Clinical Policy Title: Array comparative genomic hybridization testing

Clinical Policy Number: 02.01.03

Effective Date: September 1, 2015
Initial Review Date: May 13, 2013
Most Recent Review Date: August 17, 2016
Next Review Date: August 2017

Related policies:
CP# 02.01.01 Maternal genetic testing
CP# 02.01.02 Genetic testing for breast and ovarian cancer
CP# 02.01.04 Genetic testing for primary autosomal recessive microcephaly
CP# 02.01.08 Familial polyposis gene testing
CP# 02.01.09 Genetic testing, rare diseases
CP# 04.01.02 Genetic testing for long QT syndrome (LQTS)
CP# 11.04.02 Genetic testing for autism spectrum disorder
CP# 13.01.01 Genetic testing for prostate cancer prognosis

Policy contains:
- Chromosomal microarray analysis.
- Comparative genomic hybridization.
- Array comparative genomic hybridization.
- Single nucleotide polymorphism.
- Autism spectrum disorders.
- Developmental delay.
- Intellectual delay.
- Karyotyping.

ABOUT THIS POLICY: Prestige Health Choice has developed clinical policies to assist with making coverage determinations. Prestige Health Choice’s clinical policies are based on guidelines from established industry sources, such as the Centers for Medicare & Medicaid Services (CMS), state regulatory agencies, the American Medical Association (AMA), medical specialty professional societies, and peer-reviewed professional literature. These clinical policies along with other sources, such as plan benefits and state and federal laws and regulatory requirements, including any state- or plan-specific definition of “medically necessary,” and the specific facts of the particular situation are considered by Prestige Health Choice when making coverage determinations. In the event of conflict between this clinical policy and plan benefits and/or state or federal laws and/or regulatory requirements, the plan benefits and/or state and federal laws and/or regulatory requirements shall control. Prestige Health Choice’s clinical policies are for informational purposes only and not intended as medical advice or to direct treatment. Physicians and other health care providers are solely responsible for the treatment decisions for their patients. Prestige Health Choice’s clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, Prestige Health Choice will update its clinical policies as necessary. Prestige Health Choice’s clinical policies are not guarantees of payment.

Coverage Policy

Prestige Health Choice considers one per lifetime array comparative genomic hybridization (CGH) to be clinically proven and therefore, medically necessary when ordered by a medical geneticist, neurologist, or other qualified specialist for indications:
- Multiple congenital anomalies not specific to a well-delineated genetic syndrome.
- Apparent non-syndromic developmental delay/intellectual disability.
- Autism spectrum disorders (ASDs).
Limitations:

Coverage determinations are subject to benefit limitations and exclusions as delineated by the state Medicaid authority. The Florida Medicaid website can be accessed at http://ahca.myflorida.com/Medicaid/.

Array CGH for the purpose of identification of chromosomal regions that are recurrently lost or gained in tumors, as well as for the diagnosis and prognosis of cancer, is considered investigational and therefore not medically necessary, aside from determinations of related policies including but not limited to those identified above.

Prestige Health Choice considers array CGH to be investigational and therefore not medically necessary for other indications including but not limited to the following conditions:

- Detection of balanced rearrangements.
- Evaluation of unexplained epilepsies.
- Screening for prenatal gene mutations in fetuses without structural abnormalities, such as in advanced maternal age, positive maternal serum screen, previous trisomy, or the presence of "soft markers" on fetal ultrasound.
- Testing products of conception.
- Diagnosis of melanoma.

"Soft markers" are identified by the Society of Obstetricians and Gynecologists of Canada (SOGC) as:

- Thickened nuchal folds.
- Echogenic bowel.
- Mild ventriculomegaly.
- Echogenic focus in the heart.
- Choroid plexus cyst.
- Single umbilical artery.
- Enlarged cisterna magna.
- Pyelectasis.

Array CGH is not considered medically necessary when a diagnosis of a disorder or syndrome is readily apparent based on clinical evaluation alone.

Repeat array CGH testing has no proven value.

All requests should be looked at individually in accordance with direction from appropriate authority [e.g., Commonwealth of Pennsylvania Genetic Framework document (Appendix A)].

Alternative Covered Services:
Clinical evaluation by a network medical geneticist, neurologist, and other qualified specialist or by the primary care physician constitutes covered services.

**Background**

Chromosomal microarray analysis (CMA) is a diagnostic application suitable for identifying congenital anomalies under certain conditions (e.g., abnormal fetal ultrasound, advanced maternal age or positive maternal serum aneuploidy screening); and for evaluating individuals with unexplained developmental delay (DD), ASDs, or intellectual disability (i.e., intellectual developmental delay, mental retardation). The latter is sometimes referred to as "ID."

CMA is also known as cytogenomic microarray analysis and collectively describes two different laboratory techniques:

- Array CGH.
- Single nucleotide polymorphism (SNP) arrays.

In the prenatal setting, CMA requires an invasive procedure to collect intact fetal cells (e.g., amniocentesis or chorionic villous sampling).

While conventional karyotyping detects large changes in the structure or number of whole chromosomes (e.g., translocations, aneuploidy), CMA identifies genomic copy number variations (CNVs).

CNVs are chromosomal imbalances created as a result of the deletion and/or duplication of one or more sections of deoxyribonucleic acid (DNA).

SNP is distinguished from CGH in the specificity of its application. In SNP specific known DNA sequence variants are evaluated. CGH detects CNVs for relatively large deletions or duplications, including whole chromosome duplications as in trisomy.

CMA does not detect balanced chromosome rearrangements in which there is no gain or loss of DNA (e.g., balanced inversions or balanced translocations).

**Searches**

Prestige Health Choice searched PubMed and the databases of:

- UK National Health Services Center for Reviews and Dissemination.
- Agency for Healthcare Research and Quality’s National Guideline Clearinghouse and other evidence-based practice centers.
- The Centers for Medicare & Medicaid Services (CMS).
Searches were conducted on July 15, 2016 using the terms "comparative genomic hybridization," "chromosomal microassay analysis," and "single nucleotide polymorphisms."

We included:

- **Systematic reviews**, which pool results from multiple studies to achieve larger sample sizes and greater precision of effect estimation than in smaller primary studies. Systematic reviews use predetermined transparent methods to minimize bias, effectively treating the review as a scientific endeavor, and are thus rated highest in evidence-grading hierarchies.
- **Guidelines based on systematic reviews.**
- **Economic analyses**, such as cost-effectiveness, and benefit or utility studies (but not simple cost studies), reporting both costs and outcomes — sometimes referred to as efficiency studies — which also rank near the top of evidence hierarchies.

**Findings**

In the prenatal setting, CMA has been primarily used as an alternative to karyotyping. Karyotype versus genomic hybridization for the prenatal diagnosis of chromosomal abnormalities was evaluated in a systematic review and meta-analysis inclusive of six clinical trials and an unspecified number of patients by Saldarriaga (2014).

- Studies of pregnant women who received chorionic villus biopsies, amniocentesis, or cordocentesis and then underwent CGH and karyotype analysis were included.
- Assessment for inclusion was conducted by the quality assessment of comparative diagnostic accuracy studies (QUADAS) 2 analysis of methodology quality; however, there is an unclear risk for selection bias of reference and standard tests.
- The presence of any abnormalities in either of the two tests (karyotype or CGH) was considered a positive test, although it should be noted that in most cases karyotyping had a lower yield compared with CGH.

The authors acknowledged that CGH enjoys an advantage in the prenatal diagnosis of chromosomal and structural abnormalities over karyotyping, demonstrating significantly higher sensitivity with similar specificity.

A Committee Opinion of the American College of Obstetricians and Gynecologists (ACOG 2013) addresses the use of CMA in prenatal diagnosis:

- In patients with a fetus with one or more major structural abnormalities identified on ultrasonographic examination and who are undergoing invasive prenatal diagnosis, chromosomal microarray analysis is recommended. This test replaces the need for fetal karyotype.
- In patients with a structurally normal fetus undergoing invasive prenatal diagnostic testing, either fetal karyotyping or a chromosomal microarray analysis can be performed.
Most genetic mutations identified by chromosomal microarray analysis are not associated with increasing maternal age; therefore, the use of this test for prenatal diagnosis should not be restricted to women aged 35 years and older.

The ACOG Committee was prompted to issue its Opinion in answer to the results of a large multi-center study published in the New England Journal of Medicine (NEJM) inclusive of 4,406 women undergoing prenatal diagnosis using both CMA and karyotyping. Wapner (2012) reported that CMA revealed chromosomal deletions or duplications in 6 percent of fetuses with an abnormal ultrasound and 1.7 percent of fetuses of pregnant women of advanced maternal age or positive aneuploidy serum screening result. The chromosomal microassay analysis technique used in the study was array CGH.

Another systematic review found array CGH technology superior to conventional karyotyping in prenatal diagnosis with these observations (Hillman 2011):

- CGH testing has a clear advantage over karyotyping in the prenatal population, displaying higher sensitivity with roughly equivalent specificity.
- There appears to be an increased detection rate of chromosomal imbalances, compared with conventional karyotyping, when array CGH techniques are employed in the prenatal population.
- However, some copy number imbalances are not clinically significant. This carries implications for prenatal counseling and maternal anxiety.

Duncan (2011), on behalf of the Genetics Committee of the Society of Obstetricians and Gynecologists of Canada (SOGC) and the Prenatal Diagnosis Committee of the Canadian College of Medical Geneticists (CCMG), formed a group consensus on array CGH that was published as a "Technical Update" with the following recommendations:

- Array genomic hybridization is not recommended in pregnancies at low risk for a structural chromosomal abnormality.
- Array genomic hybridization may be an appropriate diagnostic test in cases with fetal structural abnormalities detected on ultrasound or fetal magnetic resonance imaging.
- Any pregnant woman who qualifies for microarray genomic hybridization testing should be seen in consultation by a medical geneticist.

Delay occurs when a child has not reached a developmental milestone by the expected time period. ASDs are a group of neurodevelopmental disorders defined by measurable impairments in communication and social interactions, restricted interests and activities, and stereotypical behaviors. ID is characterized by a significantly below-average score on a test of mental ability or intelligence in addition to limitations in the ability to function in areas of daily life, such as self-care, communication, social interactions, and school activities.

The ACMG (American College of Medical Genetics) guidelines were updated in 2013 to address the utility and limitations for clinical use of CMA in the detection of chromosome abnormalities. The guidelines make the following recommendations:
“CMA testing for CNV is recommended as a first-line test in the initial postnatal evaluation of individuals with the following:

- Multiple anomalies not specific to a well-delineated genetic syndrome.
- Apparent non-syndromic developmental delay/intellectual disability.
- ASD.”

The current Genetics in Medicine and ACMG Practice Guidelines update the original publication from 2008. The International Standard Cytogenomic Array (ISCA) Consortium (Miller 2010) convened two international workshops and concluded in a consensus guideline that:

- CMA offers a much higher diagnostic yield (15 percent – 20 percent) for genetic testing of individuals with unexplained DD/ID, ASDs, or multiple congenital anomalies than a G-banded karyotype.
- G-banded karyotype analysis should be reserved for individuals with obvious chromosomal syndromes (e.g., Down syndrome), a family history of chromosomal rearrangement, or a history of multiple miscarriages.
- Recommends the use of CMA in place of G-banded karyotyping as the first-tier cytogenetic diagnostic test for individuals with DD/ID, ASDs, or multiple congenital anomalies.

The use of array CGH in patients with learning disability (LD) and congenital anomalies was examined in a systematic review and meta-analysis inclusive of 19 studies and 13,926 subjects (Sagoo 2009):

- Studied patients with LD and congenital anomalies, in whom conventional cytogenetic analysis was negative.
- Found that array-based CGH could be used to identify genetic abnormalities in patients with LD or congenital anomalies in whom cytogenetic tests were negative, but there was a risk of false-positive results.

The reliability of Sagoo's conclusions is uncertain due to some unclear reporting, potential publication bias, and failure to appropriately consider study quality.

Policy updates:

In a narrative review, Szego (2016) noted that an increasing number of relatively inexpensive and rapid testing methods are changing the landscape in the genetic diagnosis of disease. Specifically, whole exome sequencing (WES) and whole genome sequencing (WGS) have shown to increase the diagnostic yield when applied to patients suspected of having the condition. Exome sequencing is a technique for sequencing all the protein-coding genes in a genome (known as the exome). It consists of first selecting only the subset of DNA that encodes proteins (known as exons), and then sequencing that DNA using any high-throughput DNA sequencing technology. WGS incorporates the protein-encoding sections of the DNA plus those sections of the strand that are not directly involved with protein creation (i.e., regulatory genes within the strand). The authors emphasize that WES and WGS do not obviate the use of CMA. Microarray testing itself is a high yield test identifying an etiology of ASD in about 10 percent of
cases. Together, WES and CMA in tandem may identify the cause of ASD in 20 percent of cases. As such, genome-wide testing has now joined CMA as a part of the standard diagnostic assessment for patients.

Tammimies (2015) tested 258 consecutively ascertained unrelated children who underwent detailed assessments to define morphology scores based on the presence of major congenital abnormalities and minor physical anomalies. The children were recruited between 2008 and 2013 in Newfoundland and Labrador, Canada. The probands were stratified into three groups of increasing morphological severity: essential, equivocal, and complex (scores of 0-3, 4-5, and ≥6). All probands underwent CMA, with WES performed for 95 proband-parent trios. Of 258 probands, 24 (9.3 percent, 95 percent CI, 6.1 – 13.5 percent) received a molecular diagnosis from CMA and 8 of 95 (8.4 percent, 95 percent CI, 3.7 – 15.9 percent) from WES. The yields were statistically different between the morphological groups. Among the children who underwent both CMA and WES testing, the estimated proportion with an identifiable genetic etiology was 15.8 percent (95 percent CI, 9.1 – 24.7 percent; 15/95 children). This included two children who received molecular diagnoses from both tests. The combined yield was significantly higher in the complex group when compared with the essential group (pairwise comparison, \( p = .002 \)). The authors concluded that the molecular diagnostic yields of CMA and WES were comparable, and the combined molecular diagnostic yield was higher in children with more complex morphological phenotypes in comparison with the children in the essential category.

**Summary of clinical evidence:**

<table>
<thead>
<tr>
<th>Citation</th>
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|                   | • Subjects were pregnant women who received chorionic villus biopsies, amniocentesis, or cordocentesis and then underwent CGH and karyotype analysis  
|                   | • Authors concluded CGH enjoys an advantage in the prenatal diagnosis of chromosomal and structural abnormalities over karyotyping. |
| ACOG (2013)       | **Key points:**  
|                   | • Recommends a fetus with one or more major structural abnormalities identified on pre-natal ultrasound that is undergoing invasive prenatal diagnosis should have CMA.  
|                   | • This test replaces the need for fetal karyotype.  
|                   | • The use of this test for prenatal diagnosis should not be restricted to women aged 35 years and older. |
| ACMG (2013)       | **Key points:**  
|                   | • CMA testing for CNV is recommended as a first-line test in the initial postnatal evaluation of individuals with the following:  
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|                   | o Apparent non-syndromic DD/ID.  
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|                   | • CMA revealed chromosomal deletions or duplications in 6 percent of fetuses with an abnormal ultrasound and 1.7 percent of fetuses of pregnant women of advanced maternal age or positive aneuploidy serum screening result. |
| Hillman (2011)    | **Key points:**  
|                   | • Systematic review and meta-analysis.  
|                   | • Found pre-natal array CGH superior to conventional karyotyping.  
|                   | • CGH demonstrated higher sensitivity with roughly equivalent specificity to karyotyping. |
| Duncan (2011)     | **Key points:**  
|                   | • CGH is not recommended in pregnancies at low risk for structural chromosomal abnormalities.  
|                   | • May be appropriate when there are fetal structural abnormalities on ultrasound or magnetic resonance imaging (MRI).  
|                   | • May be appropriate in lieu of karyotyping when a rapid aneuploidy screen is negative.  
|                   | • Pregnancies qualifying for CGH should be seen by medical geneticist before testing. |
| Miller (2010)     | **Key points:**  
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</table>

**Glossary**

**Autism spectrum disorders (ASDs)** — A collection of associated developmental disorders that affect the parts of the brain that control social interaction, verbal and non-verbal communication, and repetitive and unusual behavior.

**Balanced reciprocal translocations** — An equal exchange of material between chromosomes.

**Chromosomal (or cytogenetic) microarray analysis (CMA)** — A method used to measure the gains and losses of DNA throughout the human genome. CMA includes both single nucleotide polymorphism (SNP) and comparative genomic hybridization (CGH) arrays.

**Comparative genomic hybridization (CGH)** — A molecular technique that is used to detect chromosome gain or loss by hybridizing DNA from a target cell and a normal cell.

**Congenital anomaly** — A defect that is present at birth and may be the result of either environmental or genetic factors, or both.

**Copy number variants (CNVs)** — An alteration of the DNA of a genome that results in the cell having an abnormal number of copies of one or more sections of the DNA.

**Cytogenetics** — A branch of genetic science that focuses on the study of the structure and function of the cell, especially the chromosomes. Cytogenetics includes but is not limited to G-banded karyotyping, fluorescent in situ hybridization (FISH), and CGH.
G-banded karyotyping — A molecular chromosome analysis technique which employs Giemsa dye to stain DNA strands.

Karyotypes — The number and appearance of chromosomes under a light microscope.

Karyotyping — Analysis of the number and appearance of chromosomes under a light microscope.

Single nucleotide polymorphisms (SNP) — The most common type of genetic variation among humans.

References

Professional society guidelines/other:


Peer-reviewed references:


Clinical trials:

Searched clinicaltrials.gov on July 7, 2016, using terms array CGH | Open Studies. Two studies found, none relevant.

Centers for Medicare Services National Coverage:

National Coverage Determination (NCD) for Cytogenetic Studies (190.3)
Benefit Category

Diagnostic Tests (other)

Note: This may not be an exhaustive list of all applicable Medicare benefit categories for this item or service.

Item/Service Description

The term cytogenetic studies are used to describe the microscopic examination of the physical appearance of human chromosomes.

Indications and Limitations of Coverage

Medicare covers these tests when they are reasonable and necessary for the diagnosis or treatment of the following conditions:
• Genetic disorders (e.g., mongolism) in a fetus; (See the Medicare Benefit Policy Chapter 15, "Covered Medical and Other Health Services," §20.1)
• Failure of sexual development;
• Chronic myelogenous leukemia;
• Acute leukemias lymphoid (FAB L1-L3), myeloid (FAB M0-M7), and unclassified; or
• Myelodysplasia


Local Coverage Determinations (LCD):

LCDs for cytogenetic studies were identified for Noridian and Wisconsin Physicians Insurance companies:


Commonly submitted codes

Below are the most commonly submitted codes for the service(s)/item(s) subject to this policy. This is not an exhaustive list of codes. Providers are expected to consult the appropriate coding manuals and bill in accordance with those manuals.

<table>
<thead>
<tr>
<th>CPT Codes</th>
<th>Description</th>
<th>Comment</th>
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<tbody>
<tr>
<td>81228</td>
<td>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)</td>
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<tr>
<td>81229</td>
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<tr>
<th>ICD-10 Codes</th>
<th>Description</th>
<th>Comment</th>
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<tbody>
<tr>
<td>F70</td>
<td>Mild intellectual disabilities</td>
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<tr>
<td>F71</td>
<td>Moderate intellectual disabilities</td>
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<td>F72</td>
<td>Profound intellectual disabilities</td>
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<td>F74</td>
<td>Severe intellectual disabilities</td>
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<tr>
<td>F84.0</td>
<td>Autistic disorder</td>
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Appendix A

Commonwealth of Pennsylvania genetic framework document

Genetic testing encompasses a large number of tests for a variety of indications including diagnosis, carrier state, predisposition to a specific disease, and therapeutic decision making. There are also different types of genetic tests, such as looking at single mutations, or multiple mutations. Each managed care organization (MCO) has a variety of policies for genetic testing. Some are disease- or condition-specific and some are more general. It may make more sense for an MCO to make one general policy statement or decide to have multiple policies, some of which are disease-specific. Some of these policies may already have been reviewed and approved, but we are requesting that all guidelines/policies be reviewed and resubmitted to be sure that the following guidelines are followed in all policies:

1. The managed care organization (MCO) may require some form of genetic counseling for each test, but it does not have to be by a geneticist or genetic counselor who may not be readily accessible to consumers in certain areas of the state. It can be a requirement that the genetic counseling done by a specialist or other physician be equivalent to that provided by a genetic counselor, but it should also be appropriate for the test being requested. For example, genetic testing for a mutation that directs cancer treatment for acute lymphoblastic leukemia (ALL) is probably appropriately done by the oncologist ordering the test.
2. A genetic test is considered medically necessary if the results are expected to make a difference in the recipient’s care or treatment plan, or the recipient (or a responsible family member/legal guardian) intends to use the information in making decisions about care or treatment. An example would be family planning decisions or planning of other indicated testing in light of the diagnosis.
3. Genetic testing is medically necessary if it is a currently accepted method of diagnosis of a condition or disease. (The MCO may still require that 1 and 2 apply). Examples are the evaluation of global DD, recurrent fetal loss, or multiple congenital anomalies without an obvious etiology.
4. Genetic testing is medically necessary if by current guidelines it is consistent with the accepted standards for disease predisposition testing or screening. (The MCO may still
require that 1 and 2 apply) Examples would be testing for cystic fibrosis carrier state in women of reproductive age and BRCA testing.

5. Genetic testing is medically necessary if it is needed to determine appropriate medication or treatment. (The MCO may still require that 1 and 2 apply) An example would be for non-small cell lung cancer treatment (first line) Tarceva and Gilotrif. FDA-approved EGFR mutation test is required.

6. All requests should be considered individually, even if the above guideline criteria are not met.

7. All terms referring to genetic testing should be used correctly. Be careful when using the terms microarray, CGH, and SNP.