Clinical Policy Title: Chromosomal microarray analysis

Clinical Policy Number: CCP.1024

Effective Date: September 1, 2015
Initial Review Date: May 13, 2013
Most Recent Review Date: September 4, 2018
Next Review Date: September 2019

Related policies:
- CCP.1045 Gene expression profile testing for breast cancer
- CCP.1124 Genetic testing for autism spectrum disorders
- CCP.1153 Genetic testing for cystic fibrosis
- CCP.1175 Genetic testing for cytochrome p450 polymorphisms
- CCP.1176 Genetic testing for G1691A polymorphisms factor V Leiden
- CCP.1037 Genetic testing for long QT syndrome
- CCP.1171 Genomic tests in neurology
- CCP.1198 Genetic testing in sensorineural hearing loss
- CCP.1374 Genetic testing for maple syrup urine disease
- CCP.1233 Genetic testing for Alzheimer’s disease
- CCP.1002 Maternal genetic testing
- CCP.1012 Genetic testing for breast and ovarian cancer
- CCP.1050 Familial polyposis gene testing
- CCP.1060 Genetic testing for rare diseases
- CCP.1121 Genetic testing for prostate cancer prognosis

ABOUT THIS POLICY: Select Health of South Carolina has developed clinical policies to assist with making coverage determinations. Select Health of South Carolina’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 Select Health of South Carolina 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. Select Health of South Carolina’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. Select Health of South Carolina clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, Select Health of South Carolina will update its clinical policies as necessary. Select Health of South Carolina’s clinical policies are not guarantees of payment.

Coverage policy

Select Health of South Carolina considers chromosomal genomic hybridization testing to be clinically proven and, therefore, medically necessary when:
• A patient with a fetus with one or more major structural abnormalities identified on ultrasonographic examination is undergoing invasive prenatal diagnosis.

• A patient with a structurally normal fetus is undergoing invasive prenatal diagnostic testing.

• After fetal death or stillbirth, testing fetal tissue to conduct further cytogenetic analysis to improve detection of causative abnormalities is conducted.

• An obstetrician-gynecologist or other health care provider with expertise in genetics provides pre-test and post-test genetic counseling to the patient on benefits, limitations, and results of chromosomal microarray analysis.

• Informed consent, including discussion of the potential to identify findings of uncertain significance, nonpaternity, consanguinity, and adult-onset disease, is given along with the chromosomal microarray analysis (American College of Obstetricians and Gynecologists, 2016).

Limitations:

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 (American College of Obstetricians and Gynecologists, 2016).

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 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, autism spectrum disorder, or intellectual disability (i.e., intellectual developmental delay or mental retardation) (Centre for Genetics Education, 2015). Deletions or extra copies of chromosomal segments are known to be the cause of these disorders (Ahn, 2015).

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

- Array comparative genomic hybridization.
- Single nucleotide polymorphism arrays (Miller, 2010).

Testing by chromosomal microarray can sometimes find a copy variant that may or may not explain a health concern. It may also detect a variant with one or more genes related to health problems that were not the reason for testing (Centre for Genetics Education, 2015).

In the prenatal setting, chromosomal microarray analysis requires an invasive procedure to collect intact fetal cells (e.g., amniocentesis or chorionic villous sampling) (Van den Veyver, 2009). Blood samples can be used for infants and children (Miller, 2010).

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

For decades, G-banded karyotyping has been the accepted first-line test for detecting genetic imbalances in newborns. Chromosomal microarray analysis is a newer approach of detecting such imbalances, beginning in the mid-2000s, and has replaced G-based karotyping for detecting genomic copy number variants (Ahn, 2015). Chromosomal microarray analysis detects genomic imbalances at a much higher resolution than does G-banded karyotyping (Ahn, 2015; Miller, 2010).

Copy number variations are chromosomal imbalances created as a result of the deletion and/or duplication of one or more sections of deoxyribonucleic acid.

Single nucleotide polymorphism is distinguished from array comparative genomic hybridization in the specificity of its application. In single nucleotide polymorphism, specific known deoxyribonucleic acid sequence variants are evaluated. Array comparative genomic hybridization detects copy number variations for relatively large deletions or duplications, including whole chromosome duplications, as in trisomy.

Chromosomal microarray analysis does not detect balanced chromosome rearrangements in which there is no gain or loss of deoxyribonucleic acid (e.g., balanced inversions or balanced translocations).

Searches

Select Health of South Carolina 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.
Searches were conducted on May 2, 2018. Search terms were: "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**

A 2010 guideline that followed a systematic review of 33 studies, endorsed chromosomal microarray testing, as opposed to G-banded karyotyping, as a first-line diagnostic method for developmental delay/intellectual disabilities, autism spectrum disorder, or multiple congenital anomalies (Miller, 2010). The following year, the Canadian College of Medical Geneticists recommended that chromosomal microarray testing not be performed on women at low risk for chromosomal abnormalities (Duncan, 2011). An American College of Medical Genetics and Genomics work group produced a guideline stating array comparative genomic hybridization testing will lead to improved therapeutics from improved detection of congenital anomalies in fetuses and infants due to its higher resolution (Cooley, 2013).

A December 2016 Committee Opinion from the American College of Obstetricians and Gynecologists recommended prenatal chromosomal microarray analysis for women of all ages, for fetuses with one or more major structural abnormalities found on ultrasound, in structurally normal fetuses undergoing diagnostic testing, and in evaluation of intrauterine fetal death or stillbirth to better understand cause (American College of Obstetricians and Gynecologists, 2016).

The following systematic reviews, meta-analyses, and other large-scale studies offered evidence on the efficacy of chromosomal genomic hybridization tests:

- In a systematic review and meta-analysis of 23 studies including 5,507 pregnancy losses under 20 weeks, chromosomal microarray analysis provided informative results on copy number variants in 95 percent of cases, almost significantly greater than karyotyping 68 percent (Pauta, 2018).

- A systematic review and meta-analysis of 10 studies indicated a four percent incremental yield of chromosomal microarray analysis over karyotyping in non-malformed growth-restricted fetuses, rising to 10 percent in fetal growth restriction for fetal malformations (Borrell, 2018).
A systematic review and meta-analysis was undertaken to assay the most frequent and potentially significant copy number alterations in oral carcinogenesis. Gains were more frequent than losses in the entire dataset. High-frequency gains were identified in chromosomes 5p, 14q, 11q, 7p, 17q, 20q, 8q, and 3q, whereas high-frequency losses were identified in chromosomes 3p, 8p, 6p, 18q, and 4q. Ingenuity pathway analysis showed that the top biological function was associated with immortalization of the epithelial cells ($p = 1.93E-04$). The authors identified multiple recurrent copy number alterations that are involved in various biological annotations associated with oral carcinogenesis (Vincent-Chong, 2016).

In a meta-analysis of 17 studies of fetuses with increased nuchal translucency, genomic microarray had an incremental yield of 5.0 percent more copy number variants than karotyping (Grande, 2015).

In a meta-analysis of 13 studies of 1,131 prenatal cases with congenital heart disease, array comparative genomic hybridization had an incremental yield of 7.0 percent than karotyping (Jansen, 2015).

A systematic review and meta-analysis of nine papers addressed detection of chromosomal abnormalities. Agreement between chromosomal microarray analysis and karyotyping was observed in 86 percent of cases. Chromosomal microarray analysis detected 13 percent additional chromosome abnormalities, versus three percent for karyotyping (Dhillon, 2014).

A systematic review and meta-analysis included six studies of pregnant women who received chorionic villus biopsies, amniocentesis, or cordocentesis. Subsequent tests for genetic abnormalities showed that comparative genomic hybridization had sensitivity and specificity of 0.939 and 0.999, significantly greater — for sensitivity — than karyotyping (0.626 and 0.999) (Saldarriaga, 2014).

In a study of 4,406 high-risk pregnant women at 29 medical centers, microarray analysis detected clinically relevant deletions or duplications in 6.0 percent, and in women with a normal karyotype (Wapner, 2012).

In a systematic review of 10 articles, array comparative genomic hybridization detected 3.6 percent more genomic imbalances compared to conventional karyotyping, rising to 5.2 percent when the referral indication was a structural malformation on ultrasound (Hillman, 2011).

In a large controlled study that compared genetic tests for autism spectrum disorder, comparative microarray analysis produced significantly more abnormal results than did karotype (59/848, or 7.0 percent versus 19/852, or 2.23 percent) (Shen, 2010).
- A systematic review and meta-analysis of 19 studies (n = 13,926) addressed patients with learning disabilities or congenital anomalies in whom conventional genetic tests were negative, then tested with comparative genomic hybridization. The diagnostic yield of causal abnormalities was 10 percent, with false-positive yield of noncausal abnormalities of seven percent (Sagoo, 2009).

Although genomic microarray detects more chromosomal abnormalities than does karyotyping, a study comparing these methods showed that better detection more than offset the higher costs, and thus genomic microarray was more cost-effective than karotyping (Harper, 2014).

A literature review identified greater than 99 percent sensitivity and specificity of array comparative genomic hybridization or single nucleotide polymorphism chips among pediatric patients with developmental and intellectual disabilities, multiple congenital anomalies, and autistic spectrum disorders. A diagnostic yield of 12 to 20 percent was observed, and approximately 60 percent of these abnormalities were recurrent genomic disorders (Wei, 2013).

Studies have been conducted evaluating the efficacy of array comparative genomic hybridization to detect abnormalities in populations other than fetuses. A meta-analysis of four studies (n = 159) of persons with hepatocellular carcinoma who underwent the test found significant correlations between chromosomal aberrations on the same chromosome or different chromosomes (Guo, 2011).

Policy updates:

A total of three guidelines/other and 11 peer-reviewed references were added to, and one guideline/other were removed from this policy in July 2018.

Summary of clinical evidence:

<table>
<thead>
<tr>
<th>Citation</th>
<th>Content, Methods, Recommendations</th>
<th>Key points:</th>
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<tbody>
<tr>
<td></td>
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<td>Chromosomal microarray analysis provided informative results in 95% of cases (95% confidence interval 94% – 96%, compared with 68% (95% confidence interval, 66% – 70%) for karyotyping.</td>
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<tr>
<td></td>
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<td>Incremental yields of chromosomal microarray analysis over karyotyping were 2% (95% confidence interval, 1% – 2%) for pathogenic copy number variants and 4% (95% confidence interval, 3% – 6%) for variants of unknown significance.</td>
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<tr>
<td>Vincent-Chong (2016)</td>
<td>Immortalization of epithelial cells in oral carcinogenesis as revealed by</td>
<td>A systematic review and meta-analysis was undertaken to assay the most frequent and potentially significant copy number alterations in oral</td>
</tr>
<tr>
<td>Citation</td>
<td>Content, Methods, Recommendations</td>
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<tr>
<td>genome-wide array comparative genomic hybridization</td>
<td>Gains were more frequent than losses in the entire dataset. High-frequency gains were identified in chromosomes 5p, 14q, 11q, 7p, 17q, 20q, 6q, and 3q, whereas high-frequency losses were identified in chromosomes 3p, 8p, 6p, 18q, and 4q. Ingenuity pathway analysis showed that the top biological function was associated with immortalization of the epithelial cells ($p = 1.93\times 10^{-04}$). The authors identified multiple recurrent copy number alterations that are involved in various biological annotations associated with oral carcinogenesis.</td>
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<tr>
<td>Dhillon (2014)</td>
<td><strong>Key points:</strong></td>
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| Effectiveness comparison of techniques in diagnosis of chromosomal abnormalities | • Systematic review and meta-analysis of nine studies to detect chromosomal abnormalities in fetuses after spontaneous miscarriage.  
• Agreement between chromosomal microarray analysis and karyotyping observed in 86.0% of cases (95% confidence interval was 77.0% – 96.0%).  
• Chromosomal microarray analysis detected 13% (95% confidence interval 8.0% – 21.0%) additional chromosome abnormalities over conventional karyotyping.  
• Conventional karyotyping detected 3% (95% confidence interval 1.0% – 10.0%) additional abnormalities over chromosomal microarray analysis.  
• Authors conclude that chromosomal microarray analysis has increased ability to detect chromosomal deformities, compared to karyotyping. |
| Saldarriaga (2014)                            | **Key points:**                                                         |
| Karyotype versus genomic hybridization for the prenatal diagnosis of chromosomal abnormalities: a meta-analysis | • Systematic review and meta-analysis inclusive of six randomized controlled trials.  
• Subjects were pregnant women who received chorionic villus biopsies, amniocentesis, or cordocentesis and then underwent comparative genomic hybridization and karyotype analysis.  
• Sensitivity of genomic hybridization versus karyotype were 0.939 and 0.626.  
• Specificity of genomic hybridization and karyotype were both 0.999.  
• Authors concluded comparative genomic hybridization enjoys an advantage in the prenatal diagnosis of chromosomal and structural abnormalities over karyotyping. |
| Wapner (2012)                                 | **Key points:**                                                         |
• Chromosomal microarray analysis revealed chromosomal deletions or duplications in 6% of fetuses with an abnormal ultrasound and 1.7% of fetuses of pregnant women of advanced maternal age or positive aneuploidy serum screening result. |
| Hillman (2011)                                | **Key points:**                                                         |
| Additional information from array comparative genomic hybridization technology over conventional karyotyping in prenatal diagnosis | • Systematic review and meta-analysis.  
• Of the 135 potential articles, 10 were included in this systematic review and eight were included in the meta-analysis.  
• Array comparative genomic hybridization detected 3.6% (95% confidence interval... |
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<td>interval, 1.9 – 13.9) more than karyotyping when the referral indication was a structural malformation on ultrasound.</td>
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<td>The authors concluded there is an increased detection rate of chromosomal imbalances, compared with conventional karyotyping, when array comparative genomic hybridization techniques are employed in the prenatal population.</td>
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<td>However, some are copy number imbalances that are not clinically significant.</td>
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<td>The results carry implications for prenatal counseling and maternal anxiety.</td>
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<th>Sagoo (2009)</th>
<th>Key points:</th>
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<td>Array comparative genomic hybridization in patients with learning disability (mental retardation) and congenital anomalies</td>
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<tr>
<td></td>
<td>• Systematic review and meta-analysis inclusive of 19 studies and 13,926 subjects.</td>
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<td></td>
<td>• Concluded array comparative genomic hybridization could be used to identify genetic abnormalities in patients with learning disabilities or congenital anomalies in which cytogenetic tests were negative.</td>
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<td>• Noted a risk of false-positive results.</td>
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<td></td>
<td>• Unclear reporting, potential publication bias, and failure to appropriately consider study quality were limitations of the work.</td>
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</table>

**References**

**Professional society guidelines/other:**


Miller DT, Adam MP, Aradhya S, et al. Consensus statement: chromosomal microarray is a first-tier


**Peer-reviewed references:**


Hillman S, Pretlove S, Coomarasamy A, et. al. Additional information from array comparative genomic hybridization technology over conventional karyotyping in prenatal diagnosis: a systematic review and


**Center for Medicare and Medicaid Services National Coverage Determinations:**

National Coverage Determination 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 any 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.
- Myelodysplasia.


**Local Coverage Determinations:**

Local Coverage Determinations 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>
<td>Cytogenomic constitutional (genome-wide) microarray analysis; interrogation of genomic regions for copy number and single nucleotide polymorphism (SNP) variants for chromosomal abnormalities</td>
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<th>ICD-10 Codes</th>
<th>Description</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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<tr>
<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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<tr>
<td>F84.3</td>
<td>Childhood disintegrative disorder</td>
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<tr>
<td>F84.5</td>
<td>Asperger’s disorder</td>
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<tr>
<td>F84.9</td>
<td>Pervasive developmental disorder</td>
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<tr>
<td>Q89.7</td>
<td>Multiple congenital anomalies(unspecified)</td>
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<th>HCPCS Level II Codes</th>
<th>Description</th>
<th>Comment</th>
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<tbody>
<tr>
<td>S3870</td>
<td>Comparative genomic hybridization (CGH) microarray testing for developmental delay, autism spectrum disorder and/or intellectual disability</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 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 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 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 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 managed care organization may still require that 1 and 2 apply). Examples are the evaluation of global developmental disabilities, 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 managed care organization 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 managed care organization may still require that 1 and 2 apply) An example would be for non-small cell lung cancer treatment (first line) Tarceva and Gilotrif. Food and Drug Administration-approved epidermal growth factor receptor 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, comparative genomic hybridization, and single nucleotide polymorphisms.