIATE SITE OF TREATMENT OR SERVICE.
Effective Date:	**RETIRED 7/1/2026**

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).

Low-pass genome sequencing analysis testing may be considered **medically necessary** as an alternative to CMA testing.

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.

WHOLE EXOME SEQUENCING

Prenatal diagnostic whole exome sequencing, with or without trio testing, is considered **investigational**

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 general 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.

POLICY TITLE	INVASIVE PRENATAL (FETAL) DIAGNOSTIC TESTING
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Cross-References:

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 Blue Cross and subject to benefit variations as discussed in Section VI. Please see additional information below.

FEP PPO- Refer to FEP Medical Policy Manual. The FEP Medical Policy manual can be found at:

https://www.fepblue.org/benefit-plans/medical-policies-and-utilization-management-guidelines/medical-policies .

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.

In 2016, the American College of Obstetrics and Gynecology published Committee Opinion Number 682, which was later reaffirmed in 2020, titled Microarrays and Next-Generation Sequencing Technology: The Use of Advanced Genetic Diagnostic Tools in Obstetrics and Gynecology. In the opinion, they offered the following recommendations:

- 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 karyotype 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 karyotype are not associated with increasing maternal age; therefore, the use of this test can be considered for all women, regardless of age, who undergo prenatal diagnostic testing.
- Prenatal 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.
- Chromosomal microarray analysis of fetal tissue (i.e., amniotic fluid, placenta, or products of conception) is recommended in the evaluation of intrauterine fetal death or stillbirth when further cytogenetic analysis is desired because of the test's increased likelihood of obtaining results and improved detection of causative abnormalities.
- 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 American College of Genetics and Genomics also published a policy statement in 2012 titled “Points to Consider in the clinical application of genomic sequencing”. In this, they offered indications for diagnostic testing:

WGS/WES should be considered in the clinical diagnostic assessment of a phenotypically affected individual when:

- The phenotype or family history data strongly implicate a genetic etiology, but the phenotype does not correspond with a specific disorder for which a genetic test targeting a specific gene is available on a clinical basis.
- A patient presents with a defined genetic disorder that demonstrates a high degree of genetic heterogeneity, making WES or WGS analysis of multiple genes simultaneously a more practical approach.
- A patient presents with a likely genetic disorder, but specific genetic tests available for that phenotype have failed to arrive at a diagnosis.
- A fetus with a likely genetic disorder in which specific genetic tests, including targeted sequencing tests, available for that phenotype have failed to arrive at a diagnosis.

Prenatal diagnosis by genomic (i.e., next-generation whole-exome or whole-genome) sequencing has significant limitations. The current technology does not support short turnaround times, which are often expected in the prenatal setting. There are high rates of false positives, false negatives, and variants of unknown clinical significance. These can be expected to be significantly higher than seen when array CGH is used in prenatal diagnosis.

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. This initial position statement was replaced in 2022. 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 mutations 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."

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 (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-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.

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 (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 (2008) was organized; it established a public database containing de-identified 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.

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 expert's 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.

Low Pass Genome Sequencing

Low pass genome sequencing is a type of genomic analysis that evaluates a larger piece of genome, but at a lower coverage depth, allowing for a broader analysis of the genome. Several studies have revealed improved diagnostic yield over CMA, as well as CNV detection at higher resolutions in comparison with CMA. Other studies have highlighted higher sensitivity and lower cost.

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 rarer disorders. For most single-gene disorders, testing in the prenatal setting requires knowledge of the familial variants.

Whole Exome Sequencing

Whole exome sequencing examines specific coding regions of the genome, which generally have greater clinical relevance and applicability to patient care. Some research shows that WES is able to identify genomic abnormality in up to 20-30% of fetuses that were missed by standard genetic testing (i.e., karyotyping, CMA). The American College of Medical Genetics and Genomics recommends considering whole-exome sequencing when specific genetic tests available for a phenotype, including targeted sequencing tests, have failed to determine a diagnosis in a fetus with multiple congenital anomalies suggestive of a genetic disorder. However, 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. In general, at this time, whole-exome sequencing should be ordered only after consultation with a clinical genetics' physician. Trio testing (sequencing of the fetus and the biological parents) increases the diagnostic yield.

Whole exome sequencing does have limitations in regards to prenatal testing, including a possibility of high rates of false negatives, false positives, and variants of unknown significance. Because of this, the College and the Society for Maternal–Fetal Medicine recommend that all patients considering whole-exome sequencing receive counseling from an obstetrician–gynecologist or other health care provider with genetics expertise who is well versed in these technologies. Additionally, they currently do not recommend whole-exome sequencing for routine use in prenatal diagnosis. In select circumstances (recurrent or lethal fetal anomalies in which other approaches have been noninformative), whole-exome sequencing may be considered as a diagnostic tool, but only after other appropriate testing has been noninformative and after extensive counseling by an obstetrician–gynecologist or other health care provider with genetics expertise who is familiar with these new technologies and their limitations.

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.

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 (i.e., 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.

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VI. DISCLAIMER

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Capital Blue Cross' medical policies are used to determine coverage for specific medical technologies, procedures, equipment, and services. These medical policies do not constitute medical advice and are subject to change as required by law or applicable clinical evidence from independent treatment guidelines. Treating providers are solely responsible for medical advice and treatment of members. These polices are not a guarantee of coverage or payment. Payment of claims is subject to a determination regarding the member's benefit program and eligibility on the date of service, and a determination that the services are medically necessary and appropriate. Final processing of a claim is based upon the terms of contract that applies to the members' benefit program, including benefit limitations and exclusions. If a provider or a member has a question concerning this medical policy, please contact Capital Blue Cross' Provider Services or Member Services.

VII. 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:

Procedure Codes							
81470							

Investigational, therefore not covered:

Procedure Codes								
0335U	0336U	0469U						

Covered when medically necessary:

Procedure Codes								
81228	81229	81349	81405	0567U				

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
O35.02X0	Maternal care for (suspected) central nervous system malformation or damage in fetus, anencephaly, not applicable or unspecified

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ICD-10-CM Diagnosis Code	Description
O35.02X1	Maternal care for (suspected) central nervous system malformation or damage in fetus, anencephaly, fetus 1
O35.02X2	Maternal care for (suspected) central nervous system malformation or damage in fetus, anencephaly, fetus 2
O35.02X3	Maternal care for (suspected) central nervous system malformation or damage in fetus, anencephaly, fetus 3
O35.02X4	Maternal care for (suspected) central nervous system malformation or damage in fetus, anencephaly, fetus 4
O35.02X5	Maternal care for (suspected) central nervous system malformation or damage in fetus, anencephaly, fetus 5
O35.02X9	Maternal care for (suspected) central nervous system malformation or damage in fetus, anencephaly, other fetus
O35.10X0	Maternal care for (suspected) chromosomal abnormality in fetus, unspecified, not applicable, or unspecified
O35.10X1	Maternal care for (suspected) chromosomal abnormality in fetus, unspecified, fetus 1
O35.10X2	Maternal care for (suspected) chromosomal abnormality in fetus, unspecified, fetus 2
O35.10X3	Maternal care for (suspected) chromosomal abnormality in fetus, unspecified, fetus 3
O35.10X4	Maternal care for (suspected) chromosomal abnormality in fetus, unspecified, fetus 4
O35.10X5	Maternal care for (suspected) chromosomal abnormality in fetus, unspecified, fetus 5
O35.10X9	Maternal care for (suspected) chromosomal abnormality in fetus, unspecified, other fetus
O35.11X0	Maternal care for (suspected) chromosomal abnormality in fetus, Trisomy 13, not applicable or unspecified
O35.11X1	Maternal care for (suspected) chromosomal abnormality in fetus, Trisomy 13, fetus 1
O35.11X2	Maternal care for (suspected) chromosomal abnormality in fetus, Trisomy 13, fetus 2
O35.11X3	Maternal care for (suspected) chromosomal abnormality in fetus, Trisomy 13, fetus 3
O35.11X4	Maternal care for (suspected) chromosomal abnormality in fetus, Trisomy 13, fetus 4
O35.11X5	Maternal care for (suspected) chromosomal abnormality in fetus, Trisomy 13, fetus 5
O35.11X9	Maternal care for (suspected) chromosomal abnormality in fetus, Trisomy 13, other fetus

POLICY TITLE	INVASIVE PRENATAL (FETAL) DIAGNOSTIC TESTING
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ICD-10-CM Diagnosis Code	Description
O35.12X0	Maternal care for (suspected) chromosomal abnormality in fetus, Trisomy 18, not applicable or unspecified
O35.12X1	Maternal care for (suspected) chromosomal abnormality in fetus, Trisomy 18, fetus 1
O35.12X2	Maternal care for (suspected) chromosomal abnormality in fetus, Trisomy 18, fetus 2
O35.12X3	Maternal care for (suspected) chromosomal abnormality in fetus, Trisomy 18, fetus 3
O35.12X4	Maternal care for (suspected) chromosomal abnormality in fetus, Trisomy 18, fetus 4
O35.12X5	Maternal care for (suspected) chromosomal abnormality in fetus, Trisomy 18, fetus 5
O35.12X9	Maternal care for (suspected) chromosomal abnormality in fetus, Trisomy 18, other fetus
O35.13X0	Maternal care for (suspected) chromosomal abnormality in fetus, Trisomy 21, not applicable or unspecified
O35.13X1	Maternal care for (suspected) chromosomal abnormality in fetus, Trisomy 21, fetus 1
O35.13X2	Maternal care for (suspected) chromosomal abnormality in fetus, Trisomy 21, fetus 2
O35.13X3	Maternal care for (suspected) chromosomal abnormality in fetus, Trisomy 21, fetus 3
O35.13X4	Maternal care for (suspected) chromosomal abnormality in fetus, Trisomy 21, fetus 4
O35.13X5	Maternal care for (suspected) chromosomal abnormality in fetus, Trisomy 21, fetus 5
O35.13X9	Maternal care for (suspected) chromosomal abnormality in fetus, Trisomy 21, other fetus
O35.14X0	Maternal care for (suspected) chromosomal abnormality in fetus, Turner Syndrome, not applicable or unspecified
O35.14X1	Maternal care for (suspected) chromosomal abnormality in fetus, Turner Syndrome, fetus 1
O35.14X2	Maternal care for (suspected) chromosomal abnormality in fetus, Turner Syndrome, fetus 2
O35.14X3	Maternal care for (suspected) chromosomal abnormality in fetus, Turner Syndrome, fetus 3
O35.14X4	Maternal care for (suspected) chromosomal abnormality in fetus, Turner Syndrome, fetus 4
O35.14X5	Maternal care for (suspected) chromosomal abnormality in fetus, Turner Syndrome, fetus 5

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ICD-10-CM Diagnosis Code	Description
O35.14X9	Maternal care for (suspected) chromosomal abnormality in fetus, Turner Syndrome, other fetus
O35.15X0	Maternal care for (suspected) chromosomal abnormality in fetus, sex chromosome abnormality, not applicable or unspecified
O35.15X1	Maternal care for (suspected) chromosomal abnormality in fetus, sex chromosome abnormality, fetus 1
O35.15X2	Maternal care for (suspected) chromosomal abnormality in fetus, sex chromosome abnormality, fetus 2
O35.15X3	Maternal care for (suspected) chromosomal abnormality in fetus, sex chromosome abnormality, fetus 3
O35.15X4	Maternal care for (suspected) chromosomal abnormality in fetus, sex chromosome abnormality, fetus 4
O35.15X5	Maternal care for (suspected) chromosomal abnormality in fetus, sex chromosome abnormality, fetus 5
O35.15X9	Maternal care for (suspected) chromosomal abnormality in fetus, sex chromosome abnormality, other fetus
O35.19X0	Maternal care for (suspected) chromosomal abnormality in fetus, other chromosomal abnormality, not applicable or unspecified
O35.19X1	Maternal care for (suspected) chromosomal abnormality in fetus, other chromosomal abnormality, fetus 1
O35.19X2	Maternal care for (suspected) chromosomal abnormality in fetus, other chromosomal abnormality, fetus 2
O35.19X3	Maternal care for (suspected) chromosomal abnormality in fetus, other chromosomal abnormality, fetus 3
O35.19X4	Maternal care for (suspected) chromosomal abnormality in fetus, other chromosomal abnormality, fetus 4
O35.19X5	Maternal care for (suspected) chromosomal abnormality in fetus, other chromosomal abnormality, fetus 5
O35.19X9	Maternal care for (suspected) chromosomal abnormality in fetus, other chromosomal abnormality, 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
O35.AXX0	Maternal care for other (suspected) fetal abnormality and damage, fetal facial anomalies, not applicable or unspecified
O35.AXX1	Maternal care for other (suspected) fetal abnormality and damage, fetal facial anomalies, fetus 1

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ICD-10-CM Diagnosis Code	Description
O35.AXX2	Maternal care for other (suspected) fetal abnormality and damage, fetal facial anomalies, fetus 2
O35.AXX3	Maternal care for other (suspected) fetal abnormality and damage, fetal facial anomalies, fetus 3
O35.AXX4	Maternal care for other (suspected) fetal abnormality and damage, fetal facial anomalies, fetus 4
O35.AXX5	Maternal care for other (suspected) fetal abnormality and damage, fetal facial anomalies, fetus 5
O35.AXX9	Maternal care for other (suspected) fetal abnormality and damage, fetal facial anomalies, other fetus
O35.BXX0	Maternal care for other (suspected) fetal abnormality and damage, fetal cardiac anomalies, not applicable or unspecified
O35.BXX1	Maternal care for other (suspected) fetal abnormality and damage, fetal cardiac anomalies, fetus 1
O35.BXX2	Maternal care for other (suspected) fetal abnormality and damage, fetal cardiac anomalies, fetus 2
O35.BXX3	Maternal care for other (suspected) fetal abnormality and damage, fetal cardiac anomalies, fetus 3
O35.BXX4	Maternal care for other (suspected) fetal abnormality and damage, fetal cardiac anomalies, fetus 4
O35.BXX5	Maternal care for other (suspected) fetal abnormality and damage, fetal cardiac anomalies, fetus 5
O35.BXX9	Maternal care for other (suspected) fetal abnormality and damage, fetal cardiac anomalies, other fetus
O35.EXX0	Maternal care for other (suspected) fetal abnormality and damage, fetal genitourinary anomalies, not applicable or unspecified
O35.EXX1	Maternal care for other (suspected) fetal abnormality and damage, fetal genitourinary anomalies, fetus 1
O35.EXX2	Maternal care for other (suspected) fetal abnormality and damage, fetal genitourinary anomalies, fetus 2
O35.EXX3	Maternal care for other (suspected) fetal abnormality and damage, fetal genitourinary anomalies, fetus 3
O35.EXX4	Maternal care for other (suspected) fetal abnormality and damage, fetal genitourinary anomalies, fetus 4
O35.EXX5	Maternal care for other (suspected) fetal abnormality and damage, fetal genitourinary anomalies, fetus 5
O35.EXX9	Maternal care for other (suspected) fetal abnormality and damage, fetal genitourinary anomalies, other fetus
O35.FXX0	Maternal care for other (suspected) fetal abnormality and damage, fetal musculoskeletal anomalies of trunk, not applicable or unspecified

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ICD-10-CM Diagnosis Code	Description
O35.FXX1	Maternal care for other (suspected) fetal abnormality and damage, fetal musculoskeletal anomalies of trunk, fetus 1
O35.FXX2	Maternal care for other (suspected) fetal abnormality and damage, fetal musculoskeletal anomalies of trunk, fetus 2
O35.FXX3	Maternal care for other (suspected) fetal abnormality and damage, fetal musculoskeletal anomalies of trunk, fetus 3
O35.FXX4	Maternal care for other (suspected) fetal abnormality and damage, fetal musculoskeletal anomalies of trunk, fetus 4
O35.FXX5	Maternal care for other (suspected) fetal abnormality and damage, fetal musculoskeletal anomalies of trunk, fetus 5
O35.FXX9	Maternal care for other (suspected) fetal abnormality and damage, fetal musculoskeletal anomalies of trunk, other fetus
O35.GXX0	Maternal care for other (suspected) fetal abnormality and damage, fetal upper extremities anomalies, not applicable or unspecified
O35.GXX1	Maternal care for other (suspected) fetal abnormality and damage, fetal upper extremities anomalies, fetus 1
O35.GXX2	Maternal care for other (suspected) fetal abnormality and damage, fetal upper extremities anomalies, fetus 2
O35.GXX3	Maternal care for other (suspected) fetal abnormality and damage, fetal upper extremities anomalies, fetus 3
O35.GXX4	Maternal care for other (suspected) fetal abnormality and damage, fetal upper extremities anomalies, fetus 4
O35.GXX5	Maternal care for other (suspected) fetal abnormality and damage, fetal upper extremities anomalies, fetus 5
O35.GXX9	Maternal care for other (suspected) fetal abnormality and damage, fetal upper extremities anomalies, other fetus
O35.HXX0	Maternal care for other (suspected) fetal abnormality and damage, fetal lower extremities anomalies, not applicable or unspecified
O35.HXX1	Maternal care for other (suspected) fetal abnormality and damage, fetal lower extremities anomalies, fetus 1
O35.HXX2	Maternal care for other (suspected) fetal abnormality and damage, fetal lower extremities anomalies, fetus 2
O35.HXX3	Maternal care for other (suspected) fetal abnormality and damage, fetal lower extremities anomalies, fetus 3
O35.HXX4	Maternal care for other (suspected) fetal abnormality and damage, fetal lower extremities anomalies, fetus 4
O35.HXX5	Maternal care for other (suspected) fetal abnormality and damage, fetal lower extremities anomalies, fetus 5
O35.HXX9	Maternal care for other (suspected) fetal abnormality and damage, fetal lower extremities anomalies, other fetus

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IX. POLICY HISTORY

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MP 2.278	**07/07/2020 Consensus Review.** Policy statement unchanged. Genetic counseling information updated. References updated.
	08/11/2021 Consensus Review. Updated FEP and references. No changes to coding.

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	12/02/2021 Administrative Update. Added new code 81349. Effective date 01/01/2022.
	07/27/2022 Administrative Update. Added 98 new ICD-10 codes. Deleted 6 ICD-10 codes (O35.1XX1-O35.1XX5 and O35.1XX9). Added new Procedure codes: 0335U & 0336U Effective 10/01/2022.
	10/24/2022 Minor Review. Added low pass sequencing as MN, and whole exome sequencing as NMN. Codes 0335U and 0336U are now NMN. Updated background, FEP, references. Coding reviewed.
	10/11/2023 Consensus Review. No changes to policy statement. Updated references. Coding reviewed, no changes.
	06/12/2024 Administrative Update. Added 0469U as NMN. Effective 07/01/2024.
	11/07/2024 Minor Review. Updated prenatal diagnostic whole exome sequencing to INV from NMN along with 0335U, 0336U, and 0469U. Updated references.
	06/10/2025 Administrative Update. Added 0567U as NMN. Effective 07/01/2025.
	06/12/2025 Administrative Update. Removed Benefit Variations Section and updated Disclaimer.
	08/14/2025 Consensus Review. No changes to policy statement.
	03/09/2026 Retirement Review. EviCore Delegation.

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