CLINICAL MEDICAL POLICY	
Policy Name:	Chromosomal Microarray Analysis: Comparative Genomic Hybridization (CGH) and Single Nucleotide Polymorphism (SNP)
Policy Number:	MP-012-MD-DE
Responsible Department(s):	Medical Management
Provider Notice Date:	04/01/2019; 04/15/2018; 11/01/2016
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Products:	Highmark Health Options Medicaid
Application:	All participating hospitals and providers
Page Number(s):	1 of 12

DISCLAIMER

Highmark Health Options medical policy is intended to serve only as a general reference resource regarding 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

Highmark Health Options may provide 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 warrant individual consideration, based upon review of applicable medical records.

The qualifications of the policy will meet the standards of the National Committee for Quality Assurance (NCQA) and the Delaware Department of Health and Social Services (DHSS) and all applicable state and federal regulations.

DEFINITIONS

Autism Spectrum Disorder (ASD) – 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 – A term 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 – An 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 – A term that defines 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 - The loss of a minute piece of chromosome. 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 – A 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 is 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 must be 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 one of the following conditions:
        1) Multiple* congenital anomalies not specific to a well-delineated genetic syndrome;
        Multiple congenital anomalies are defined as:
            - Two or more major anomalies affecting different organ systems;

- One major and two or more minor anomalies affecting different organ systems

[Major structural anomalies are generally serious enough as to require medical treatment (such as surgery) and are not minor developmental variations that may or may not suggest an underlying disorder]; OR

2) Apparently non-syndromic developmental delay/intellectual disability; OR
3) Autism Spectrum Disorder; AND

D. When a specific diagnosis is being considered.
E. CMA analysis of amniotic fluid, placenta or products of conception (POC) for evaluation of pregnancy loss in the following conditions:
   1)In cases of pregnancy loss at 20 weeks of gestation or earlier when there is a maternal history of recurrent miscarriage (history of 2 or more failed pregnancies); OR
   2)In all cases of pregnancy loss after 20 weeks of gestation
F. Note: This policy does not address the use of CMA for preimplantation genetic diagnosis or preimplantation genetic screening.

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 patient and intends to see the person after testing has been performed for counseling:

A. Board Eligible or Board Certified Genetic Counselor
B. Advanced Genetics Nurse
C. Genetic Clinical Nurse
D. Advanced Practice Nurse in Genetics
E. Board Eligible or Board Certified Clinical Geneticist
F. A physician with experience in cancer genetics
G. A physician specializing in pediatric neurology and/or developmental pediatrics

3. When the laboratory services are not covered

A. 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).
B. CGH is not medically necessary when the diagnosis is readily apparent and can be confirmed on clinical evaluation alone.
C. CGH is unproven and not medically necessary for all other patient populations and conditions.
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.
E. CMA testing of fetal tissue for the evaluation of pregnancy loss when the patient selection criteria is not met are considered not medically necessary.

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

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

GOVERNING BODIES APPROVAL

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 is available at:
http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/IVDRegulatoryAssistance/ucm124105.htm.

CODING REQUIREMENTS

Procedure Codes

CPT Codes/ HCPCS 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
S3870	Comparative genomic hybridization (CGH) microarray testing for developmental delay, autism spectrum disorder and/or intellectual disability.

Diagnosis Codes

ICD-10 Codes	Description
F70	Mild intellectual disabilities
F71	Moderate intellectual disabilities
F72	Severe intellectual disabilities
F73	Profound intellectual disabilities
F78	Other intellectual disabilities
F79	Unspecified intellectual disabilities
F80.0	Phonological disorder
F80.1	Expressive language disorder
F80.2	Mixed receptive-expressive language disorder
F80.4	Speech and language development delay due to hearing loss
F80.81	Childhood onset fluency disorder
F80.82	Social pragmatic communication disorder
F80.89	Other developmental disorders of speech and language

F80.9	Developmental disorder of speech and language, unspecified
F81.0	Specific reading disorder
F81.2	Mathematics disorder
F81.81	Disorder of written expression
F81.89	Other developmental disorders of scholastic skills
F81.9	Developmental disorder of scholastic skills, unspecified
F82	Specific developmental disorder of motor function
F84.0	Autistic Disorder
F84.3	Other childhood disintegrative disorder
F84.5	Asperger's syndrome
F84.8	Other pervasive developmental disorders
F84.9	Pervasive developmental disorder, unspecified
F88	Other disorders of psychological development
F89	Unspecified disorder of psychological development
F90.8	Attention-deficit hyperactivity disorder, other type
H93.25	Central auditory processing disorder
N96	Recurrent pregnancy loss
O26.20	Pregnancy care for patient with recurrent pregnancy loss, unspecified trimester
O26.21	Pregnancy care for patient with recurrent pregnancy loss, first trimester
O26.22	Pregnancy care for patient with recurrent pregnancy loss, second trimester
O26.23	Pregnancy care for patient with recurrent pregnancy loss, third trimester
P02.9	Newborn (suspected to be) affected by abnormality of membranes, unspecified
Q00.0	Anencephaly
Q00.1	Craniorachischisis
Q00.2	Iniencephaly
Q01.0	Frontal encephalocele
Q01.2	Nasofrontal encephalocele
Q01.8	Occipital encephalocele
Q01.8	Encephalocele, unspecified
Q01.9	Encephalocele of other sites
Q02	Microcephaly
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
Q04.0	Congenital malformations of corpus callosum
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
Q05.0	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
Q06.0	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
Q07.0	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
Q89.7	Multiple congenital malformations, not elsewhere classified
Q89.9	Congenital malformation, 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
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
R48.0	Dyslexia and alexia
R62.0	Delayed milestone in childhood
R62.50	Unspecified lack of expected normal physiological development in childhood
R62.59	Other lack of expected normal physiological development in childhood
R89.8	Other abnormal findings in specimens from other organs, systems and tissues
R62.51	Failure to thrive (child)
Z37.60	Multiple births, unspecified, some live born
Z37.61	Triplets, some live born
Z37.62	Quadruplets, some live born
Z37.63	Quintuplets, some live born
Z37.64	Sextuplets, some live born
Z37.69	Other multiple births, some live born

REIMBURSEMENT

Participating facilities will be reimbursed per their Highmark Health Options contract.

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.

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 Developmental Disability/Intellectual Disability (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 society 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

The American College of Medical Genetics and Genomics (ACMG) guideline states that ordering providers should be aware of cytogenomic aberrations not detectable by CMA, including those relevant to various microarray platforms (e.g., single-nucleotide polymorphism [SNP] versus oligonucleotide).

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 commercially available NGS panels related to the clinical and analytical validity or the clinical utility of the diagnostic test.

Most pregnancy losses happen in early pregnancy. Pregnancy loss occurring before the 20th week of gestation is referred to as spontaneous abortion, early pregnancy loss, or miscarriage. Fetal loss occurring after 20 weeks gestation is referred to as stillbirth or intrauterine fetal death (IUFD). Early pregnancy loss is defined as a nonviable intrauterine pregnancy with either an empty gestational sac or an embryo/fetus without cardiac activity at <13 weeks gestation (ACOG 2015). It is estimated that early pregnancy loss occurs commonly and affects 10% to 15% of recognized pregnancies under 20 weeks. The overall risk of miscarriage in the next pregnancy remains at 15% after one miscarriage, rises to 17% from 13% after two consecutive miscarriages, and climbs to 25% to 46% after three or more miscarriages (UpToDate, 2017). There is no preventative therapy for women with threatened early pregnancy loss and a work-up on the cause of the loss, is not recommended until after the second consecutive loss.

Genetic evaluation of the products of conception has traditionally been performed using karyotyping of metaphase cells after cells are culture in tissue. Using this method, only visible rearrangements are detected. There are risks for maternal cell contamination which can impact karyotyping. An alternative genetic testing method has been utilized, chromosomal microarray testing.

The American College of Obstetrics and Gynecology (ACOG) and the Society for Maternal-Fetal Medicine (SMFM) recommend use of CMA when genetic analysis is desired because of fetal congenital anomalies or intrauterine fetal death or stillbirth (UpToDate 2018). CMA is useful in the valuation of stillbirth because both chromosomal abnormalities and culture failure are common. Paula and colleagues (2018) reported the results of systematic review of twenty-three studies in which CMA and karyotyping were performed concurrently. The analysis revealed that CMA showed a significant increase in test success rate and incremental diagnostic yield in early pregnancy loss. CMA revealed informative results in 95% of the 5,507 pregnancy losses reviewed while karyotyping results were 68%.

A congenital anomaly is defined as something that is unusual or different at birth (Medicine Net, 2016). The anomaly can be classified as a minor anomaly in which the defect is an unusual anatomic feature that is of no serious medical or cosmetic consequence. Examples of a minor anomaly can include protruding ears, ptosis, anteverted nostrils, hypotelorism, minor hypospadias, partial syndactyly between 2-3 toes, and plagiocephaly.

Major anomaly is a defect that has serious medical and cosmetic consequences. Examples of a major anomaly can include cleft lip and palate, absence or limb deficiencies, hydrocephaly, hypoplasia or coarctation of the aorta, micrognathia severe, pectus excavatum, spina bifida, and Tetralogy of Fallot.

POLICY SOURCE(S)

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Policy History

Date	Activity
09/06/2016	Policy approved at QI/UM Meeting
12/01/2016	Provider effective date
02/13/2017	Revisions: Revised Operational Guidelines, additional formatting changes, New ICD-10 code added
03/14/2017	QI/UM Committee Review
08/10/2017	Added Disclaimer Statement in opening of medical policy; ICD 10 Diagnosis code was corrected (R92.51 to R62.51). ICD 10 Diagnosis codes Q01, Q03, Q04, Q05, Q06, Q07, and Q07 have been removed (section headers and are invalid). Revisions: Issue Date added to opening policy box, effective date corrected to read 2016 instead of 2017; Under Definitions, reference to PA act 62 was removed; on page 3, under the non-covered section - A & C 'considered not medically necessary was added; The word "Covered" was added to the titles of Table B & C.
12/11/2017	Clinical Review: Added Autism Spectrum to medically necessary criteria under procedure (section 1); Reformatted criteria under procedure section; Reformatted non-covered section (section 3) under Procedures; Added HCPCS code S3870. Deleted stillborn ICD-10 codes.
03/13/2018	QI/UM Committee Review Approval
04/25/2018	Revision: Removed the word 'Covered' from the procedure and diagnosis code tables in Attachments B & C
05/15/2018	New provider effective date
03/12/2019	Annual Review: Updated Procedure section with clarification of congenital anomalies, added criteria for microarray analysis in the evaluation of pregnancy loss; updated noncovered section related to analysis of fetal tissue; deleted CPT code 96040; added ICD-10 diagnosis N96, O26.20 – O26.23; updated the summary of literature and reference section; removed hyperlinks from the reference section; Updated reference from ACOG recommendation to December 2016.
03/12/2019	QI/UM Committee Review Approval
03/27/2019	Added diagnosis code F84.0 as eligible diagnosis code to coincide with patient selection criteria.
05/06/2019	Provider effective date
05/08/2019	Corrected typographical error in the Diagnosis Code section. Changed R92.61 to R62.51, no changes required for the code description.