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CLINICAL MEDICAL POLICY

Policy Name:	Chromosomal Microarray Analysis: Comparative Genomic Hybridization (CGH) and Single Nucleotide Polymorphism (SNP)
Policy Number:	MP-012-MD-PA
Approved By:	Medical Management
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Application:	All participating hospitals and providers
Page Number(s):	1 of 10

Disclaimer

Gateway Health℠ (Gateway) medical payment and prior-authorization policy is intended to serve only as a general reference resource regarding payment and coverage for the services described. This policy does not constitute medical advice and is not intended to govern or otherwise influence medical decisions.

POLICY STATEMENT:

Gateway Health Plan® provides coverage under the medical benefits of the Company's Medicaid products for medically necessary chromosomal microarray analysis which includes Comparative Genomic Hybridization (CGH) and Single Nucleotide Polymorphism (SNP) laboratory procedures.

This policy is designed to address medical necessity guidelines that are appropriate for the majority of individuals with a particular disease, illness or condition. Each person's unique clinical circumstances warrants individual consideration, based upon review of applicable medical records.

(Current applicable PA HealthChoices Agreement Section V. Program Requirements, B. Prior Authorization of Services, 1. General Prior Authorization Requirements.)

DEFINITIONS:

Prior Authorization Review Panel – a panel of representatives from within the PA Department of Human Services who have been assigned organizational responsibility for the review, approval and denial of all PH-MCO Prior Authorization policies and procedures.

Autism Spectrum Disorder – Per the PA Act 62, autism is defined as any of the pervasive developmental disorders defined by the most recent edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM), or its successor, including autistic disorder, Asperger's disorder and pervasive developmental disorder not otherwise specified.

Comparative Genomic Hybridization Microarray testing – a laboratory test performed to detect unbalanced genomic copy number of variations such as microdeletions and/or microduplications at a higher resolution level than conventional genetic evaluation (e.g., karyotype analysis or fluorescence in situ hybridization [FISH]). The test can be performed on blood, body fluid or tissue specimens.

Developmental Delay – term that is used to describe children younger than five years of age who present with delays in the attainment of development milestones at the expected age.

Intellectual Disability – intellectual disability (previously referred to as mental retardation) may be used to describe persons five years of age and older (when standardized measures of intelligence become reliable and valid) who exhibit deficits in intelligence (IQ), adaptive behavior, and systems of support (American Association on Mental Retardation, 2002).

Karyotype – this term is defined as the number of chromosomes in a given cell. In normal human beings 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).

Microdeletions - are the loss of a minute piece of chromosome and microduplications are the gain of a minute piece of a chromosome. To detect the microdeletions or microduplications high resolution techniques such as DNA analysis is required.

Next-Generation Sequencing – method of DNA sequencing genome technology at high speed. Also known as second generation sequencing or massively parallel sequencing.

Syndrome – a pattern of recognizable multiple malformations. The diagnosis of syndromes are often relatively straightforward and common enough to be clinically recognized without specialized testing. Syndrome examples would include Down syndrome and achondroplasia. In the very young or in the case of syndromes with variable presentation, confident identification may be difficult without additional testing.

PROCEDURES

1. The following medical necessity criteria for postnatal children when one of the following criteria are met:

    a. The child must be under the age of 21; AND
    b. The child's parents have been engaged in face-to-face genetic counseling with a healthcare professional; AND
    c. The child must exhibit *multiple* congenital anomalies, including dysmorphic features and developmental delay not specific to a well-delineated genetic syndrome; OR
    d. When a specific diagnosis is being considered

2. Genetic Counseling

Pre- and post-test genetic counseling is required to be performed by an independent (not employed by a genetic testing lab) genetic provider prior to genetic counseling for mutations. This service is necessary in order to inform persons being tested about the benefits and limitations of a specific genetic test for the specific patient. Genetic testing for mutation requires documentation of medical necessity from one of the following providers who has evaluated the member and intends to see the person after testing has been performed for counseling:

- Board Eligible or Board Certified Genetic Counselor
- Advanced Genetics Nurse
- Genetic Clinical Nurse
- Advanced Practice Nurse in Genetics
- Board Eligible or Board Certified Clinical Geneticist
- A physician with experience in cancer genetics
- A physician specializing in pediatric neurology and/or developmental pediatrics

3. When the laboratory services are not covered
   a. For conditions other than those listed above scientific evidence has not been established.

   b. CGH is considered experimental/investigational when used to determine a *single* congenital anomaly (i.e., mental retardation, developmental delay, autism spectrum disorder, without other diagnoses).

   c. CGH is not medically necessary when used to confirm a diagnosis of a disorder or syndrome that is routinely diagnosed based on clinical evaluation alone.

   d. Panel testing using next-generation gene sequencing is considered experimental/investigational in all cases of suspected genetic abnormality in children with developmental delay/intellectual disability, autism spectrum disorder, or congenital anomalies.

4. Post-payment Audit Statement
   The medical record must include documentation that reflects the medical necessity criteria and is subject to audit by Gateway Health Plan® at any time pursuant to the terms of your provider agreement.

5. Governing Bodies Approval
   FDA
   Genetic testing are laboratory developed tests that do not require premarket approval by the FDA. These types of tests are regulated under the Clinical Laboratory Improvement Amendments (CLIA) Act of 1998. The regulations of the CLIA Amendments do not include validation of specific test but rather there is procedural compliance. Additional information available at:
   http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/IVDRegulatoryAssistance/ucm124105.htm.

6. Place of Service
   The place of service for CGH laboratory testing is outpatient.

Summary of Literature

Chromosomal Microarray Analysis (CMA) can identify genomic abnormalities that are associated with a wide range of developmental disabilities, including cognitive impairment, behavioral abnormalities, and congenital abnormalities. CMA can detect copy number variants (CNVs) and the frequency of disease-causing CNVs is highest (20%-25%) in

children with moderate to severe intellectual disability accompanied by malformations or dysmorphic features. Disease-causing CNVs have been identified in 5% to 10% of cases of autism, being more frequent in severe phenotypes.

Chromosomal microarray analysis (CMA) includes both comparative genomic hybridization (CGH) and single nucleotide polymorphism (SNP) arrays. CGH microarray testing, also known as array comparative genomic hybridization (CGH) is a technology that can be used for the detection of genomic copy number variations (CNVs). CNVs are alterations that include deletion and/or duplication of one or more sections of DNA. This method allows the detection of chromosome imbalances that can provide more information than detected by conventional chromosome analysis [e.g., standard karyotype or fluorescence in situ hybridization (FISH)]. The array CGH approach compares patient DNA extracted from skin, blood, or fetal cells to a control or reference DNA from a normal individual. These are labelled separately with different colored fluorescent dyes and then mixed together and allowed to combine or hybridize to an array containing known DNA sequences called probes. The amount of hybridization is measured by the amount and color of light emitted from each spot. Computer analysis of the fluorescent signals is used to read and interpret the findings. Areas of unequal hybridization, mostly large deletions and duplications, signify a DNA alteration. CNVs may be benign, with no effect on clinical phenotype, or may be pathogenic and result in a variety of phenotypic abnormalities (Kearney et al., 2011). If an unknown CNV is detected, a genomic database is used to determine if the abnormality has been previously reported and if it has been associated with a benign or proposed pathogenic condition.
The disadvantages of array CGH testing include the detection of a large number of variants of unknown clinical significance, potential false positives results that will require further testing, and the inability to detect certain anomalies such as those with balanced rearrangements where there is no net gain or loss of the chromosomes (Fruhman and Van den Veyver 2010; Bui 2011).

The evidence for CMA testing in individuals diagnosed with DD/ID, ASD or multiple congenital anomalies not specific to a well-defined genetic syndrome includes case series. The evidence is sufficient to determine that the CMA testing is accurate, valid and results in meaningful improvement in health outcomes.

The American Academy of Neurology and the Practice Committee of the Child Neurology Society have determined that CMA testing has the highest diagnostic yield in children with DD/ID (Michelson et al., 2011). In addition, the organization determined that CMA should be considered the first-line test in children with DD/ID. The authors note that the assistance of a medical geneticist is necessary.

The American College of Medical Genetics published guidelines on the array-based technologies and the clinical utilization for detecting chromosomal abnormalities (Manning, 2010). The CMA testing for copy number variation (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

Next-generation sequencing (NGS) panel testing allows for simultaneous analysis of a large number of genes and the testing has been proposed as a way to identify single-gene causes of syndromes that have autism as a significant clinical feature in patients with normal CMA testing. To date, there are no peer-reviewed full length publications on the commercial available NGS panels related to the clinical and analytic validity or the clinical utility of the diagnostic test.

AUTHORIZATION and CODING REQUIREMENTS:
Procedure Codes

CPT Code	Description
81228	Cytogenomic constitutional (genome–wide) microarray analysis; interrogation of genomic regions for copy number variants (e.g. bacterial artificial chromosome [BAC] or oligo-based comparative genomic hybridization [CGH] microarray analysis)
81229	Cytogenomic constitutional (genome-wide) microarray analysis; interrogation of genomic regions for copy number and single nucleotide polymorphism (SNP) variants for chromosomal abnormalities
96040	Genetic Counseling

Diagnosis Codes

ICD-10 Diagnosis Code	Description
F84.3	Other childhood disintegrative disorder
F84.5	Asperger's syndrome
F84.8	Other pervasive developmental disorders
F84.9	Pervasive developmental disorder, unspecified
F81.0	Specific reading disorder
R48.0	Dyslexia and alexia
F81.81	Disorder of written expression
F81.2	Mathematics disorder
F81.89	Other developmental disorders of scholastic skills
F80.1	Expressive language disorder
F80.2	Mixed receptive-expressive language disorder
H93.25	Central auditory processing disorder
F80.4	Speech and language development delay due to hearing loss
F80.81	Childhood onset fluency disorder
F80.0	Phonological disorder
F80.89	Other developmental disorders of speech and language
F80.9	Developmental disorder of speech and language, unspecified
F82	Specific developmental disorder of motor function
F88	Other disorders of psychological development
F81.9	Developmental disorder of scholastic skills, unspecified
F89	Unspecified disorder of psychological development
F90.8	Attention-deficit hyperactivity disorder, other type
F70	Mild intellectual disabilities
F71	Moderate intellectual disabilities
F72	Severe intellectual disabilities
F73	Profound intellectual disabilities
F78	Other intellectual disabilities
F79	Unspecified intellectual disabilities
P02.9	Newborn (suspected to be) affected by abnormality of membranes, unspecified
Q00.0	Anencephaly
Q00.1	Cranioarchischisis
Q00.2	Iniencephaly
Q01	Encephalocele
Q01.0	Frontal encephalocele

Q01.2	Nasofrontal encephalocele
Q01.8	Occipital encephalocele
Q01.9	Encephalocele of other sites
Q01.8	Encephalocele, unspecified
Q02	Microcephaly
Q03	Congenital hydrocephalus
Q03.0	Malformations of aqueduct of Sylvius
Q03.1	Atresia of foramina of Magendie and Luschka
Q03.8	Other congenital hydrocephalus
Q03.9	Congenital hydrocephalus
Q04	Other congenital malformations of brain
Q04.0	Congenital malformations of corpus callosum
ICD-10 Diagnosis Code	**Description**
Q04.1	Arhinencephaly
Q04.2	Holoprosencephaly
Q04.3	Other reduction deformities of brain
Q04.4	Septo-optic dysplasia of brain
Q04.5	Megalencephaly
Q04.6	Congenital cerebral cysts
Q04.8	Other specified congenital malformations of the brain
Q04.9	Congenital malformation of brain, unspecified
Q05	Spina bifida
Q05.0	Cervical spina bifida with hydrocephalus
Q05.1	Thoracic spina bifida with hydrocephalus
Q05.2	Lumbar spina bifida with hydrocephalus
Q05.3	Sacral spina bifida with hydrocephalus
Q05.4	Unspecified spina bifida with hydrocephalus
Q05.5	Cervical spina bifida without hydrocephalus
Q05.6	Thoracic spina bifida without hydrocephalus
Q05.7	Lumbar spina bifida without hydrocephalus
Q05.8	Sacral spina bifida without hydrocephalus
Q05.9	Spina bifida, unspecified
Q06	Other congenital malformations of spinal cord
Q06.0	Amyelia
Q06.1	Hypoplasia and dysplasia of spinal cord
Q06.2	Diastematomyelia
Q06.3	Other congenital cauda equine malformations
Q06.4	Hydromyelia
Q06.8	Other specified congenital malformations of spinal cord
Q06.9	Congenital malformation of spinal cord, unspecified
Q07	Other congenital malformations of nervous system
Q07.0	Arnold-Chiari syndrome
Q07.00	Arnold-Chiari syndrome without spina bifida or hydrocephalus
Q07.01	Arnold-Chiari syndrome with spina bifida
Q07.02	Arnold-Chiari syndrome with hydrocephalus

Q07.03	Arnold-Chiari syndrome with spina bifida and hydrocephalus
Q07.8	Other specified congenital malformation of nervous system
Q07.9	Congenital malformation of nervous system, unspecified
Q90.0	Trisomy 21, nonmosaicism (meiotic nondisjunction)
Q90.1	Trisomy 21, mosaicism (mitotic nondisjunction)
Q90.2	Trisomy 21, translocation
Q90.9	Down syndrome, unspecified
Q91.0	Trisomy 18, nonmosaicism (meiotic nondisjunction)
Q91.1	Trisomy 18, mosaicism (mitotic nondisjunction)
Q91.2	Trisomy 18, translocation
Q91.3	Trisomy 18, unspecified
Q91.4	Trisomy 13, nonmosaicism (meiotic nondisjunction)
Q91.5	Trisomy 13, mosaicism (mitotic nondisjunction)
Q91.6	Trisomy 13, translocation
Q91.7	Trisomy 13, unspecified
Q92.0	Whole chromosome trisomy, nonmosaicism (meiotic nondisjunction)
Q92.1	Whole chromosome trisomy, mosaicism (mitotic nondisjunction)
Q92.2	Partial trisomy
Q92.5	Duplications with other complex rearrangements
ICD-10 Diagnosis Code	**Description**
Q92.61	Marker chromosomes in normal individual
Q92.62	Marker chromosomes in abnormal individual
Q92.7	Triploidy and polyploidy
Q92.8	Other specified trisomies and partial trisomies of autosomes
Q92.9	Trisomy and partial trisomy of autosomes, unspecified
Q93.0	Whole chromosome monosomy, nonmosaicism (meiotic nondisjunction)
Q93.1	Whole chromosome monosomy, mosaicism (mitotic nondisjunction)
Q93.2	Chromosome replaced with ring, dicentric or isochromosome
Q93.4	Deletion of short arm of chromosome 5
Q93.5	Other deletions of part of a chromosome
Q93.7	Deletions with other complex rearrangements
Q93.81	Velo-cardio-facial syndrome
Q93.88	Other microdeletions
Q93.89	Other deletions from the autosomes
Q93.9	Deletion from autosomes, unspecified
Q95.2	Balanced autosomal rearrangement in abnormal individual
Q95.3	Balanced sex/autosomal rearrangement in abnormal individual
Q99.8	Other specified chromosome abnormalities
Q99.9	Chromosomal abnormality, unspecified
Q89.7	Multiple congenital malformations, not elsewhere classified
Q89.9	Congenital malformation, unspecified
R62.0	Delayed milestone in childhood
R62.50	Unspecified lack of expected normal physiological development in childhood
R92.51	Failure to thrive (child)
R62.59	Other lack of expected normal physiological development in childhood

R89.8	Other abnormal findings in specimens from other organs, systems and tissues
Z37.1	Single stillbirth
Z37.3	Twins, one liveborn and one stillborn
Z37.4	Twins, both stillborn
Z37.60	Multiple births, unspecified, some liveborn
Z37.61	Triplets, some liveborn
Z37.62	Quadruplets, some liveborn
Z37.63	Quintuplets, some liveborn
Z37.64	Sextuplets, some liveborn
Z37.69	Other multiple births, some liveborn
Z37.7	Other multiple births, all stillborn

Policy Source(s)

American Association on Mental Retardation. Mental Retardation: Definition, Classification, and Systems of Supports. 10th ed. Washington, DC: American Association on Mental Retardation; 2002.
Available at: http://www.aamr.org/. Accessed on April 21, 2016.

The American College of Obstetricians and Gynecologist and Society for Maternal-Fetal Medicine. The use of chromosomal microarray analysis in prenatal diagnosis: Genetics Committee Opinion. Number 581, December 2013. Reaffirmed 2015.
Available at: https://www.acog.org/-/media/Committee-Opinions/Committee-on-Genetics/co581.pdf?dmc=1&ts=20160421T1148056751. Accessed on April 21, 2016.

Bartnik M, Wiśniowiecka-Kowalnik B, Nowakowska B, et al. The usefulness of array comparative genomic hybridization in clinical diagnostics of intellectual disability in children. Dev Period Med. 2014 Jul-Sep;18(3):307-17. Available at: http://devperiodmed.pl/articles/2014-3-3.pdf. Accessed on April 21, 2016.

Bremer A, Giacobini M, Eriksson M, et al. Copy number variation characteristics in subpopulations of patients with autism spectrum disorders. Am J Med Genet B Neuropsychiatr Genet. 2011 Mar;156(2):115-24. doi: 10.1002/ajmg.b.31142. Abstract available at: http://onlinelibrary.wiley.com/doi/10.1002/ajmg.b.31142/abstract. Accessed on April 16, 2016.

ECRI Institute. Hotline Response. Array-based Comparative Genomic Hybridization for Diagnosing Developmental Disorders in Fetuses, Infants, and Children. January 2014.

ECRI Institute. Hotline Response. Array-based Comparative Genomic Hybridization for Screening or Diagnosing Clinical Conditions. January 2014.

Fruhman G, Van den Veyver IB. Applications of array comparative genomic hybridization in obstetrics. Obstet Gynecol Clin North Am. 2010 Mar;37(1):71-85. Abstract available at: http://www.ncbi.nlm.nih.gov/pubmed/20494259. Accessed on April 21, 2016.

Gijsbers AC, Lew JY, Bosch CA, et al. A new diagnostic workflow for patients with mental retardation and/or multiple congenital abnormalities: test arrays first. *Eur J Hum Genet*. 2009;17(11):1394-1402. Available at: http://www.nature.com/ejhg/journal/v17/n11/full/ejhg200974a.html. Accessed on April 21, 2016.

Hayes, Inc. Hayes Genetic Testing Evaluation (GTE) Report. Genomic Microarray Analysis for Intellectual Disability, Developmental Delay, Multiple Congenital Anomalies, and Autism Spectrum Disorders. Lansdale, PA: Hayes, Inc.; May 2013. Updated May 2014.

Kearney HM, Thorland EC, Brown KK, et al.; Working Group of the American College of Medical Genetics Laboratory Quality Assurance Committee. American College of Medical Genetics standards and guidelines for interpretation and reporting of postnatal

constitutional copy number variants. *Genet Med*. 2011;13(7):680-685. Available at: https://www.acmg.net/StaticContent/SGs/CNV.pdf. Accessed on April 21, 2016.

Manning M, Hudgins L; Professional Practice and Guidelines Committee. Array-based technology and recommendations for utilization in medical genetics practice for detection of chromosomal abnormalities. Genet Med. 2010 Nov;12(11):742-5. Available at: https://www.acmg.net/StaticContent/PPG/Array_based_technology_and_recommendations_for.13.pdf. Accessed on April 21, 2016.

Michelson DJ, Shevell MI, Sherr EH, et al. Evidence report: Genetic and metabolic testing on children with global developmental delay: report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. Neurology. 2011 Oct 25;77(17):1629-35. Available at: http://www.neurology.org/content/77/17/1629.long. Accessed on April 21, 2016.

Moeschler JB, Shevell M, American Academy of Pediatrics Committee on Genetics. Clinical genetic evaluation of the child with mental retardation or developmental delays. Pediatrics 2006;117(6):2304-16. DOI: 10.1542/peds.2006-1006. Available at: http://pediatrics.aappublications.org/content/pediatrics/117/6/2304.full.pdf. Accessed on April 21, 2016.

National Institute for Health and Care Excellence (NICE). Autism in Children and Young People. Clinical Guideline. September 2011. Available at: http://guidance.nice.org.uk/CG128/Guidance/pdf/English Accessed April 21, 2016.

Nicholl J, Waters W, Mulley JC, et al.; Array Referral Consortium, Friend K, Bain SM, Yu S. Cognitive deficit and autism spectrum disorders: prospective diagnosis by array CGH. Pathology. 2014 Jan;46(1):41-5. Abstract available at: http://journals.lww.com/pathologyrcpa/Abstract/2014/01000/Cognitive_deficit_and_autism_spectrum_disorders__.8.aspx. Accessed on April 21, 2016.

Saam J, Gudgeon J, Aston E, Brothman AR. How physicians use array comparative genomic hybridization results to guide patient management in children with developmental delay. *Genet Med*. 2008;10(3):181-186. Available at: http://www.nature.com/gim/journal/v10/n3/pdf/gim200827a.pdf. Accessed on April 21, 2016.

Shen, Y, Dies, KA, Holm, IA, et al. Clinical genetic testing for patients with autism spectrum disorders. *Pediatrics*. 2010;125(4):e727-e735. Available at: http://pediatrics.aappublications.org/content/125/4/e727.full. Accessed on April 21, 2016.

Van den Veyver IB, Patel A, Shaw CA, et al. Clinical use of array comparative genomic hybridization (aCGH) for prenatal diagnosis in 300 cases. Prenat Diagn. 2009;29(1):29-39. Available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3665952/. Accessed on April 21, 2016.

Wagenstaller J, Spranger S, Lorenz-Depiereux B, et al. Copy-number variations measured by single-nucleotide–polymorphism oligonucleotide arrays in patients with mental retardation. *Am J Hum Genet*. 2007;81(4):768-779. Available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2227926/. Accessed on April 21, 2016.

Pennsylvania Department of Human Services. Technology Assessment Group Coverage Decisions. Managed Care Operations Memorandum: OPS # 05/2010-009. May 5, 2010. Accessed April 21, 2016.