# Test Specific Guidelines

# Chromosomal Microarray for Prenatal Diagnosis

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## Introduction

**Chromosomal microarray analysis for prenatal diagnosis is addressed by this guideline.**

**Procedures Addressed**

**The inclusion of any procedure code in this table is provided for informational purposes and is not a guarantee of coverage nor an indication that prior authorization is required.**

| Procedures addressed by this guideline | Procedure codes |
|---|---|
| Chromosomal Microarray [BAC or CGH], Constitutional | 81228 |
| Chromosomal Microarray [SNP], Constitutional | 81229 |
| Cytogenomic (genome-wide) analysis for constitutional chromosomal abnormalities; interrogation of genomic regions for copy number and loss-of-heterozygosity variants, low-pass sequencing analysis | 81349 |

## What Are Copy Number Variants in Developmental Disorders?

## Introduction

**Copy number variation is a difference in the number of copies of genetic material between individuals.**

**Copy Number Variants (CNVs)**

**Copy number variants (CNVs) are deletions and duplications of genetic material. CNVs account for a significant proportion of congenital anomalies and developmental disorders without a clear etiology based on clinical findings. CNVs are detected using chromosomal microarray (CMA) testing. CMA is known by**

several names including array-comparative genomic hybridization (aCGH) and single-nucleotide polymorphism arrays (SNP-array).

## Prevalence

Intellectual disability (ID) and congenital anomalies affect approximately 3-4% of the general population.[1-3] Sixty to eighty percent of major structural anomalies are identified prenatally by ultrasound evaluation.[4]

## Cause

The etiology of congenital anomalies is complex. Some developmental problems may be caused by environmental factors, such as injury and infection. However, genetic causes also play a significant role.[1-3]

## First-line Test

Routine chromosome analysis (karyotyping) by chorionic villus sampling (CVS) or amniocentesis has historically been the first-line test in the evaluation of a pregnancy identified with congenital birth defects.[5] In 2010, CMA was recommended as the first-line postnatal test for individuals with developmental disabilities or congenital anomalies.[1-2] In 2012, a large multi-center study showed that prenatal CMA detected more clinically significant chromosomal abnormalities and CNVs than karyotyping. The additional yield was 6% when ultrasound showed a fetal abnormality and 1.7% when the reason for testing was maternal age or abnormal maternal serum screen results.[6]

CMA on chorionic villi or amniocytes is indicated in any pregnancy in which diagnostic testing for chromosome abnormalities and CNVs is desired.[5-7] Identifying an underlying genetic cause in these individuals may:[1]

- provide diagnostic and prognostic information
- guide prenatal management and decision-making, and
- allow for testing of family members and accurate recurrence risk counseling.

## Clinical Classification of CNVs

In a joint consensus recommendation, the American College of Medical Genetics and Genomics (ACMG) and the Clinical Genome resource (ClinGen) introduced updated standards to help reduce discordance in clinical classifications of CNVs, including those detected during postnatal or prenatal testing.[8] The standards include a semi-quantitative point-based scoring system metric for CNV classification, including separate scoring metrics for copy number losses and copy number gains. Evaluation of the inheritance pattern, including whether the CNV is inherited or a new (de novo) genetic change, factors into this scoring system.

# Test Information

## Introduction

**Prenatal diagnosis may include chromosomal microarray (CMA) testing.**

**Chromosomal Microarray**

**CMA testing generally works by fluorescently tagging DNA from an individual's test sample with one color and combining it with a control sample tagged in a different color. The two samples are mixed and then added to the array chip, where they compete to hybridize with the DNA fragments on the chip. By comparing the test sample versus the control, computer analysis can determine where genetic material has been deleted or duplicated in the individual.**

**There are a growing number of CMA testing platforms, including non-chip based applications, which differ in approach and resolution. Clinical laboratories may not only differ in the arrays that they utilize but also in their reporting practices. Although testing guidelines do not endorse one CMA over another, it is typically advisable that coverage of an ordered CMA is better than that offered by a standard karyotype and that the minimum resolution of the CMA provided by the laboratory is adequate. The inclusion of analysis of subtelomeric regions and known microdeletion syndromes with CMA testing obviates the need for additional FISH analysis.**

**CMA testing offers advantages over conventional karyotyping with regard to resolution and yield. However, there are some limitations of CMA testing including:**

- **the inability to detect**
  - **balanced chromosomal rearrangements such as translocations or inversions**
  - **certain forms of polyploidy**
  - **sex chromosome aneuploidy dependent on the gender control used**
  - **low level mosaicism**
  - **some marker chromosomes**
- **the detection of CNVs of uncertain clinical significance**
- **the inability to differentiate free trisomies from unbalanced Robertsonian translocations.**

# Guidelines and Evidence

## Introduction

**This section includes relevant guidelines and evidence pertaining to CMA for**

prenatal diagnosis.

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 (ACOG and SMFM, 2016) published a joint practice bulletin regarding the application of chromosomal microarray in the prenatal setting. This practice bulletin recommended CMA "as the primary test (replacing conventional karyotype) for patients undergoing prenatal diagnosis for the indication of a fetal structure abnormality detected by ultrasound examination...It is recommended that chromosomal microarray analysis be made available to any patient choosing to undergo invasive diagnostic testing."[5]

Diagnostic Yield of CMA

Diagnostic yield of CMA testing differs based on clinical presentation. The results of one recent multicenter trial of CMA in the prenatal setting were published in 2012.[6] This study reported that CMA identified a clinically relevant deletion or duplication in 6% of prenatal cases with a structural anomaly and normal karyotype. In addition, 1.7% of prenatal cases with an indication of advanced maternal age or positive screening results and normal karyotype had a clinically relevant deletion or duplication identified by CMA.[6]

In a large series of fetuses with ultrasound anomalies and normal conventional karyotype, CMA detected chromosome abnormalities in 5% of fetuses and up to 10% in those with 3 or more anatomic abnormalities.[9]

## Criteria

### Introduction

Requests for CMA for prenatal diagnosis are reviewed using these criteria.

- Genetic Counseling:
  - Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing:
  - No previous chromosomal microarray testing in the same pregnancy, AND
- Diagnostic Prenatal Testing:‡
  - The member has sufficient risk of fetal CNV to justify invasive prenatal diagnosis. [It is important to note that invasive diagnostic procedures such as chorionic villus sampling and amniocentesis are associated with risks; the provider and member must have determined that the associated benefits outweigh the risks.]

**‡Microarray may also be used in association with in utero fetal demise, stillbirth, or neonatal death. For information on microarray analysis on fetal tissue after delivery, please refer to the guideline *Chromosomal Microarray Testing for Developmental Disorders* as this testing is not addressed here.**

**Chromosomal Microarray (CMA) Exclusions and Considerations**

**If routine karyotype and CMA are ordered simultaneously, only the most appropriate test based on clinical history will be considered for coverage. If CMA has been performed, the following tests are often excessive and thus not considered medically necessary. Each test may require medical necessity review.**

- **Routine karyotype: Full karyotype in addition to CMA is typically considered excessive. However, a limited 5 cell analysis may be approved in addition to CMA if criteria for CMA are met. This approval may be subject to claims review to ensure that the appropriate procedure code for a limited 5 cell analysis is billed (CPT 88261 x1, 88230 x1, 88291 x1).**
- **FISH Analysis**
- **Telomere Analysis**
- **More than one type of microarray analysis (i.e. if 81228 performed, 81229 is not medically necessary)**

**Billing and Reimbursement Considerations**

- **FISH or other procedure codes that do not accurately describe the test methodology performed (e.g. 88271) are not eligible for reimbursement of CMA.**

## References

### Introduction

**These references are cited in this guideline.**

1. **Manning M, Hudgins L; for the Professional Practice and Guidelines Committee. American College of Medical Genetics Practice Guidelines: Array-based technology and recommendations for utilization in medical genetics practice for detection of chromosomal abnormalities. *Genet Med*. 2010 Nov 12(11);742-5.doi: 10.1097/GIM.0b013e3181f8baad**
2. **Manning M, Hudgins L; for the Professional Practice and Guidelines Committee. American College of Medical Genetics Clinical Practice Resource (Addendum to 2010): Array-based technology and recommendations for utilization in medical genetics practice for detection of chromosomal abnormalities. *Genet Med.* Reaffirmed 2020;22:2126.**

3. Miller DT, Adam MP, Aradhya S, et al. Consensus statement: Chromosomal Microarray Is a First-Tier Clinical Diagnostic Test for Individuals with Developmental Disabilities or Congenital Anomalies. *Am J Hum Genet*. 2010 May:86(5):749-64.
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6. Wapner RJ, Martin CI, Levy B, et al. Chromosomal Microarray versus Karyotyping for Prenatal Diagnosis. *N Engl J Med*. Dec:367(23):2175-84.
7. Hay SB, Sahoo T, Travis MK, et al. ACOG and SMFM guidelines for prenatal diagnosis; Is karyotyping really sufficient? *Prenat Diagn*. 2018 Feb: 38(3):184-89.
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9. Hillman SC, Pretlove S, Coomarasamy A, et al. Additional information from array comparative genomic hybridization technology over conventional karotyping in prenatal diagnosis: a systemic review and meta-analysis. *Ultrasound Obstet Gynecol*. 2011 Jan:37(1):6-14.