Chromosomal Microarray Testing For Developmental Disorders

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Introduction

Chromosomal microarray testing for developmental disorders 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.

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<th>Procedures addressed by this guideline</th>
<th>Procedure codes</th>
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What are copy number variants in developmental disorders

Introduction

Copy number variants (CNVs) are small deletions and duplications of genetic material and account for a significant proportion of 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 birth defects affect approximately 3-4% of the general population.1 Autism spectrum disorders (ASD), which now includes autistic disorder, pervasive developmental disorder not otherwise specified (PDD-NOS), and Asperger syndrome are also of increasing concern, with recent CDC incidence figures estimating 1 in 54 affected children.2
Cause

The etiology of developmental disorders 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{1,3}

A causative explanation can be determined in about 40-60\% of patients with ID\textsuperscript{3} and in over 30\% of patients with ASD.\textsuperscript{3} Identifying an underlying genetic cause in these patients may:\textsuperscript{3-5}

\begin{itemize}
  \item provide diagnostic and prognostic information
  \item improve health screening and prevention for some conditions
  \item allow for testing of family members and accurate recurrence risk counseling, and
  \item empower the patient and family to acquire needed services and support.
\end{itemize}

Diagnostic yield

Diagnostic yield differs based on clinical presentation:

\begin{itemize}
  \item Approximately 10-19\% of people with unexplained ID or developmental delay (DD) will have CNVs.\textsuperscript{5-8}
  \item The diagnostic yield in individuals with ASD is higher in those with a syndromic presentation, meaning that they have additional findings.\textsuperscript{3}
  \item About 13\% of spontaneous pregnancy losses that occurred between 10 and 20 weeks gestation had CNVs identified in one small prospective study.\textsuperscript{9} Whereas data on earlier losses is conflicting. One meta-analysis shows only about a 2\% increase in diagnostic yield when performing CMA instead of karyotype, and another shows an approximate 55\% diagnostic yield when performing CMA in first trimester losses.\textsuperscript{10,11}
  \item Chromosomal microarray may also be useful in the workup of non-immune fetal hydrops.\textsuperscript{12,13}
\end{itemize}

Parental testing

If a CNV is detected in a child, it may be helpful to test both parents to determine whether the CNV is inherited or a new (de novo) genetic change. This information along with parental 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{6,7} A de novo variant is more likely to represent a pathologic abnormality.\textsuperscript{6}
Test information

Introduction

Testing for developmental disorders may include chromosomal microarray 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 is 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.⁶

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.

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:⁵

- 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 chromosomal microarray testing for developmental disorders.

American College of Medical Genetics

The American College of Medical Genetics (ACMG, 2010 reaffirmed 2020) Professional Practice and Guidelines Committee recommends CMA as a first-tier test for the evaluation of individuals who have the following:4,5

- “Multiple anomalies not specific to a well-defined genetic syndrome.”
- “Apparently non-syndromic DD [developmental delay]/ID [intellectual disability].”
- “Autism spectrum disorders”

International Standard Cytogenomic Array Consortium

The International Standard Cytogenomic Array Consortium (ISCA, 2010) recommends offering CMA as a first-tier genetic test, in place of karyotype, for patients with unexplained developmental delay/intellectual disability, autism spectrum disorders, or birth defects.6

American College of Obstetricians and Gynecologists and Society for Maternal Fetal Medicine

The American College of Obstetricians and Gynecologists (ACOG, 2016) and Society for Maternal Fetal Medicine (SMFM, 2016) joint committee opinion on chromosomal microarray states that:14

- “Chromosomal microarray analysis of fetal tissue (i.e. amniotic fluid, placenta, or products of conception) is recommended in the evaluation of intrauterine 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.”
- “Additional information is needed regarding the clinical use and cost-effectiveness in cases of recurrent miscarriage and structurally normal pregnancy losses at less than 20 weeks of gestation.”
- “[T]he 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.”
Society for Maternal Fetal Medicine

The Society for Maternal Fetal Medicine (SMFM, 2016) published a consult series that states:

- “We recommend that CMA be offered when genetic analysis is performed in cases with fetal structural anomalies and/or stillbirth and replaces the need for fetal karyotype in these cases (GRADE 1A).”

Criteria

Introduction

Requests for chromosomal microarray testing for developmental disorders are reviewed using these criteria.

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 (CMA) testing, AND
- Diagnostic Testing for Symptomatic Individuals:
  - Testing performed on living child or adult, and
  - Diagnosis cannot be made on clinical evaluation alone, and
  - Common aneuploidy (trisomy 13, 18, 21, or sex chromosome) is not a suspected diagnosis, and
  - One of the following presentations:
    - Isolated DD/ID, or
    - DD/ID associated with other findings that are not consistent with an easily recognizable syndrome, or
    - Autism spectrum disorder, or
    - Multiple congenital anomalies† not specific to a well-delineated genetic syndrome, OR
- Diagnostic Testing for Intrauterine Fetal Demise or Stillbirth:
  - Common aneuploidy (trisomy 13, 18, 21, or sex chromosome) is not a suspected diagnosis, and
- Multiple congenital anomalies† not specific to a well-delineated genetic syndrome, or
- Fetal demise or stillbirth occurred at 20 weeks of gestation or later

*Microarray is considered a first tier test in the evaluation of postnatal developmental disorders. Therefore, it often is not necessary to do chromosome analysis or FISH in conjunction with microarray. Microarray requests following such testing will require review.

†Multiple congenital anomalies defined as 1) two or more major anomalies affecting different organ systems or 2) one major and two or more minor anomalies affecting different organ systems. [Major structural abnormalities are generally serious enough as to require medical treatment on their own (such as surgery) and are not minor developmental variations that may or may not suggest an underlying disorder.]

**If microarray will be performed on prenatally-obtained sample, refer to the Chromosomal Microarray Testing for Prenatal Diagnosis guideline.

Exclusions and other considerations

- CMA is not considered medically necessary in cases of family history of chromosome rearrangement in phenotypically normal individuals
- CMA is not considered medically necessary in individuals experiencing infertility, structurally normal pregnancy losses that occur at less than 20 weeks, or recurrent pregnancy loss.15
- 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 are 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).
  - FISH analysis
  - Telomere/subtelomere analysis
  - More than one type of microarray analysis (i.e. if 81228 performed, 81229 is not medically necessary)
- When a multigene deletion/duplication panel is being requested and billed using a microarray procedure code (typically 81228 or 81229), please refer to the Genetic Testing by Multigene Panels clinical use guideline; do not apply the criteria in this guideline.
• CMA for delineation of translocation breakpoints will be reviewed on a case by case basis.
• CMA for determination of whether a translocation is balanced or unbalanced will be reviewed on a case by case basis.

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.


