Chromosomal Microarray for Prenatal Diagnosis

Introduction

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

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan’s procedure code list for management requirements.

<table>
<thead>
<tr>
<th>Procedures addressed by this guideline</th>
<th>Procedure codes</th>
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<tr>
<td>Chromosomal Microarray [BAC or CGH], Constitutional</td>
<td>81228</td>
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<tr>
<td>Chromosomal Microarray [SNP], Constitutional</td>
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What are copy number variants in developmental disorders

Introduction

Copy number variants (CNVs) are deletions and duplications of genetic material that are too small to be seen with routine chromosome analysis (karyotyping). CNVs account for a significant proportion of congenital anomalies and developmental disorders without a clear etiology based on clinical findings.\(^1\)\(^2\) CNVs are detected using chromosomal microarray analysis (CMA). CMA is known by several names including comparative genomic hybridization (CGH) and single-nucleotide polymorphism arrays (SNP-array).\(^1\)\(^2\)

Prevalence

Intellectual disability (ID) and congenital birth defects affect approximately 3-4% of the general population.\(^1\)\(^2\) Sixty to eighty percent of major structural birth defects are identified prenatally by ultrasound evaluation.\(^3\)
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.\textsuperscript{1,2}

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.\textsuperscript{4} In 2010, CMA was recommended as the first-line postnatal test for individuals with developmental disabilities or congenital anomalies.\textsuperscript{1} 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.\textsuperscript{5}

CMA on chorionic villi or amniocytes is indicated in any pregnancy in which diagnostic testing for chromosome abnormalities and CNVs is desired.\textsuperscript{6,7} Identifying an underlying genetic cause in these patients may:

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

CNV detected in fetus

If a unique CNV is detected in a fetus, it is usually necessary to test both parents to determine whether the CNV is inherited or a new (de novo) genetic change. This information along with parental clinical findings can be used to weigh the possibilities of a benign vs. pathogenic variant. However, even with parental studies, the clinical outcome may remain unclear.\textsuperscript{8} A de novo variant is more likely to represent a pathogenic abnormality.\textsuperscript{8}

Test information

Introduction

Prenatal diagnosis may include chromosomal microarray (CMA) testing.

Chromosomal microarray

Chromosomal microarray (CMA) testing generally works by fluorescently tagging DNA from a patient 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.

**Coverage and resolution**

There are a growing number of CMA testing platforms, including non-chip based applications, which differ in approach and resolution. Testing guidelines do not endorse one CMA over another. However, international consensus guidelines do suggest that CMAs should have coverage better than that offered by a standard karyotype (~5 Mb), and resolution of greater than or equal to 400 kb throughout the genome.\(^4\)

**Subtelomeric and disease-specific FISH tests not needed**

CMAs include the subtelomeric regions and all known chromosome microdeletion syndrome regions, such as those for 22q11.2 (DiGeorge) syndrome, Williams syndrome (7p11.2), and Smith-Magenis syndrome (17p11.2). Therefore, subtelomeric and disease-specific FISH tests are not needed in parallel with CMA, or as follow-up to normal CMA results.

**Cell division in culture not required**

In contrast to typical chromosome analysis, CMA testing does not require dividing cells in culture. This makes testing possible in samples that may be difficult to culture, such as those from perinatal losses.\(^5,6\)

**Limitations of CMA**

While there are significant advantages of CMA over conventional karyotyping with regard to resolution and yield, there are disadvantages as well. Limitations of CMA include

- the inability to detect
  - balanced translocations or inversions
  - certain forms of polyploidy
  - low level mosaicism
  - some marker chromosomes, and
- the detection of CNVs of uncertain clinical significance
- the inability to differentiate free trisomies from unbalanced Robertsonian translocations, and
- the high cost of testing as compared to traditional karotyping.\(^2\)
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 (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."\(^6\)

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.\(^5\) 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.\(^5\)

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.\(^12\)

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:\(^2\)
  - 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 patient 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. If microarray will be performed on fetal tissue after delivery, reference the Chromosomal Microarray Testing for Developmental Disorders guideline.

Exclusions and other 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.


