# Comparative Genomic Hybridization/Chromosomal Microarray Analysis

Humana

**Medical Coverage Policy**

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**Change Summary:** Updated References

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State and federal law, as well as contract language, including definitions and specific inclusions/exclusions, take precedence over clinical policy and must be considered first in determining eligibility for coverage. Coverage may also differ for our Medicare and/or Medicaid members based on any applicable Centers for Medicare & Medicaid Services (CMS) coverage statements including National Coverage Determinations (NCD), Local Medical Review Policies (LMRP) and/or Local Coverage Determinations. Refer to the CMS website. The member's health plan benefits in effect on the date services are rendered must be used. Clinical policy is not intended to pre-empt the judgment of the reviewing medical director or dictate to health care providers how to practice medicine. Health care providers are expected to exercise their medical judgment in rendering appropriate care. Identification of selected brand names of devices, tests and procedures in a medical coverage policy is for reference only and is not an endorsement of any one device, test or procedure over another. Clinical technology is constantly evolving, and we reserve the right to review and update this policy periodically. 

## Description

Comparative genomic hybridization (CGH) (also known as array CGH [aCGH]) is a laboratory method to aid in the detection of extra (duplicated) or missing (deleted) chromosomal segments, often referred to as copy number variants (CNVs). CGH may also be referred to as chromosomal microarray analysis (CMA).

CGH is a microchip-based test that provides analysis of many pieces of deoxyribonucleic acid (DNA). The technique works by comparing the DNA content of an individual undergoing testing to that of a reference sample. A difference between the two samples indicates a variant. aCGH offers a higher resolution than conventional CGH.

Two common microarray platforms include oligonucleotide (oligos) and single nucleotide polymorphism (SNP) arrays. Oligonucleotides are short single strands of chemically synthesized (laboratory-made) DNA or RNA. SNP arrays are used to detect DNA variations that occur when a single nucleotide (adenine, thymine, cytosine or guanine) in the genome sequence is altered.

The design of microarrays include whole genome and targeted arrays. Whole genome arrays cover the entire human genome while targeted arrays analyze specific regions of the genome.

CGH can be used for a variety of indications including, but may not be limited to, the evaluation of autism spectrum disorder (ASD), hematologic malignancies, hereditary myeloid malignancy predisposition syndromes (HMMPS), global developmental delay (GDD), intellectual disability (ID) (eg, intellectual development disorder), melanoma, microcephaly, microdeletion/microduplication syndromes, multiple congenital anomalies, pregnancy loss and prenatal assessment of fetal structural anomalies.

*FMRI* gene testing for fragile X syndrome is often ordered adjunctively with CGH for the evaluation of individuals diagnosed with ASD, GDD or ID. For information regarding **gene testing for fragile X syndrome,** please refer to Genetic Testing for Diagnosis of Noncancer Indications Medical Coverage Policy.

CGH has been suggested for preimplantation genetic testing for aneuploidy (PGT-A). For information regarding **PGT-A,** please refer to Preimplantation Genetic Testing Medical Coverage Policy.

For information regarding **genetic testing for the following,** please refer to Genetic Testing Medical Coverage Policy:

- DNA banking or preservation
- General population screening
- Individual 17 years of age or younger for adult-onset conditions
- Interpretation and reporting for molecular pathology procedure
- Polygenic risk score (PRS) and single nucleotide polymorphisms (SNPs)
- Repeat germline or somatic genetic testing
- Retrieved archival tissue

Humana recognizes that the field of genetic testing is rapidly changing and that other tests may become available.

## Coverage Determination

**Pregnancy Loss and Prenatal Indications**

**Any state mandates for CGH/CMA take precedence over this medical coverage policy.**

**Genetic testing may be excluded by certificate. Please consult the member's individual certificate regarding Plan coverage.**

Apply General Criteria for Genetic and Pharmacogenomics Tests when disease- or gene-specific criteria are not available on a medical coverage policy. For information regarding **general criteria for genetic tests,** please refer to Genetic Testing Medical Coverage Policy.

Humana member may be eligible under the Plan for **CGH/CMA for the following pregnancy loss and prenatal indications** when criteria are met:

- Evaluation of fetal tissue (amniotic fluid, placenta or products of conception) for intrauterine fetal demise or stillbirth when karyotype has been performed and a specific cause cannot be determined (If viable tissue is not available, karyotype prior to CGH/CMA is not required); **OR**

- Evaluation of one or more major fetal structural anomalies (which include brain abnormalities, cleft lip and/or palate and heart defects) detected on prenatal ultrasound. If a structural abnormality is strongly suggestive of a particular aneuploidy in the fetus (eg, duodenal atresia which is characteristic of trisomy 21), karyotype with or without fluorescence in situ hybridization (FISH) is indicated prior to CGH/CMA; **OR**

- Noninvasive prenatal screening (NIPS) using cfDNA for any of the following:

  - No-call result due to low fetal fraction if maternal blood for NIPS was drawn at an appropriate gestational age; **OR**

- Positive for microdeletions and/or microduplications or smaller copy-number change

**Maternal cell contamination (MCC) studies (81265} is considered integral to the primary procedure and not separately reimbursable.**

*Coverage Limitations*

Humana members may **NOT** be eligible under the Plan for **CGH/CMA** for any pregnancy loss and prenatal indication other than those listed above including, but may not be limited to:

- Confirmation of diagnosis of a syndrome that can be routinely diagnosed by clinical evaluation alone
- Detection of deletions/duplications and/or gene or genomic sequencing for single gene disorders (eg, *BRCA, CFTR, DMD, MECP2, PTEN)*
- Evaluation of any of the following indications:
  - Advanced maternal age only
  - Pregnancy losses by parental blood samples
  - Recurrent pregnancy loss
- Any of the following soft markers:
  - Absent nasal bone
  - Choroid plexus cysts
  - Echogenic bowel
  - Echogenic intracardiac focus
  - Pyelectasis
  - Shortened long bones (eg, femur, humerus)
- Evaluation of the following without the presence of fetal structural anomalies:
  - Abnormal serum screening
  - Hydrops fetalis
  - Nuchal translucency

- Prenatal invasive diagnostic genetic testing

- NIPS using cfDNA is positive for TI3, T18, T21, sex chromosome aneuploidy (SCA), other aneuoploidy, triploidy and karyotype confirmed results

- Known family history of chromosomal rearrangement

These are considered experimental/investigational as they are not identified as widely used and generally accepted for any other proposed uses as reported in nationally recognized peer-reviewed medical literature published in the English language.

## Coverage Determination

**Pediatric and Postnatal Indications**

**Any state mandates for CGH/CMA take precedence over this medical coverage policy.**

**Genetic testing may be excluded by certificate. Please consult the member's individual certificate regarding Plan coverage.**

Apply General Criteria for Genetic and Pharmacogenomics Tests when disease- or gene-specific criteria are not available on a medical coverage policy. For information regarding **general criteria for genetic tests,** please refer to Genetic Testing Medical Coverage Policy.

Humana members may be eligible under the Plan for **CGH/CMA (eg, 0209U) for the following pediatric and postnatal indications** when criteria are met:

- At least one major congenital anomaly (eg, brain abnormalities, cleft lip and/or palate and heart defects); **OR**

- ASD in an individual who exhibits developmental delays or persistent deficits in social communication and social interaction across multiple contexts (see testing strategy for adjunctive fragile X gene testing)*; **OR**

- NIPS using cell-free DNA (cfDNA) is positive for trisomy 13 (T13), trisomy 18 (T18), trisomy 21 (T21), other aneuploidy or triploidy; **AND**

- Neonatal physical examination indicates abnormal clinical phenotype; **AND**
- Cytogenetic analysis (eg, fluorescence in situ hybridization (FISH) or karyotype) is normal; **OR**

- NIPS using cfDNA is positive for smaller copy-number changes; **OR**
- Unexplained significant GDD (see Coverage Limitation section regarding developmental delay [DD]) (see testing strategy for adjunctive fragile X syndrome gene testing)*; **AND**
  - Delays of six months or more in two or more developmental areas (domains). Developmental domains include: cognitive skills, social and emotional skills, speech and language skills, fine and gross motor skills and activities of daily living; **OR**
- Unexplained ID (see testing strategy for adjunctive fragile X syndrome gene testing)*; **AND**
  - Limitations of adaptive functioning affecting at least one of three domains: conceptual, practical, social; **AND**
  - Limitations of intellectual functioning (eg, abstract thinking, judgment, learning, problem solving, reasoning); **AND**
  - No family history of chromosomal rearrangement or recurrent pregnancy loss; **OR**
- Microcephaly in an individual 5 years of age or younger; **AND**
  - Occipitofrontal circumference (OFC or head circumference) greater than two standard deviations (SD) below the mean (less than 3rd percentile) for age and sex determined by a standardized head circumference chart (eg, Centers for Disease Control and Prevention [CDC], World Health Organization [WHO]); **OR**

- Serial OFC measurements demonstrate progressive decrease in head size (downward crossing of at least two major percentiles [eg, 90th, 75th, 25th, 10th]) for age and sex determined by a standardized head circumference chart (eg, CDC, WHO) between health supervision visits; **OR**

- Microdeletion or microduplication syndromes (eg, DiGeorge syndrome, Kleefstra syndrome) (for information regarding coverage determination/limitations for **Angelman and Prader-Willi syndromes,** please refer to Genetic Testing for Angelman and Prader-Willi Syndromes Medical Coverage Policy); **AND**

  - Individual to be tested presents with clinical findings suggestive of a known microdeletion or microduplication syndrome and FISH is normal; **OR**

  - Individual to be tested has a first-degree relative with a known microdeletion or microduplication syndrome that is too small to be detected by FISH

***Testing strategy:** *FMR1* gene testing for fragile X syndrome may be ordered adjunctively with CMA for ASD, GDD or ID if criteria for fragile X syndrome testing are met. For information regarding coverage determination/limitations for **fragile X syndrome,** please refer to Genetic Testing for Diagnosis of Noncancer Indications Medical Coverage Policy.

*Coverage Limitations*

Humana members may **NOT** be eligible under the Plan for **CGH/CMA for pediatric or postnatal indications** other than those listed above including, but may not be limited to:

- Confirmation of diagnosis of a syndrome that can be routinely diagnosed by clinical evaluation alone

- Detection of deletions/duplications and/or gene or genomic sequence sequencing for single gene disorders (eg, *BRCA, CFTR, DMD, MECP2, PTEN)*

- Evaluation of any of the following indications when not part of a more generalized condition (ASD, GDD or ID):

  - Delayed puberty

- Epilepsy
- Hearing loss
- Hypogonadism
- Klinefelter syndrome
- Language delay
- Turner syndrome

- Known family history of chromosomal rearrangement

- NIPS using cfDNA is positive for T13, T18, T21, sex chromosome aneuploidy (SCA), other aneuoploidy, triploidy and neonatal physical exam indicates normal clinical phenotype

These are considered experimental/investigational as they are not identified as widely used and generally accepted for any other proposed uses as reported in nationally recognized peer-reviewed medical literature published in the English language.

Humana members may **NOT** be eligible under the Plan for **CGH/CMA for developmental delay (DD).** This is considered not medically necessary as defined in the member's individual certificate. Please refer to the member's individual certificate for the specific definition.

## Coverage Determination

**Cancer**

**Any state mandates for CGH/CMA take precedence over this medical coverage policy.**

**Genetic testing may be excluded by certificate. Please consult the member's individual certificate regarding Plan coverage.**

Apply General Criteria for Genetic and Pharmacogenomics Tests when disease- or gene-specific criteria are not available on a medical coverage policy. For information regarding **general criteria for genetic tests,** please refer to Genetic Testing Medical Coverage Policy.

Humana members may be eligible under the Plan for **CGH/CMA for the evaluation of the following cancer** indications when criteria are met:

- Acute lymphoblastic leukemia {ALL) (adult and pediatric) in cases of aneuploidy or failed karyotype (chromosome analysis); **OR**
- HMMPS when any of the following indications are present:
  - Allogeneic sibling donor is a hematopoietic stem cell transplant {HSCT) candidate when HSCT recipient is diagnosed with acute leukemia or myelodysplastic syndrome {MDS); **OR**
  - Personal history of any of the following:
    - Acute myeloid leukemia {AML) or MDS diagnosed before 50 years of age; **OR**
    - Aplastic anemia; **OR**
    - Congenital limb anomalies (eg, especially thumb/forearm); **OR**
    - Hypocellular MDS; **OR**
    - Immune deficiencies (eg, B lymphopenia, monocytopenia); **OR**
    - Monosomy 7 and 30 years of age or younger; **OR**
    - Multiple cancers, two or more; **OR**
    - Primary fibrosis; **OR**
    - Severe and/or recurrent infections (eg, atypical mycobacterial, fungal or viral infections); **OR**
  - First-degree relative diagnosed with any of the following:
    - Acute leukemia; **OR**

- Bone marrow failure; **OR**
- Congenital limb anomalies (especially thumb/forearm); **OR**
- Early-onset malignancy; **OR**
- Excessive toxicity with chemotherapy or radiation; **OR**
- Genetically defined inherited bone marrow failure/acute leukemia/MOS predisposition syndrome; **OR**
- Hypocellular marrow; **OR**
- Macrocytosis; **OR**
- MDS; **OR**
- Poor stem cell mobilizer; **OR**
- Pulmonary fibrosis; **OR**
- Severe and/or recurrent infections (eg, atypical mycobacterial, fungal or viral infections); **OR**
- Unexplained cytopenia (eg, anemia, leukopenia and/or thrombocytopenia); **AND**

  Concomitant diseases (eg, infection, nutritional deficiencies, medication use and alcohol consumption) have been ruled out as a source of cytopenia; **AND**

  Routine tests** have not detected the source of cytopenia

**Spitz Tumor**

Humana members may be eligible under the Plan for **CGH/CMA to evaluate atypical Spitz tumor** to differentiate from melanoma when histological findings are equivocal.

**Examples of routine tests to detect cytopenia include, but may not be limited to: complete blood count, platelet count, blood smear, prothrombin time, partial thromboplastin time and/or basic or comprehensive metabolic panel. Refer to reference intervals provided by laboratory.

*Coverage Limitations*

Humana members may **NOT** be eligible under the Plan for **CGH/CMA for any cancer indications** other than those listed above including, but may not be limited to:

- Detection of deletions/duplications and/or gene or genomic sequencing for single gene disorders (eg, *BRCA, CFTR, DMD, MECP2, PTEN)*
- Evaluation of the following malignancies:
  - Chronic lymphoblastic (lymphocytic) leukemia (CLL)
  - Melanoma
  - Multiple myeloma

These are considered experimental/investigational as they are not identified as widely used and generally accepted for any other proposed uses as reported in nationally recognized peer-reviewed medical literature published in the English language.

## Background

Additional information about **autism, fetal demise, global developmental delay, intellectual disability, leukemia or melanoma** may be found from the following websites:

- American Academy of Dermatology
- American Academy of Neurology
- American Academy of Pediatrics
- American Association on Intellectual and Developmental Disabilities

- American Cancer Society
- Centers for Disease Control and Prevention
- Genetics Home Reference
- Leukemia & Lymphoma Society
- National Library of Medicine
- Society for Maternal-Fetal Medicine

## Medical Alternatives

Alternatives to **CGH/CMA for ASD, GDD and** ID include, but may not be limited to, the following:

- Analysis of single genes (please refer to Genetic Testing for Diagnosis of Noncancer Indications Medical Coverage Policy)
- Brain imaging
- FISH
- Fragile X gene testing (please refer to Genetic Testing for Diagnosis of Noncancer Indications Medical Coverage Policy)
- Karyotype (chromosome analysis)
- Metabolic studies

Alternatives to **CGH/CMA for congenital anomalies** include, but may not be limited to:

- Analysis of single genes (please refer to Genetic Testing for Diagnosis of Noncancer Indications Medical Coverage Policy)
- FISH
- Karyotype (chromosome analysis)

Alternatives to **CGH/CMA for prenatal indications** include, but may not be limited to:

- FISH
- Karyotype (chromosome analysis)

Physician consultation is advised to make an informed decision based on an individual's health needs.

Humana may offer a disease management program for this condition. **The member may call the number on his/her identification card to ask about our programs to help manage his/her care.**

**Provider Claims Codes**

Any CPT, HCPCS or ICD codes listed on this medical coverage policy are for informational purposes only. Do not rely on the accuracy and inclusion of specific codes. Inclusion of a code does not guarantee coverage and or reimbursement for a service or procedure.

| CPT® Code(s) | Description | Comments |
|---|---|---|
| 81228 | 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) | **Not Covered if used to report any test outlined in Coverage Limitations section** |
| 81229 | Cytogenomic constitutional (genome-wide) microarray analysis; interrogation of genomic regions for copy number and single nucleotide polymorphism (SNP) variants for chromosomal abnormalities | |
| 81277 | Cytogenomic neoplasia (genome-wide) microarray analysis, interrogation of genomic regions for copy number and loss-of-heterozygosity variants for chromosomal abnormalities | |
| 81349 | Cytogenomic (genome-wide) analysis for constitutional chromosomal abnormalities; interrogation of genomic regions for copy number and loss-of-heterozygosity variants, low-pass sequencing analysis | |
| 81405 | MOLECULAR PATHOLOGY PROCEDURE LEVEL 6 | |

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|---|---|---|
| 81406 | MOLECULAR PATHOLOGY PROCEDURE LEVEL 7 | |
| 81479 | Unlisted molecular pathology procedure | |
| 88262 | Chromosome analysis; count 15-20 cells, 2 karyotypes, with banding | |
| 88289 | Chromosome analysis; additional high resolution study | |
| 0209U | Cytogenomic constitutional (genome-wide) analysis, interrogation of genomic regions for copy number, structural changes and areas of homozygosity for chromosomal abnormalities | |
| **CPT® Category III Code(s)** | **Description** | **Comments** |
| No code(s) identified | | |
| **HCPCS Code(s)** | **Description** | **Comments** |
| 53870 | Comparative genomic hybridization (CGH) microarray testing for developmental delay, autism spectrum disorder and/or intellectual disability | |

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**Appendix A - Family Relationships**

| Degree of Relationship | Relative of the Individual to be Tested |
|---|---|
| First-degree | Child, full-sibling, parent |
| Second-degree | Aunt, uncle, grandchild, grandparent, nephew, niece, half-sibling |
| Third-degree | First cousin, great-aunt, great-uncle, great-grandchild, great-grandparent, half-aunt, half-uncle |