Guidelines for Medical Necessity Determination for Chromosomal Microarray Analysis

These *Guidelines for Medical Necessity Determination* (Guidelines) identify the clinical information that MassHealth needs to determine medical necessity for chromosomal microarray analysis. These Guidelines are based on generally accepted standards of practice, review of the medical literature, and federal and state policies and laws applicable to Medicaid programs.

Providers should consult MassHealth regulations at 130 CMR 433.000 and 130 CMR 450.000 and Subchapter 6 of the *Physician Manual* for information about coverage, limitations, service conditions, and prior-authorization (PA) requirements.

Providers serving members enrolled in a MassHealth-contracted accountable care partnership plan (ACPP), managed care organization (MCO), One Care Organization, Senior Care Options (SCO) plan, or a Program of All-inclusive Care for the Elderly (PACE) should refer to the ACPP's, MCO's, One Care organization's, SCO's, or PACE's medical policies, respectively, for covered services.

MassHealth requires PA for chromosomal microarray analysis and reviews PA requests on the basis of medical necessity. If MassHealth approves the request, payment is still subject to all general conditions of MassHealth, including member eligibility, other insurance, and program restrictions.

1 SECTION I. GENERAL INFORMATION

Chromosomal microarray analysis (CMA) is a technique used to detect chromosomal abnormalities, such as deletions or duplications, with a high sensitivity for submicroscopic abnormalities as small as 10-20 kb, which are typically too small to detect by karyotyping. Conventional karyotyping requires a labor-intensive process where the cells are cultured, and chromosomes in the metaphase are prepared on slides and examined by light microscopy. While this test is useful in the detection of balanced chromosome rearrangements, whole chromosome, or large segments of deletion and duplication, it does not consistently identify genomic defects that are submicroscopic or smaller than are visible under a light microscope.

CMA, also referred to as array comparative genomic hybridization (aCGH) or molecular karyotyping, is done by hybridizing or binding the DNA obtained from a sample specimen to an array platform consisting of DNA probes on a microscope slide, silicon chip, or nylon membrane. Both the sample specimen and the DNA probes are fluorescently labelled with different dyes, and the fluorescence ratio of the test and reference signals after hybridization is determined at different positions along the genome. The resulting fluorescent ratios are measured and plotted relative to each clone's position in the genome. This provides information on the relative copy number of sequences or copy number variants (CNV) present.

The CNV revealed by CMA in the prenatal and postnatal setting enable the detection of pathologic microdeletions or duplications that may identify the cause of neurodevelopmental disorders and

congenital anomalies. Advantages of CMA include increased sensitivity and faster availability of results than karyotyping, since DNA can be obtained from uncultured specimens for CMA. Drawbacks of CMA include the detection of chromosomal variants of unknown clinical significance and the inability to detect balanced chromosomal rearrangements (translocations or inversions); some instances of mosaicism; point mutations; or tiny duplications or deletions within a single gene.

All genetic testing should be accompanied by comprehensive pre-test and post-test genetic counseling by a geneticist who can explain the limitations and significance of genetic testing. Informed consent should be obtained and should include a discussion of the potential to identify variants of unknown significance, non-paternity, consanguinity, and disease.

MassHealth considers approval for coverage of CMA on an individual, case-by-case basis, in accordance with 130 CMR 433.000 and 130 CMR 450.000.

PRENATAL CMA TESTING

Prenatal CMA testing is recommended in place of karyotyping for its increased sensitivity, detection of clinically relevant genomic imbalances, and decreased turnaround times in a fetus with one or more major structural abnormalities identified on ultrasonographic examination and/or who is undergoing invasive prenatal testing, such as amniocentesis or chorionic villus sampling (CVS). Most genetic changes identified by CMA but not on standard karyotype are not associated with maternal age.

The prevalence of significant abnormalities identified by CMA in cases of normal karyotype and normal ultrasound was 1 in 60 (1.7 percent). For this reason, the choice of CMA or conventional karyotyping can be offered to a woman who has a normal obstetric ultrasound but is undergoing invasive CVS, after discussing the benefits and limitations of both CMA and conventional karyotyping. CMA is unable to detect balanced chromosome rearrangements, but these are unlikely to be clinically significant. An accurate diagnosis is essential to providing an appropriate care plan, prognosis, risk of complications, and genetic counseling for future pregnancies.

Miscarriages mostly occur within the first trimester and can occur in 10-15 percent of all recognized pregnancies. Chromosomal abnormalities account for about half of these miscarriages, the majority of which are aneuploidies (abnormal number of chromosomes), such as trisomies (one extra chromosome) or polyploidies (extra complete set of chromosomes). CMA of fetal tissue is recommended over conventional karyotyping in the evaluation of intrauterine fetal demise ≥ 20 weeks (including stillbirth) because of its increased sensitivity. It is recommended for intrauterine fetal demise less than 20 weeks with associated structural abnormalities on ultrasound. An accurate diagnosis is essential to providing an appropriate care plan and genetic counseling for future pregnancies.

There is insufficient data to support the clinical use and cost effectiveness of CMA testing of fetal tissue at less than 20 weeks of gestation in cases of a single miscarriage.

Preimplantation genetic testing and diagnosis is considered infertility treatment, which is not a covered MassHealth service. See 130 CMR 433.404(C) and 433.451(B).

POSTNATAL CMA TESTING IN THE EVALUATION OF GLOBAL DEVELOPMENTAL DELAY, INTELLECTUAL DISABILITIES, MULTIPLE CONGENITAL ANOMALIES, AND AUTISM SPECTRUM DISORDERS IN CHILDREN

The term "intellectual disability" (ID) is defined by the American Association on Intellectual and Developmental Disability as a disability originating before 18 years of age, characterized by significant limitations in both intellectual functioning and in adaptive behavior, expressed in many everyday social and practical skills. Adaptive behavior includes conceptual, social, and practical skills. Intellectual functioning includes mental capacity such as learning, reasoning, and problem solving.

"Global developmental delay" (GDD) is a significant delay in two or more developmental domains (gross or fine motor, speech/language, cognitive, social/personal, or activities of daily living) recorded by developmental specialists. GDD is the term used typically in younger children (generally under the age of five), and ID is used for older children. The incidence of GDD/ID is almost three percent in the general population.

Congenital anomalies are also known as birth defects, congenital disorders, or congenital malformations, and can be common, affecting an estimated two-to-three infants in every 100 births. Congenital anomalies occur during intrauterine life and can be identified prenatally or at birth, or sometimes may be detected only postnatally. Examples of congenital anomalies include organ malformations or craniofacial malformations.

The autism spectrum disorders (ASD) include a collection of disorders that exhibit impaired socialization and communication, with stereotypic behaviors. The diagnosis of ASD is made by a developmental specialist (developmental pediatrician or pediatric neurologist). The diagnosis can be made using the Autism Diagnostic Interview—Revised and the Autism Diagnostic Observation Schedule. Developmental specialists may also use a series of standardized evaluation instruments. ASD affects one of every 150 individuals.

An accurate diagnosis for children with GD/ID, multiple congenital anomalies, and ASD is essential to providing an appropriate care plan, a prognosis, an explanation of the risk of complications, and genetic counseling about future siblings. Work-up for children with any of these conditions should begin with a comprehensive history and exams, including

- prenatal and birth history, if available;
- family history which, if available, includes a pedigree of three generations or more;
- a comprehensive physical, neurological, and behavioral exam; and
- laboratory testing, imaging, and consultations, if indicated by history and physical.

The above exams may provide or suggest a syndrome or diagnosis. If, after the above exams, causal diagnosis is still unknown for GDD/ID, multiple congenital anomalies, or ASD, then CMA is appropriate.

CMA is now considered a first-tier genetic diagnostic test in all children with GDD/ID, multiple congenital anomalies, and autism spectrum disorder for whom a diagnosis is not known. However, without other evidence, children with isolated speech and language delay are not appropriate candidates for comprehensive genetic evaluations such as CMA, as isolated speech and language delays are unlikely to be caused by a significant, identifiable genetic abnormality.

2 SECTION II. CLINICAL GUIDELINES

A. CLINICAL COVERAGE

MassHealth bases its determination of medical necessity for CMA on clinical data including, but not limited to, indicators that would affect the relative risks and benefits of the test. These criteria include, but are not limited to, the following.

1. PRENATAL CMA TESTING

Prenatal CMA testing is medically necessary when the following criteria are met.

a. A fetus is undergoing invasive prenatal testing (such as amniocentesis or chorionic villus sampling); there is intrauterine fetal demise after ≥ 20 weeks (including stillbirth); or the pregnant person has had two or more miscarriages at ≤ 20 weeks;

AND

b. Comprehensive genetic counseling has been performed by a provider with genetics expertise (genetic counselor, geneticist, or developmental specialist).

2. POSTNATAL CMA TESTING

Postnatal CMA testing is medically necessary for the detection of chromosomal abnormalities in the evaluation of GDD, ID, multiple congenital anomalies, and/or ASD in children when the following criteria are met.

a. A diagnosis of intellectual disability (ID) as defined by the American Association on Intellectual and Developmental Disability, made by a treating physician, which includes ALL of the following.

i. The child is younger than 18.

ii. The child has significant limitations in intellectual functioning as determined by standardized testing (e.g., IQ less than 70).

iii. The child has significant limitations in adaptive behavior (conceptual, social, and practical skills) demonstrated on standardized testing.

OR

b. A diagnosis of global developmental delay (GDD), defined as a significant delay in two or more developmental domains thought to predict a future diagnosis of ID, including any of the following developmental domains:

i. gross or fine motor;

ii. speech/language;

iii. cognitive;

iv. social/personal; and

v. activities of daily living.

The diagnosis must be made by an experienced developmental specialist (pediatric neurologist or developmental pediatrician), using norm-referenced and age-appropriate standardized measures of development;

OR

a diagnosis of multiple congenital anomalies, such as organ malformations or craniofacial malformations;

OR

a diagnosis of ASD made by a licensed physician or psychologist experienced in the diagnosis and treatment of autism;

AND

a comprehensive history and exams do not identify an obvious diagnosis, genetic disorder, or metabolic derangement responsible for the clinical findings. Such history and exams include, but are not limited to,

1. consultations;
2. prenatal and birth history, if available;
3. family history which, if available, includes a pedigree of three generations or more;
4. a comprehensive physical, neurological, and behavioral exam;
5. laboratory testing, imaging, and consultations, if indicated by history and physical; and
6. comprehensive genetic counseling has been performed by a clinician with genetics expertise (genetic counsellor, geneticist, or developmental specialist).

B. NONCOVERAGE

MassHealth does not consider CMA to be medically necessary under certain circumstances. Examples of such circumstances include, but are not limited to, the following.

1. PRENATAL CMA TESTING

a. In cases of a single miscarriage with pregnancy loss at less than 20 weeks of gestation, where the fetus is structurally normal, or pregnancy losses where structural condition of the pregnancy(ies) is unknown.

OR

b. An obvious diagnosis, genetic disorder, or metabolic derangement is responsible for the obstetric ultrasound findings or pregnancy loss (including stillbirth), based on a comprehensive history and exams, including

   i. prenatal and birth history, if available;
   ii. family history which, if available, includes a pedigree of three generations or more;
   iii. a comprehensive physical, neurological, and behavioral exam; and
   iv. laboratory testing, imaging, and consultations, if indicated by history and physical.

2. POSTNATAL CMA TESTING

CMA is not considered medically necessary

a. in children with isolated delays, such as in speech or motor; or

b. when an obvious diagnosis, genetic disorder, or metabolic derangement is responsible for the clinical findings, based on a comprehensive history and exams, including

   i. prenatal and birth history, if available;

   ii. family history which, if available, includes a pedigree of three generations or more;

   iii. a comprehensive physical, neurological, and behavioral exam; and

   iv. laboratory testing, imaging and consultations, if indicated by history and physical.

SECTION III. SUBMITTING CLINICAL DOCUMENTATION

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Requests for PA for chromosomal microarray analysis must be submitted by the treating medical geneticist or physician and accompanied by clinical documentation that supports the medical necessity for this procedure.

Documentation of medical necessity must include all of the following.

1. Diagnoses
2. A comprehensive history and exams, including prenatal and birth history, if available, which includes a pedigree of three generations or more performed by a developmental specialist (pediatric neurologist or developmental pediatrician)
3. A current comprehensive physical, neurological, and behavioral exam performed by a developmental specialist (pediatric neurologist or developmental pediatrician)
4. Results of laboratory testing, imaging, and consultations, where indicated by history and physical
5. Copies of all standardized testing performed and any accompanying report
6. Documentation of genetic counselling performed by a provider with genetics expertise
7. A completed MassHealth Prior Authorization Request form signed by the ordering provider
8. Any other clinical information that MassHealth may request

All PA requests must be submitted by a medical geneticist or physician. Providers must electronically submit PA requests and all supporting documentation using the Provider Online Service Center (POSC), unless the provider has a currently approved electronic claims waiver (hereinafter, "waiver"). Please see All Provider Bulletin 369 for further waiver information. If you have questions about POSC access, please contact the MassHealth Customer Service Center at (800) 841-2900, TDD/TTY: 711.

For PA requests that are not submitted using the POSC, providers with currently approved waivers must include the MassHealth Prior Authorization Request (PA-1 Form) and all supporting documentation. The PA-1 Form can be found at mass.gov/prior-authorization-for-masshealth-providers.

CODE	DEFINITION
81228	Cytogenomic constitutional (genome-wide) microarray analysis; interrogation of genomic regions for copy number variants [e.g., bacterial artificial chromosome (BAC) or oligo-based comparative genomic hybridization (CGH) microarray analysis]
81229	Cytogenomic constitutional (genome-wide) microarray analysis; interrogation of genomic regions for copy number and single nucleotide polymorphism (SNP) variants for chromosomal abnormalities

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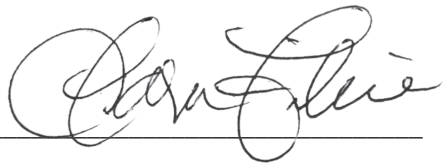
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These Guidelines are based on review of the medical literature and current practice in chromosomal microarray analysis. MassHealth reserves the right to review and update the contents of these Guidelines and cited references as new clinical evidence and medical technology emerge.

This document was prepared for medical professionals to assist them in submitting documentation supporting the medical necessity of the proposed treatment, products, or services. Some language used in this communication may be unfamiliar to other readers; such readers are encouraged to contact their health care provider for guidance or explanation.

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