Chromosomal Microarray Analysis: Comparative Genomic Hybridization (CGH) and Single Nucleotide Polymorphism (SNP)

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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 medical surgical benefits of the Company's Medicaid products for medically necessary chromosomal microarray analysis, comparative genomic hybridization and single nucleotide polymorphism.

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

Highmark Health Options (HHO) – Managed care organization serving vulnerable populations that have complex needs and qualify for Medicaid. Highmark Health Options members include individuals and families with low income, expecting mothers, children, and people with disabilities. Members pay nothing to very little for their health coverage. Highmark Health Options currently services Delaware Medicaid: Delaware Healthy Children Program (DHCP) and Diamond State Health Plan Plus members.

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 each 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

A prior authorization is required.

The following medical necessity criteria for postnatal children must be met:

- The child must be under the age of 21; AND
- The child's parents have been engaged in face-to-face genetic counseling with a health care professional; AND
- The child must exhibit one of the following conditions:
  - 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
  - Apparently non-syndromic developmental delay/intellectual disability; OR
  - Autism Spectrum Disorder; AND

- When a specific diagnosis is being considered.
- CMA analysis of amniotic fluid, placenta or products of conception (POC) for evaluation of pregnancy loss in the following conditions:
  - 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
  - In all cases of pregnancy loss after 20 weeks of gestation

- Note: This policy does not address the use of CMA for preimplantation genetic diagnosis or preimplantation genetic screening.

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:

- 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

When the laboratory services are not covered:

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

Post-payment Audit Statement

The medical record must include documentation that reflects the medical necessity criteria and is subject to audit by Highmark Health Options at any time pursuant to the terms of your provider agreement.

Place of Service: Outpatient

CODING REQUIREMENTS

CPT code	Description
81127	Cyp2c9 (cytochrome P450, family 2, subfamily C, polypeptide 9) (e.g., drug metabolism), gene analysis, common variants (e.g., *2, *3, *5, *6).

Covered Diagnosis Codes

- 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 Cranioarchischisis
- 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 nonsyndromic 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.

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POLICY UPDATE HISTORY

<Date>	<Event>