Introduction

Invasive prenatal testing is done before a baby is born. This testing is usually done when the baby has been identified as having a higher risk of problems with chromosomes. It’s also done when there’s a family history of a disorder caused by a change to a single gene, such as sickle cell anemia. Tests are done on samples of cells taken from the placenta (chorionic villi sampling) or a small sample of the fluid that surrounds the baby (amniocentesis). Different types of testing can then be done on these samples. Chromosomal microarray analysis (CMA) looks at chromosomes for extra or missing pieces of genetic material. Single-gene testing is done to see if the baby has inherited a changed gene from a parent that is known to cause a specific disorder. This policy describes when invasive prenatal testing may be considered medically necessary. Next-generation sequencing, which looks at many genes at one time to try to find a genetic disorder, is considered investigational (unproven). There is not enough high-quality medical evidence to determine if this kind of testing improves health results.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.
## Policy Coverage Criteria

<table>
<thead>
<tr>
<th>Testing</th>
<th>Medical Necessity</th>
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</table>
| **Chromosomal microarray analysis** | Chromosomal microarray analysis (CMA) testing may be considered medically necessary as an alternative or as a follow up test to karyotyping for any of the following indications:  
  - A fetus with one or more major structural abnormalities identified on ultrasound  
  - Women age 35 and older  
  - An abnormal maternal serum screen (e.g., quad screen)  
  - Further workup of a known chromosomal abnormality that was found by karyotype or FISH |
| **Single-gene disorders**           | Invasive diagnostic prenatal (fetal) genetic testing for single-gene disorders may be considered medically necessary when a pregnancy has been identified as being at high risk such as:  
  - For autosomal dominant conditions, at least 1 of the parents has a known pathogenic mutation  
  - 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 have high penetrance  
    - **AND**  
    - The genetic test has adequate sensitivity and specificity to guide clinical decision making and residual risk is understood  
    - **AND** |
<table>
<thead>
<tr>
<th>Testing</th>
<th>Medical Necessity</th>
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<tbody>
<tr>
<td></td>
<td>o An association of the marker with the disorder has been established.</td>
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</table>

If the above criteria for molecular analysis for single-gene disorders are not met, invasive diagnostic prenatal (fetal) testing is considered investigational.

<table>
<thead>
<tr>
<th>Testing</th>
<th>Investigational</th>
</tr>
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<tbody>
<tr>
<td>Next-generation sequencing</td>
<td>The use of next-generation sequencing in the setting of invasive prenatal testing is considered investigational.</td>
</tr>
</tbody>
</table>

## Coding

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>CPT</td>
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<tr>
<td>81228</td>
<td>Cytogenomic constitutional (genome-wide) microarray analysis; interrogation of genomic regions for copy number variants (eg, bacterial artificial chromosome [BAC] or oligo-based comparative genomic hybridization [CGH] microarray analysis)</td>
</tr>
<tr>
<td>81229</td>
<td>Interrogation of genomic regions for copy number and single nucleotide polymorphism (SNP) variants for chromosomal abnormalities</td>
</tr>
<tr>
<td>81405</td>
<td>Cytogenomic constitutional targeted microarray analysis of chromosome 22q13 by interrogation of genomic regions for copy number and single nucleotide polymorphism (SNP) variants for chromosomal abnormalities</td>
</tr>
<tr>
<td>81470</td>
<td>X-linked intellectual disability (XLID) (eg, syndromic and non-syndromic XLID); genomic sequence analysis panel, must include sequencing of at least 60 genes, including ARX, ATRX, CDKL5, FGD1, FMR1, HUWE1, IL1RAPL, KDM5C, L1CAM, MECP2, MED12, MID1, OCRL, RPS6KA3, and SLC16A2</td>
</tr>
<tr>
<td>81471</td>
<td>X-linked intellectual disability (XLID) (eg, syndromic and non-syndromic XLID); duplication/deletion gene analysis, must include analysis of at least 60 genes, including ARX, ATRX, CDKL5, FGD1, FMR1, HUWE1, IL1RAPL, KDM5C, L1CAM, MECP2, MED12, MID1, OCRL, RPS6KA3, and SLC16A2</td>
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</table>

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**Definition of Terms**

**Amniocentesis:** A test that removes a small amount of fluid that surrounds the fetus in the womb 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 there are more or fewer 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.
**Genotype:** The genetic makeup of an organism.

**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.

**Invasive prenatal (fetal) testing:** Direct testing of fetal tissue, typically by chorionic villus sampling (CVS) or amniocentesis. 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.

**Karyotyping:** A test that examines chromosomes in a sample of cells (ie, from amniotic fluid and CVS), and counts the number of chromosomes and looks 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]).

**Phenotype:** The observable characteristics or traits that are expressed by genes

**Structural chromosome abnormality:** There is a normal number of chromosomes (46), however, a segment(s) of chromosome(s) is missing (deleted), extra (inserted), or rearranged (translocated or inverted).

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

**Trisomy:** The presence of an extra chromosome (eg, 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.
Chromosomal Microarray Analysis

The American College of Obstetricians and Gynecologists has recommended that chromosomal microarray analysis (CMA) testing be performed in patients who are undergoing invasive prenatal diagnostic testing in the following situations:

- Prenatal CMA analysis is recommended for a patient with a fetus with 1 or more major structural abnormalities identified on ultrasonographic examination and who is undergoing invasive prenatal diagnosis. This test typically can replace the need for fetal karyotype.
- In a patient with a structurally normal fetus who is undergoing invasive prenatal diagnostic testing, either fetal karyotyping or CMA analysis can be performed.

Fetal Structural 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;
- CNS: 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 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 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.

Genetic Counseling

Genetic counseling is primarily aimed at patients who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is being 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.

Evidence Review

Description

Invasive prenatal (fetal) diagnostic testing may be used to confirm the presence of a pathogenic abnormality after it has been determined by prenatal screening that the fetus is at increased risk for one of these conditions. This policy will only address the use of chromosomal microarray testing, molecular diagnosis of single-gene disorders, and next-generation sequencing.
Background

The focus of this policy is on the use of certain invasive diagnostic testing methodologies in the prenatal (fetal) setting and 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 in order to assist with pregnancy management, eg, 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 policy 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 point mutations or very small deletions and use molecular methods to diagnose (mainly PCR, but also MLPA)
- NGS

This policy applies only if there is not a separate medical policy that outlines specific criteria for diagnostic testing. If a separate medical policy does exist, then the criteria for medical necessity in that policy supersede the guidelines in this policy. This policy does NOT cover the use of:

- Prenatal carrier testing (see Related Policies)
- Preimplantation genetic diagnosis or screening (see Related Policies)
- Noninvasive prenatal testing (see Related Policies)
- Testing in the setting of fetal demise (see Related Policies)

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 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.

**Chromosomal Microarray Analysis**

CMA technology has several advantages over karyotyping, including improved resolution (detection of smaller chromosomal variants that are undetectable using standard karyotyping). As a result, CMA testing can better detect 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.

**Types of CMA Technologies**

There are some 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 BAC. These 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 2 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 exist as to 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 Variants of Unknown Significance**

CNVs (copy number variants) 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, polymerase chain reaction [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 polymorphisms whereas those appearing de novo are likely pathogenic. Etiology may become more certain as other similar cases accrue.

In 2008, the International Standards for Cytogenomic Arrays (ISCA) Consortium was organized. It established a public database containing de-identified whole genome microarray data from a subset of the ISCA Consortium’s member clinical diagnostic laboratories. Array analysis was carried out on subjects with phenotypes including intellectual disability, autism, and developmental delay. As of June 2016, there were over 53,900 total cases in the database. Data are currently hosted on ClinGen. Use of the database includes an intra-laboratory curation process, whereby laboratories are alerted to any inconsistencies among their own reported CNVs or other mutations, as well as any not consistent with the ISCA’s “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 inter-laboratory curation process, whereby a group of expert curates reported CNVs/mutations 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) DisordersSingle-gene (Mendelian) disorders include those with an inheritance mode of autosomal dominant or recessive, or 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.

Summary of Evidence

Chromosomal Microarray (CMA) Analysis

For individuals who are undergoing invasive diagnostic prenatal (fetal) testing who receive chromosomal microarray (CMA) 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 uncertain clinical significance. However, such results can be minimized by the use of targeted arrays, testing phenotypically normal parents for the copy number variant (CNV), and the continued accumulation of pathogenic variants in international databases. The highest yield of pathogenic CNVs by CMA testing has been found in fetuses with malformations identified by ultrasound. As a result of testing, changes in reproductive decision making could include:

- Whether to continue a pregnancy
- Deciding how and when to treat an identified fetal condition (treating it medically or surgically, either in utero or immediately after birth and
- Birthing decisions (place and route of delivery).

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. Therefore this testing is considered medically necessary and is covered as noted.

**Single-gene Disorders**

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 accuracy, test validity, and changes in reproductive decision making. The analytic validity in the diagnosis of single-gene disorders depends on the individual variant being tested. 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 of testing for the variant in other family members is expected to be very high. Changes in reproductive decision making could include:

- Whether to continue a pregnancy
- Deciding how and when to treat an identified fetal condition (treating it medically or surgically, either in utero or immediately after birth and
• Birthing decisions (place and route of delivery).

The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome. Therefore, this testing is considered medically necessary and is covered as noted.

**Invasive diagnostic Prenatal (Fetal Testing) using NGS**

For individuals who are undergoing invasive diagnostic prenatal (fetal) testing who receive next-generation sequencing (NGS), the evidence is lacking. Relevant outcomes are test accuracy, test validity, and changes in reproductive decision making. There are concerns about interpretation of data generated by NGS and the data’s clinical relevance. The analytic and clinical validity of NGS in the prenatal setting are unknown. The evidence is insufficient to determine the effects of the technology on health outcomes. Therefore, this is considered investigational and not covered.

**Ongoing and Unpublished Clinical Trials**

A search of [ClinicalTrials.gov](https://clinicaltrials.gov) in April 2017 did not identify any ongoing or unpublished trials that would likely influence this review.

**Practice Guidelines and Position Statements**

*The American College of Obstetricians and Gynecologists Committee on Genetics and the Society for Maternal Fetal Medicine*

The American College of Obstetricians and Gynecologists and the Society for Maternal-Fetal Medicine have offered recommendations in 2016 on the use of chromosomal microarray analysis testing and next-generation sequencing in prenatal diagnosis:

• 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 karyotyping.

• 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.

**Medicare National Coverage**

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

**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.
References


<table>
<thead>
<tr>
<th>Date</th>
<th>Comments</th>
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<tr>
<td>12/08/14</td>
<td>New Policy. Policy created with literature review through August 28, 2014. 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.</td>
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<td>02/18/15</td>
<td>Update Related Policies. Change title to 4.01.21.</td>
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<tr>
<td>01/12/16</td>
<td>Update Related Policies and Background information. Replace 12.04.107 with 12.04519; policy renumbered.</td>
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<tr>
<td>01/01/17</td>
<td>Annual Review, approved December 13, 2016. Policy statement revised: Medically necessary criteria added for chromosomal microarray testing. Reference 10 added.</td>
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