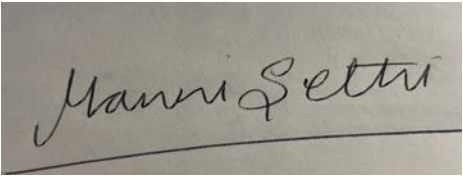


**Prior Authorization Review Panel
MCO Policy Submission**

A separate copy of this form must accompany each policy submitted for review.
Policies submitted without this form will not be considered for review.

Plan: AmeriHealth Caritas Pennsylvania	Submission Date: 10/27/2023
Policy Number: ccp.1024	Effective Date: 9/2013 Revision Date: October 1, 2023
Policy Name: Chromosomal microarray analysis in prenatal and postnatal care	
Type of Submission – Check all that apply: New Policy <input checked="" type="checkbox"/> Revised Policy* Annual Review – No Revisions Statewide PDL	
*All revisions to the policy <u>must</u> be highlighted using track changes throughout the document. Please provide any clarifying information for the policy below: See tracked changes below.	
Name of Authorized Individual (Please type or print): Manni Sethi, MD, MBA, CHCQM	Signature of Authorized Individual: 

Chromosomal microarray analysis in prenatal and postnatal care

Clinical Policy ID: CCP.1024

Recent review date: 9/2023

Next review date: 1/2025

Policy contains: Chromosomal microarray analysis, comparative genomic hybridization, developmental delay, karyotyping, single nucleotide polymorphism.

AmeriHealth Caritas Pennsylvania has developed clinical policies to assist with making coverage determinations. AmeriHealth Caritas Pennsylvania 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 AmeriHealth Caritas Pennsylvania 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. AmeriHealth Caritas Pennsylvania 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. AmeriHealth Caritas Pennsylvania clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, AmeriHealth Caritas will update its clinical policies as necessary. AmeriHealth Caritas Pennsylvania clinical policies are not guarantees of payment.

Coverage policy

Chromosomal microarray analysis is clinically proven and, therefore, medically necessary when all of the following criteria are met (American College of Obstetricians and Gynecologists, 2016, 2020; Miller, 2010):

- Any of the following indications:
 - Evaluation of a fetus with one or more major structural abnormalities identified on ultrasonographic examination who is undergoing invasive prenatal diagnosis.
 - Evaluation of a structurally normal fetus who is undergoing invasive prenatal diagnostic testing.
 - Postnatal evaluation of members with unexplained developmental delay/intellectual disabilities, autism spectrum disorder, or multiple congenital anomalies.
 - After fetal death or stillbirth, testing fetal tissue to conduct further cytogenetic analysis to improve detection of causative abnormalities.
- An obstetrician-gynecologist or other health care provider with expertise in genetics provides pre-test and post-test genetic counseling to the member on benefits, limitations, and results of chromosomal microarray analysis.
- Informed consent, including discussion of the potential to identify findings of uncertain significance, non-

paternity, consanguinity, and adult-onset disease, is given along with the chromosomal microarray analysis.

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).

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

Conventional karyotyping, specifically G-banded karyotyping, has been the accepted first-line test for detecting large changes in the structure or number of whole chromosomes in newborns (e.g., translocations, aneuploidy) (Miller, 2010). Advances in molecular testing methods, such as chromosomal microarray analysis and next-generation sequencing, permit improved detection of chromosomal variants at a much higher resolution level in fetuses and newborns.

Chromosomal microarray analysis detects deletions and duplications of one or more sections of deoxyribonucleic acid (known as copy number variations). It is also known as cytogenomic microarray analysis, microarray-based genomic copy-number analysis, or molecular karyotyping, and collectively describes two different laboratory techniques (Miller, 2010):

- Array comparative genomic hybridization, which detects copy number variations for relatively large deletions or duplications, including whole chromosome duplications, as in trisomy.
- Single nucleotide variant arrays, which detect specific known deoxyribonucleic acid sequence variants.

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). Chromosomal microarray may also detect copy variants of unclear clinical significance, and it may detect a variant with one or more genes related to health problems that were not the reason for testing (Ahn, 2015; Shao, 2021).

In the prenatal setting, chromosomal microarray analysis requires an invasive procedure to collect intact fetal cells (e.g., amniocentesis or chorionic villous sampling) (Shao, 2021). Blood samples can be used for infants and children (Miller, 2010).

Approvals from the U.S. Food and Drug Administration for chromosomal microarray analysis devices were granted for CytoScan® Dx Assay in 2014, and GenetiSure Dx Postnatal Assay in 2017 (U.S. Food and Drug Administration, 2014, 2017).

Findings

The role of chromosomal microarray analysis relative to conventional karyotyping and next-generation sequencing in prenatal and newborn care continues to evolve. While higher resolution molecular testing increases the detection of chromosomal variants over that of karyotyping, it also increases detection of variants of uncertain significance and other incidental findings, creating uncertainty in interpreting and applying the information into health care decisions.

Additional testing after a normal or abnormal chromosomal microarray analysis may be needed to clarify the

results or to identify genomic events that chromosomal microarray cannot detect, such as balanced rearrangements, possible mosaicism, or the genetic mechanism associated with a copy number variation. This suggests a complementary role for chromosomal microarray analysis in certain fetal diagnoses and for newborns with neurodevelopmental issues and birth defects (Waggoner, 2018; Klapwijk, 2021).

To mitigate the uncertainty, guidelines emphasize the importance of local policy and protocols, providing phenotype information, understanding the strengths and limitations of molecular testing, multidisciplinary consultation, using trio analysis to aid in interpretation, and pre- and post-test genetic counselling (Klapwijk, 2021).

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 guideline, recognizing that a genetic basis for autism can be found in 30% to 40% of cases, recommended that genetic testing should be discussed with all patients and families with autism spectrum disorder (Schaefer, 2013).

A December 2016 Committee Opinion from the American College of Obstetricians and Gynecologists recommended prenatal chromosomal microarray analysis for women of all ages. The opinion recommended the analysis 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 American College of Obstetricians and Gynecologists (2020) issued a strong recommendation for incorporating microarray analysis into the stillbirth workup to improve test success rate and detection of genetic anomalies compared with conventional karyotyping.

A 2018 guideline from the Canadian College of Medical Geneticists and Society of Obstetricians and Gynaecologists updated the group's 2011 recommendations for genetic counsellors, medical geneticists, maternal fetal medicine specialists, clinical laboratory geneticists, and other practitioners regarding the use of chromosomal microarray analysis for prenatal diagnosis (Armour, 2018). A 2021 update from the Canadian group recommended diagnostic amniocentesis with chromosomal microarray and amniotic fluid alpha fetoprotein and acetylcholinesterase as one means of genetic testing for neural tube defects (Wilson, 2021).

The Society for Maternal-Fetal Medicine recommended that women be offered fetal diagnostic testing, including chromosomal microarray analysis, when fetal growth restriction is detected and a fetal malformation, polyhydramnios, or both are also present regardless of gestational age. The Society also recommends that pregnant women be offered prenatal diagnostic testing with chromosomal microarray analysis when unexplained isolated fetal growth restriction is diagnosed prior to 32 weeks gestation (Martins, 2020).

The American College of Medical Genetics and Genomics updated their technical laboratory standards in 2021. They presented the advantages and limitations of chromosome microarray analysis and confirmed the indications established by the American College of Medical Genetics and Genomics, American College of Obstetricians and Gynecologists, and the Society for Maternal-Fetal Medicine (Shao, 2021).

The following systematic reviews, meta-analyses, and other large-scale studies offered evidence on the efficacy of chromosomal microarray analysis. The most frequent fetal anomalies studied were congenital heart diseases, multiple malformations, and central nervous system malformations detected on fetal imaging. Studies reported the incidence of normal and abnormal genetic results. There is insufficient evidence quantifying the incremental

impact of chromosomal microarray analysis on clinical outcomes or cost benefit. At this time, the benefit of a genetic diagnosis allows for more accurate genetic counseling and informed reproductive decision making.

The evidence for prenatal testing includes the following analyses:

- In a systematic review/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% of cases, almost significantly greater than karyotyping (68%) (Pauta, 2018).
- A systematic review/meta-analysis of 10 studies indicated a 4% incremental yield of chromosomal microarray analysis over karyotyping in non-malformed growth-restricted fetuses, rising to 10% in fetal growth restriction for fetal malformations (Borrell, 2018).
- Of a total of 3,223 in a prenatal sample, 54.2% met the American College of Obstetricians and Gynecologists guideline criteria for either chromosomal microarray analysis or karyotype. Of these, 2.5% had clinically significant chromosomal abnormalities that would have been missed had karyotype been selected (Hay, 2018).
- In a meta-analysis of 17 studies of fetuses with increased nuchal translucency, genomic microarray had an incremental yield of 5.0% more copy number variants than karyotyping (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% greater than karyotyping (Jansen, 2015).
- A systematic review/meta-analysis of nine papers revealed agreement in detecting abnormalities with chromosomal microarray analysis and karyotyping in 86% of cases. Chromosomal microarray analysis detected 13% additional chromosome abnormalities, versus 3% for karyotyping (Dhillon, 2014).
- A systematic review/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% of women with a normal karyotype (Wapner, 2012).
- In a group of 2,858 pregnancies with normal karyotypes, microarray analysis identified clinically significant genomic alterations in 6.5% of cases with > 1 abnormal ultrasound findings (Shaffer, 2012).
- In a systematic review of 10 articles, array comparative genomic hybridization detected 3.6% more genomic imbalances compared to conventional karyotyping, rising to 5.2% when the referral indication was a structural malformation on ultrasound (Hillman, 2011).
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- A systematic review/meta-analysis of seven studies including 903 stillborn fetuses compared success rates in determining genetic causes. Chromosomal microarray analysis succeeded more than conventional cytogenetic analysis, 90% versus 75% (Martinez-Portilla, 2019).
- A systematic review of 25 articles addresses diagnosis of oculoauriculovertebral spectrum congenital craniofacial malformation conditions. The review concludes comparative genomic hybridization, multiplex polymerase chain reaction, and karyotype analysis methods are all viable approaches (Glaeser, 2020).
- A meta-analysis of 55 studies of genetic testing of pregnancy loss tissue revealed a 48% prevalence using array-comparative genomic hybridization, compared with 47% for conventional karyotyping, 60% for single nucleotide polymorphism array, 38% for fluorescence in-situ hybridization, and 25% for

multiplex ligation-dependent probe amplification. Authors concluded that detection of specific chromosomal abnormalities in pregnancy loss tissue has no clinical benefit and do not recommend routine testing of tissue for chromosomal abnormalities (Smits, 2020).

While genomic microarray detects more chromosomal abnormalities than does karyotyping, a cost analysis comparing these methods alone and sequentially showed microarray alone appeared to be the preferred cost-effective strategy for sonographically-detected anomalies. Karyotyping alone and chromosomal microarray following a normal karyotype were also acceptable strategies, but performing both tests simultaneously did not appear to improve diagnosis and added more costs (Harper, 2014).

A study of 258 children with autism spectrum disorder found 9.3% and 8.4% received a molecular diagnosis from chromosomal microarray analysis and whole-exome sequencing, respectively. A total of 15.8% of this group received a molecular diagnosis, with only two subjects overlapping in both groups, indicating that testing with both methods is a useful diagnostic tool (Tammimies, 2015).

A meta-analysis of 30 articles on testing for neurodevelopmental disorders compared exome sequencing with chromosomal microarray analysis. The yield of exome sequencing was 36% overall, superior to the 15% to 20% in prior studies of chromosomal array analysis (Srivastava, 2019).

In 2022, we focused the policy on chromosomal microarray analysis for non-neoplastic conditions encompassing prenatal and postnatal indications. We added to the list of indications postnatal testing for members with unexplained developmental delay/intellectual disabilities, autism spectrum disorder, or multiple congenital anomalies, as recommended by the International Standard Cytogenomic Array Consortium (Miller, 2010).

We added three systematic reviews and meta-analyses that examined the incremental diagnostic yield of chromosomal microarray analysis in diagnosing fetal cardiovascular anomalies (Mastromoro, 2022a, 2022b; Sun, 2021). The new research results confirm previous policy findings and warrant no additional policy changes.

In 2023, we added a recommendation from the American College of Obstetricians and Gynecologists (2020) to incorporate microarray analysis in stillbirth evaluation. No policy changes are warranted.

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On August 18, 2023, we searched PubMed and the databases of the Cochrane Library, the U.K. National Health Services Centre for Reviews and Dissemination, the Agency for Healthcare Research and Quality, and the Centers for Medicare & Medicaid Services. Search terms were "prenatal diagnosis" (Mesh), "genetic testing" (Mesh), "comparative genomic hybridization," "chromosomal microarray analysis," "cytogenomic microarray analysis," "copy number analysis," "molecular karyotyping," and "single nucleotide polymorphisms." We included the best available evidence according to established evidence hierarchies (typically systematic reviews, meta-analyses, and full economic analyses, where available) and professional guidelines based on such evidence and clinical expertise.

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Policy updates

5/2013: initial review date and clinical policy effective date: 9/2013

9/2014: Policy references updated.

9/2015: Policy references updated.

9/2016: Policy references updated.

9/2017: Policy references updated.

9/2018: Policy references updated.

10/2019: Policy references updated. Policy ID changed to CCP.1024.

10/2020: Policy references updated.

10/2022: Policy references updated. Policy title and coverage modified.

10/2023: Policy references updated.