TITLE: COMPARATIVE GENOMIC HYBRIDIZATION (CGH) MICROARRAY TESTING

EFFECTIVE DATE: June 17, 2019

This policy was developed with input from specialists in pathology; genetics; and neonatology and endorsed by the Medical Policy Committee.

IMPORTANT INFORMATION – PLEASE READ BEFORE USING THIS POLICY

These services may or may not be covered by all Medica plans. Please refer to the member’s plan document for specific coverage information. If there is a difference between this general information and the member’s plan document, the member’s plan document will be used to determine coverage. With respect to Medicare and Minnesota Health Care Programs, this policy will apply unless those programs require different coverage. Members may contact Medica Customer Service at the phone number listed on their member identification card to discuss their benefits more specifically. Providers with questions about this Medica utilization management policy may call the Medica Provider Service Center toll-free at 1-800-458-5512.

Medica utilization management policies are not medical advice. Members should consult with appropriate health care providers to obtain needed medical advice, care and treatment.

PURPOSE

To promote consistency between reviewers in utilization management decision-making by providing the criteria that generally determine the medical necessity of comparative genomic hybridization (CGH) microarray testing for neurodevelopmental chromosomal imbalances. The Benefit Considerations box below outlines the process for addressing the needs of individuals who do not meet these criteria.

BACKGROUND

Definitions

A. Chromosomal microarray analysis is a laboratory test performed to detect genetic imbalances (microdeletions and/or microduplications) at a higher resolution level than karyotype analysis or fluorescence in situ hybridization (FISH). Chromosomal microarray analysis may be performed utilizing array-based comparative genomic hybridization or single nucleotide polymorphism arrays.

B. Array-based comparative genomic hybridization, also referred to as oligonucleotide array comparative genomic hybridization, compares an individual’s genome (DNA extracted from blood, skin, or fetal cells) with a control sample (DNA extracted from a normal individual), which are differentially labeled with fluorochromes and placed onto microarrays for analysis. The fluorescent signal intensity of the individual’s DNA relative to that of the control is then analyzed, allowing for identification of copy number variants. This in situ hybridization technique allows for detection of genetic deletions, duplications, and amplifications across the entire genome, with the goal of identifying pathogenic chromosomal aberrations or copy number variants responsible for an observed clinical phenotype. Copy number variants are typically classified as abnormal (pathogenic, clinically significant), likely benign, or of uncertain significance (potentially pathogenic); variants of uncertain significance are sometimes included in calculating the overall diagnostic yield. Although array-based comparative genomic hybridization has the potential to identify new copy number variants that predispose to disease, the majority are of uncertain significance. Array-based comparative genomic hybridization cannot detect balanced chromosomal rearrangements and may be limited in detecting low-level mosaicism (ie, below 20%).

C. Single nucleotide polymorphism arrays utilize single nucleotide polymorphisms instead of oligonucleotides as interrogating probes. Unlike array-based comparative genomic hybridization, this platform requires hybridization of only the individual’s sample onto the array. In addition to copy number variants and chromosome copy number, single nucleotide polymorphism arrays can identify loss of heterozygosity, consanguinity, and uniparental disomy.
**D. Karyotype** is the number of chromosomes in a given cell. In normal humans there are 46 chromosomes (23 pairs). The first 22 pairs are called the autosomes and are numbered from one to twenty-two according to length, longest to shortest. The 23rd pair is the sex chromosomes (X or Y).

**E. Karyotype (G-banded analysis)** is a conventional cytogenetic evaluation that can detect larger chromosomal abnormalities (e.g., loss or gain of an entire chromosome or of large parts of chromosomes), or chromosomal rearrangements such as translocations (i.e., when a portion of a chromosome breaks off and rejoins with another chromosome). Cells from blood, tissue, or body fluid (e.g., bone marrow, amniotic fluid) are cultured so that the chromosomes are visible; these cells are then treated to reveal banding patterns that are specific to each chromosome. Examination of these cells by standard light microscopy permits trained technologists and cytogeneticists to examine the chromosomes for abnormalities of number or structure. Examples of constitutional conditions (i.e., those present at birth) detectable by karyotype analysis include Down Syndrome (trisomy 21), Turner Syndrome (monosomy X), and Klinefelter syndrome (XXY). Acquired conditions (i.e., those that develop after birth, typically associated with malignancy) can also be detected.

**F. Fluorescence in situ hybridization (FISH)** is a molecular cytogenetic genetic evaluation that typically is used to identify the presence, absence, or rearrangement of specific DNA sequences on chromosomes. These sequences are usually smaller than those revealed by traditional karyotyping. FISH uses fluorescent probes that bind to only those parts of the chromosome that have a complementary DNA sequence. Fluorescence microscopy is used to identify if and where the fluorescent probe is bound to the chromosomes. Examples of diseases detectable using FISH include Prader-Willi syndrome, Angelman syndrome, DiGeorge syndrome, chronic myelogenous leukemia, acute lymphoblastic leukemia, and Down syndrome.

**G. Copy number variation** refers to a large category of possible structural variation that result in gain or loss of DNA from a person’s genome. These variations can involve large parts of chromosomes or conversely extremely small parts of the chromosome. Rearrangements that are unbalanced (i.e., that result in gain or loss of DNA) can be detected by CGH microarray; balanced rearrangements (i.e., those that change the structure of a chromosome but do not result in gain or loss of DNA) cannot be detected by CGH microarray.

**H. Maternal-fetal medicine** is a subspecialty of obstetrics focusing on the diagnosis and treatment of expectant mothers and their unborn child(ren). Maternal fetal medicine physicians specialize in the care of pregnant women who are at high risk for problems during their pregnancies.

**I. Microdeletions** (the loss of a minute piece of a chromosome) and **microduplications** (the gain of a minute piece of a chromosome), typically require high resolution techniques such as DNA analysis (e.g., CGH microarray) for detection. Although FISH can be used to detect microdeletions or microduplications that cause well-characterized genetic syndrome (e.g., 22q11.2 deletions/duplications, Prader-Willi and Angelman syndromes), microdeletions or microduplications involving regions of DNA not associated with such well-characterized syndromes are often first identified and localized by CHG microarray.

**J. A genetic counselor** is a health professional with specialized training and clinical experience in the areas of medical genetics and counseling that has completed an accredited Masters or Doctorate Degree program and has been certified by the American Board of Genetic Counseling or the American Board of Medical Genetics. Genetic counselors work as members of a health care team providing information and support to individuals and/or families who have birth defects or genetic disorders or who may be at risk for a variety of inherited conditions. Genetic counseling services may be provided both before and after genetic testing and include, but are not limited to the following services:

1. The collection, documentation and interpretation of family and medical histories to assess the risk of disease occurrence or recurrence
2. Education regarding inheritance and the nature, risks and potential outcomes of genetic testing
3. Assessment and review of the psychological and societal risks and benefits of genetic testing
4. Supportive counseling to promote informed consent
5. Identification of and referral to appropriate follow-up care and support services.

**K. A medical geneticist** is licensed physician with specialty training in medical genetics and counseling who has been certified by the American Board of Medical Genetics. In addition to genetic counseling, the medical geneticist can conduct physical examinations, make diagnoses of genetic disorders, and manage the clinical care of these disorders.

**BENEFIT CONSIDERATIONS**

1. Prior authorization for CGH microarray testing **is required** for the following indications: (1) outpatient/clinic evaluation of an individual for neurodevelopmental chromosomal imbalances, (2) prenatal testing, (3) fetal demise or stillbirth evaluation, (4) evaluation of biological parents, and (5) hematological malignancies. Please see the prior authorization list for product specific prior authorization requirements.
2. Prior authorization is **not required** for CGH microarray testing for neurodevelopmental chromosomal imbalances for neonates in the **NICU setting**. Medica reserves the right to conduct a medical necessity review following receipt of a claim submission for CGH microarray testing.

3. Comparative genomic hybridization (CGH) microarray testing is **investigative and therefore not covered** for all other indications not addressed in this policy, including but not limited to: attention deficit disorder; delayed growth; learning disabilities; neurodegenerative disorders; psychiatric disorders; repeated pregnancy loss; speech articulation disorders; or non-neurodevelopmental disorders including but not limited to non-hematological oncology indications.

4. Genetic testing is **excluded and therefore not covered** when performed in the absence of symptoms or high risk factors for a genetic disease or when knowledge of genetic status will not affect treatment decisions or screening for the disease. (See Medica’s **Genetic and Pharmacogenetic Testing coverage policy**)

5. Coverage may vary according to the terms of the member’s plan document. Please see the prior authorization list for product specific prior authorization requirements.

6. If it appears that the Medical Necessity and Coverage Criteria are not met, the individual’s case will be reviewed by the medical director or an external reviewer. Practitioners are advised of the appeal process in their Medica Provider Administrative Manual.

### MEDICAL NECESSITY CRITERIA

#### Neurodevelopmental Indications:

I. Indications for **Neonates in the Neonatal Intensive Care Unit (NICU)**

   NOTE: Prior authorization is not required for neonates in the neonatal intensive care unit (NICU) setting. While prior authorization is not required, Medica reserves the right to conduct a medical necessity review following receipt of a claim submission for CGH microarray testing.

   Comparative genomic hybridization (CGH) microarray testing for neurodevelopmental chromosomal imbalances is considered medically necessary in the NICU when documentation in the medical record indicates that **all of the following** criteria are met:

   A. The neonate presents with **all of the following**:
      1. A life threatening condition
      2. **Multiple** congenital anomalies.

   B. The test is ordered by a **medical geneticist, maternal-fetal medicine specialist, neonatologist, or pediatric cardiologist**.

   C. Results of testing will be used in determining urgent care management decisions.

   D. An underlying genetic condition or syndrome is suspected that is unrelated to a well-delineated genetic syndrome normally evaluated with conventional genetic evaluation (e.g., karyotyping or fluorescence in situ hybridization [FISH]).

II. Indications for **Prenatal Testing**

   NOTE: Prior authorization is **required** for CGH microarray testing for prenatal testing.

   CGH microarray testing for prenatal diagnosis is considered medically necessary when documentation in the medical record indicates that **all of the following** criteria are met:

   A. A detailed family history and/or pedigree and genetic counseling conducted by a **medical geneticist, maternal-fetal medicine specialist, or certified and licensed** (where required) genetic counselor not employed by the laboratory performing the test.

   B. The test is ordered by a clinician who is not employed by the laboratory performing the test.

   C. The test is ordered by **one of the following**:
      1. A **medical geneticist, genetic counselor, maternal-fetal medicine specialist, obstetrician-gynecologist (OB-GYN)**, or a **family medicine practitioner with obstetrical privileges**
      2. A physician assistant or nurse practitioner, if working within the practice of a clinician mentioned in C.1., above.

   D. Based on medical history, an unconfirmed genetic syndrome is suspected.

   E. Amniocentesis, chorionic villus sampling, or fetal tissue testing is scheduled for another suspected prenatal indication(s). Examples include, but are not limited to, suspected aneuploidy, hydrocephalus, ventricular septal defect, echogenic kidneys.
III. Indications for **Intrauterine Fetal Demise or Stillbirth Evaluation**

**NOTE:** Prior authorization is required for CGH microarray testing for intrauterine fetal demise or stillbirth.

CGH microarray testing is considered medically necessary when documentation in the medical record indicates that all of the following criteria are met:

A. A detailed family history and/or pedigree and genetic counseling by a medical geneticist, maternal-fetal medicine specialist or certified and licensed (where required) genetic counselor not employed by the laboratory performing the testing.

B. The test is ordered by a clinician who is not employed by the laboratory performing the test.

C. The test is ordered by one of the following:
   1. A medical geneticist, genetic counselor, maternal-fetal medicine specialist, OB-GYN, or a family medicine practitioner with obstetrical privileges.
   2. A physician assistant or nurse practitioner, if working within the practice of a clinician mentioned in C.1., above.

D. An unconfirmed genetic syndrome may be present, based on all of the following:
   1. Fetal physical examination observations
   2. Family medical history/pedigree.

E. Conventional genetic evaluation is not possible (i.e., viable cells are not retrievable).

IV. Indications for **Individuals in the Outpatient/Clinic Setting**

**NOTE:** Prior authorization is required for CGH microarray testing for neurodevelopmental chromosomal imbalances in the outpatient/clinic setting.

CGH microarray testing is considered medically necessary when documentation in the medical record indicates that all of the following criteria are met:

A. A detailed family history and/or pedigree and genetic counseling by a medical geneticist or certified and licensed (where required) genetic counselor not employed by the laboratory performing the testing.

B. The test is ordered by a clinician who is not employed by the laboratory performing the test.

C. The test is ordered by one of the following:
   1. A medical geneticist, genetic counselor, or physician.
   2. A physician assistant or nurse practitioner, if working within the practice of a clinician mentioned in C.1., above.

D. **One of the following** criteria is met:
   1. The individual is clinically suspected of having an underlying genetic condition or syndrome unrelated to a well-delineated genetic syndrome normally evaluated with conventional genetic evaluation (e.g., karyotyping or fluorescence in situ hybridization [FISH]) and who presents with one of the following:
      a. Autism spectrum disorder
      b. Non-syndromic developmental delay
      c. Dysmorphic features
      d. Intellectual disabilities (mental retardation)
      e. Multiple congenital anomalies
      f. An isolated congenital anomaly, and all of the following criteria are met:
         1. Family history suggests autosomal dominant or X-linked inheritance
         2. Genetic association of the anomaly has not been indicated with previous conventional genetic evaluation.
   2. Evaluation of biological parents when all of the following criteria are met:
      a. Postnatal CGH microarray testing of a previous offspring confirms a genetic condition or syndrome.
      b. Conventional genetic evaluation is not adequate.

E. A summary of how test results will lead to changes in treatment decisions (e.g., medical or surgical management, lifestyle modifications, surveillance and/or other protective measures).

**Non-Neurodevelopmental Indications:**

I. CGH microarray testing is considered medically necessary when documentation in the medical record indicates that all of the following criteria are met:

A. The individual has been diagnosed with a hematological malignancy (e.g., leukemia, lymphoma, multiple myeloma).
B. A board-certified and licensed (where required) genetic counselor, medical geneticist, or oncologist, independent of the laboratory performing the test, has reviewed and documented family history, created a pedigree, advised the patient of the potential benefits and harms of the testing and implications of the test results, and obtained written informed consent (genetic professionals are not excluded if they are employed by or contracted with a laboratory that is part of an integrated health system which routinely delivers health care services beyond just the laboratory test).

C. The test is ordered by a physician with expertise in the diagnosis and/or management of hematological malignancies (e.g., oncologist, pathologist) or board-certified and licensed (where required) genetic counselor independent of the laboratory performing the testing (genetic professionals are not excluded if they are employed by or contracted with a laboratory that is part of an integrated health system which routinely delivers health care services beyond just the laboratory test).

D. A summary of how test results will lead to changes in treatment decisions (e.g., medical or surgical management, lifestyle modifications, surveillance and/or other protective measures).

CENTERS FOR MEDICARE & MEDICAID SERVICES (CMS)

- For Medicare members, refer to the following, as applicable at: http://www.cms.hhs.gov/mcd/search.asp?

DOCUMENT HISTORY

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References

Pre-04/2015 Medical Technology Assessment Committee (MTAC) and Medical Policy Committee (MPC):


37. Miller, DT. Use of chromosomal microarray in obstetrics. In: *UpToDate™*, Basow, DS (Ed), UpToDate, Waltham, MA, 2014.


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120. Szigeti K. New Genome-Wide Methods for Elucidation of Candidate Copy Number Variations (CNVs) Contributing to Alzheimer's Disease Heritability.


04/2018 MPC:

04/2019 MPC: