Corporate Medical Policy

Chromosomal Microarray AHS – M2033

File Name: chromosomal_microarray
Origination: 01/01/2019
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Next CAP Review: 03/2021
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Description of Procedure or Service

Description
Chromosomal microarray (CMA) testing refers to the use of comparative genomic hybridization (CGH) arrays to detect small (10 to 100kb) duplications or deletions of chromosomal DNA (copy number variants), similarity in single nucleotide sequences (homozygosity), and triploidy (Schrijver, Zehnder, & Cherry, 2019) when chromosomal abnormality is suspected based on clinical presentation.

***Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.

Policy

BCBSNC will provide coverage for chromosomal microarray testing when it is determined the medical criteria or reimbursement guidelines below are met.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When chromosomal microarray testing is covered

1. Reimbursement for genetic counseling is allowed and is recommended for individuals being considered for chromosomal microarray testing.
2. Chromosomal microarray testing of the products of conception such as fetal tissue and/or the fetus is considered medically necessary for the evaluation of any pregnancy loss.
3. Chromosomal microarray testing is considered medically necessary for prenatal use when any one of the following is met:
   A. Diagnostic testing for fetal aneuploidy is needed for women undergoing invasive prenatal testing (i.e. amniocentesis, chorionic villus sampling or fetal tissue sampling), OR
   B. Non-invasive prenatal screening (NIPS) results need to be confirmed, OR
   C. As a follow-up testing for any smaller copy-number changes that are reported as positive by NIPS, OR
   D. Ultrasound examination reveals one or more (≥) structural abnormalities, OR
   E. The fetus is at high risk for a chromosome abnormality, detectable by chromosomal microarray, due to family history or other indications as documented in the patient’s medical record, OR
F. There is intrauterine fetal demise or stillbirth in the third trimester, with an indication to determine the potential cause

4. Chromosomal microarray testing is considered medically necessary for the postnatal evaluation when one of the following is met:

A. Multiple congenital anomalies not specific to a well-delineated genetic condition and cannot be identified based on clinical evaluation alone, OR
B. Nonsyndromic developmental delay/intellectual delay, OR
C. Autism spectrum disorder
D. Sex determination by NIPS is discordant with physical examination, or clinical findings suggestive of a disorder of sexual differentiation

5. Maternal cell contamination analysis performed in parallel with fetal diagnostic testing is considered medically necessary.

When chromosomal microarray testing is not covered

Postnatal chromosomal microarray testing is considered not medically necessary when a chromosomal trisomy is suspected.

Chromosomal microarray testing that does not meet the above criteria is considered investigational except for microarray for neoplasia.

Policy Guidelines

Background

Chromosomal abnormalities are associated with a variety of disorders including developmental delay (DD), intellectual disability (ID), and congenital anomalies (D. T. Miller et al., 2010), as well as pregnancy loss (Reddy, Page, Saade, et al., 2012).

Chromosomal microarray (CMA) array testing to detect copy number variations, homozygosity, and triploidy has replaced karyotyping as the first-tier diagnostic tool for many cases where chromosomal abnormality is suspected (Lalani, 2017; D. T. Miller et al., 2010; Schrijver et al., 2019). CMA is significantly more sensitive (10 to 100kb) than traditional karyotyping (5 to 10 Mb). Additionally, CMA does not require cell culture, which reduces the turnaround time for results (D. Miller, 2017) and provides an alternative to karyotyping when dividing cells are not available for analysis.

CMA uses comparative genomic hybridization (CGH) to compare the DNA of a patient with a normal control using standard sets of DNA probes immobilized on a glass slide or glass beads (Aradhya & Cherry, 2007). CGH arrays have been designed to cover the entire genome, or for targeted analysis of known microdeletion/microduplication syndromes as well as known loci of inherited mutations (Schrijver et al., 2019). Array sensitivity varies based on the size and type of probes used. Oligonucleotide probes (~60 base pairs) or single nucleotide polymorphism (SNP) probes (32-40 base pairs) are most common. Oligonucleotide probes can be used to cover the entire genome at an average resolution of about 35 kb. Current arrays generally use a combination of copy number probes (oligonucleotide) to detect copy gains and losses and single nucleotide polymorphism (SNP) probes to detect similarity in single nucleotide sequences (homozygosity). The combination of probes detects runs of homozygosity between the maternal and paternal copy of each chromosome, enabling diagnosis of triploidy, uniparental disomy, consanguinity and improves detection of low levels of mosaicism (D. Miller, 2017).

Analytic Validity

Although chromosomal microarray testing can vary widely in technology, resolution, and the likelihood of producing results of unknown significance, studies have demonstrated that CMA provides chromosomal evaluation at a much higher resolution than karyotyping (D. T. Miller et al., 2010; Schrijver et al., 2019). Miller et al noted that most clinical CMA platforms available in 2010 could
detect copy number changes at a resolution of 400 kb; this was considered at least a “10-fold” improvement over G-banded karyotyping (D. T. Miller et al., 2010).

Clinical Validity and Utility
A review of 33 studies, comparing traditional karyotyping to CMA, has shown that CMA increases the detection rate for chromosomal abnormalities in individuals with DD/ID or autism spectrum disorder (ASD). CMA detected pathogenic genomic imbalances with an average diagnostic yield of 12.2% across all studies in this patient population, about 10% more than karyotyping alone (D. T. Miller et al., 2010).

Hillman et al performed both a meta-analysis and cohort study evaluating CMA’s detection rate of chromosomal abnormalities. The authors investigated 243 women who had both a CMA and karyotype performed, and the meta-analysis included 25 primary studies. Overall, CMA was found to detect 4.1% more abnormalities compared to karyotyping in the cohort study and 10% more in the meta-analysis (Hillman et al., 2013).

Reddy et al compared the detection rates of microarray and traditional karyotyping. 532 stillbirths were examined. The authors found that microarrays provided more results than karyotyping (87.4% compared to 70.5%) and identified more genetic abnormalities (8.3% vs 5.8%). Microarray analysis also found more genetic abnormalities among 443 antepartum stillbirths (8.8% vs 6.5%) and among 67 stillbirths with congenital abnormalities (29.9% vs 19.4%). Overall, microarray analysis provided a relative increase in the diagnosis of genetic abnormalities of 41.9% in all stillbirths, 34.5% in antepartum stillbirths, and 53.8% in stillbirths with anomalies compared to karyotyping (Reddy, Page, Saade, et al., 2012).

CMA, as all genetic tests, can have variable clinical sensitivity due to the numerous types of genetic abnormalities that can impact gene expression. Some genetic conditions are caused by a change in copy number and/or a sequence change in the gene that is undetectable by CMA. If a genetic condition in which a subset of cases are caused by sequence changes, then other testing should be considered either in place of, or in addition to, CMA (D. Miller, 2017).

Coulter et al assessed impact of CMA results on clinical decision making. A total of 1792 patients were examined, and 235 of them had either an “abnormal” result (n = 131) or a “variant of possible significance” (VPS) (n = 104). Clinical action was recommended for 54% of the patients in the “abnormal” cohort and 34% of the patients in the VPS cohort (Coulter et al., 2011).

Brady et al performed a prospective study of fetuses with abnormalities detected on ultrasound. 383 prenatal samples were examined. Causal imbalances were found in 37 samples, submicroscopic CNVs were found in 10 of the 37 samples, and arrays added “valuable information” over conventional karyotyping in 15 of 37 samples. The authors concluded that there was added value of chromosomal microarrays for prenatal diagnosis in the presence of ultrasound anomalies (Brady et al., 2013).

Borrell et al performed a meta-analysis of literature to estimate the incremental yield of CMA over karyotyping in fetal growth restriction (FGR). The authors identified 10 studies and found a 4% incremental yield of CMA over karyotyping in “nonmalformed growth-restricted fetuses” and a 10% incremental yield in FGR when associated with fetal malformations (Borrell, Grande, Pauta, Rodriguez-Revenga, & Figueras, 2017).

Robson et al compared karyotyping and CMA in fetuses with ultrasound anomalies. Out of 629 cases with structural anomalies, CMA detected copy number variants (CNVs) and more pathogenic CNVs than karyotyping. CMA was also found to have a turnaround time of five days quicker than karyotyping. Finally, CMA was found to be £113 more expensive per patient than karyotyping. The authors conclude, “CMA is a robust, acceptable and probably cost-effective method to detect more clinically significant chromosomal imbalances in the anomalous fetus. The results suggest that CMA should replace karyotyping in these care pathways (Robson et al., 2017).”
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Li et al performed a study investigating the cost effectiveness of karyotyping, CMA, and NGS in genetic diagnosis of unexplained global developmental delay. The authors found that: “CMA testing results in more genetic diagnoses at an incremental cost of US $2692 per additional diagnosis compared with karyotyping, which has an average cost per diagnosis of US $11,033 (Li, Anderson, Ginns, & Devlin, 2018).” The authors also found that performing both tests sequentially results in the same number of diagnoses but costs less when CMA testing is done first and karyotyping second. The authors also analyzed the cost-effectiveness of a variant of unknown significance. When CMA testing yields a variant of unknown significance, additional genetic diagnoses can be obtained “at an incremental cost of US $4220 by CMA testing of both parents, and when parents are not available or the patient had a normal CMA result, targeted NGS of the patient can add diagnoses at a further incremental cost of US $12,295.” The authors concluded that “These results provide a cost effectiveness rationale for the use of CMA as the first-tier test for the genetic diagnosis of unexplained GDD/ID and further indicate that testing of both parents may be cost effective when a variant of unknown significance is detected in the patient (Li et al., 2018).”

Applicable Federal Regulations
In 2014 the FDA approved CytoScan® Dx Assay as a “qualitative assay intended for the postnatal detection of copy number variations (CNV) in genomic DNA obtained from peripheral whole blood in patients referred for chromosomal testing based on clinical presentation. CytoScan® Dx Assay is intended for the detection of CNVs associated with developmental delay, intellectual disability, congenital anomalies, or dysmorphic features.”

In 2017 the FDA approved GenetiSure Dx Postnatal Assay as a “qualitative assay intended for the postnatal detection of copy number variations (CNV) and copy-neutral loss of heterozygosity (cnLOH) in genomic DNA obtained from peripheral whole blood in patients referred for chromosomal testing based on clinical presentation. GenetiSure Dx Postnatal Assay is intended for the detection of CNVs and cnLOH associated with developmental delay, intellectual disability, congenital anomalies, or dysmorphic features.”

Guidelines and Recommendations
The American College of Medical Genetics and Genomics (ACMG) recommend CMA testing “as a first-line test in the initial postnatal evaluation of individuals with the following (Manning & Hudgins, 2010):

A. “Multiple anomalies not specific to a well-delineated genetic syndrome.”

B. “Apparently nonsyndromic DD/ID.”

C. “Autism spectrum disorders.”

The ACMG also recommends “further determination of the use of CMA testing for the evaluation of the child with growth retardation, speech delay, and other less well-studied indications…, particularly by prospective studies and after-market analysis.” Additionally, ACMG recommends “appropriate follow-up … in cases of chromosome imbalance identified by CMA, to include cytogenetic/FISH studies of the patient, parental evaluation, and clinical genetic evaluation and counseling.”

A guidelines update from ACMG states that a stepwise or tiered approach to the clinical genetic diagnostic evaluation of autism spectrum disorder is recommended, with the recommendation being for first tier to include fragile X syndrome and chromosomal microarray analysis (CMA).

In 2016 the ACMG (Gregg et al., 2016) published guidelines on the use of noninvasive prenatal screening for the diagnosis of fetal aneuploidy which recommends:

• “Informing all pregnant women that NIPS is the most sensitive screening option for traditionally screened aneuploidies (i.e., Patau, Edwards, and Down syndromes).”

• “Allowing patients to select diagnostic or screening approaches for the detection of fetal aneuploidy and/or genomic changes that are consistent with their personal goals and preferences.”

• “Offering diagnostic testing (CVS or amniocentesis) with CMA when NIPS identifies a CNV”
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- “Offering diagnostic testing with CMA when a no-call result is obtained after NIPS due to possible UPD or parental consanguinity.”

In 2017 the ACMG (Cherry et al., 2017) published a laboratory practice resource outlining an algorithm for diagnostic cytogenetic testing following positive noninvasive prenatal screening results which recommends:

- “CMA testing on either CVS or amniotic fluid may be used as confirmatory diagnostic testing in cases with positive NIPS results, or as reflex testing in cases with initial normal results from chromosome analysis.”
- CMA is recommended as follow-up testing for any smaller copy-number changes that are reported as positive by NIPS.
- They also suggest that when “prenatal diagnostic testing may not be performed due to loss of the pregnancy before testing is possible. In such instances, testing of the products of conception and/or the fetus by either chromosome analysis or CMA should be considered on a case-by-case basis.”
- In newborns for whom the screen is suggestive of aneuploidy, but further testing is declined a genetics consultation with physical examination is sufficient for neonates, however, “if the neonate has an abnormal physical examination that is not suggestive of the trisomy in question, CMA is recommended.”
- CMA is also recommended when the sex determination by NIPS is discordant with physical examination, or clinical findings suggestive of a disorder of sexual differentiation.

The 2014 American Academy of Pediatric guidance for the comprehensive evaluation of children with intellectual disability or global developmental delays noted that “chromosome microarray is designated as a first-line test and replaces the standard karyotype and fluorescent in situ hybridization subtelomere tests for the child with intellectual disability of unknown etiology.” (Moeschler & Shevell, 2014). It further added that “CMA is now the standard for diagnosis of patients with GDD/ID, as well as other conditions, such as autism spectrum disorders or multiple congenital anomalies”.

The American Academy of Neurology published coverage policies for chromosomal microarray analysis for intellectual disabilities in 2015(Satya-Murti, 2017). The policy document notes the criteria do not represent a binding standard of care and that the criteria are proposed as clinical contexts that readily support the use of microarray testing. The authors note that chromosomal microarray analysis is reasonable and medically necessary for diagnosing a genetic abnormality when all of the following conditions are met(Satya-Murti, 2017):

- In children with developmental delay/intellectual disability (DD/ID) or an autism spectrum disorder (ASD) according to accepted Diagnostic and Statistical Manual of Mental Disorders-IV criteria;
- If warranted by the clinical situation, biochemical testing for metabolic diseases has been performed and is negative;
- Targeted genetic testing, (for example: FMR1 gene analysis for Fragile X), if or when indicated by the clinical and family history, is negative;
- The results for the testing have the potential to impact the clinical management of the patient;
- Face-to-face genetic counseling with an appropriately trained and experienced healthcare professional has been provided to the patient (or legal guardian(s) if a minor child). Patient or legal guardians have given their consent for testing. Cognitively competent adolescent patients have given their assent for testing as well.

The document notes the presence of major and minor congenital malformations and dysmorphic features should be considered evidence that microarray testing will be more likely to yield a diagnosis. However, dysmorphic and syndromic features are not required for testing(Satya-Murti, 2017).
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In 2013, the American College of Obstetricians and Gynecologists (ACOG) and Society for Maternal-Fetal Medicine (SMFM) recommended the following use of CMA for prenatal diagnosis:

A. “In patients with a fetus with one or more major structural abnormalities identified on ultrasonographic examination and who are undergoing invasive prenatal diagnosis, chromosomal microarray analysis is recommended. This test replaces the need for fetal karyotype.”

B. “In patients with a structurally normal fetus undergoing invasive prenatal diagnostic testing, either fetal karyotyping or a chromosomal microarray analysis can be performed.”

C. “Most genetic mutations identified by chromosomal microarray analysis are not associated with increasing maternal age; therefore, the use of this test for prenatal diagnosis should not be restricted to women aged 35 years and older.”

D. “In cases of intrauterine fetal demise or stillbirth when further cytogenetic analysis is desired, chromosomal microarray analysis on fetal tissue (ie, amniotic fluid, placenta, or products of conception) is recommended because of its increased likelihood of obtaining results and improved detection of causative abnormalities.”

ACOG and SMFM do not recommend use of CMA for evaluation of first- and second-trimester pregnancy loss due to limited clinical utility information. Additionally, they recommend pre- and post-test genetic counseling “from qualified personnel such as a genetic counselor or geneticist regarding the benefits.”

In 2016, ACOG (ACOG, 2016) and SMFM (Gregg et al., 2016) reaffirmed the above recommendations. In addition, the guidelines state “the routine use of whole-genome or whole-exome sequencing for prenatal diagnosis is not recommended outside the context of clinical trials until sufficient peer-reviewed data and validation studies are performed (ACOG, 2016).”

A 2018 study of these guidelines analyzed 3223 prenatal samples undergoing CMA. Cases were categorized into 2 groups: those that met ACOG guidelines for CMA versus those that met ACOG guidelines for either CMA or karyotype. They found that “in patients who could have elected either CMA or karyotype, 2.5% had clinically significant chromosomal abnormalities (CSCA) that would have been missed if the patient had elected to pursue karyotype (Hay et al., 2018).”

2012 American Society for Reproductive Medicine

In 2012, ASRM published a committee opinion on evaluation and treatment of recurrent pregnancy loss with clinical practice recommendations. ASRM recommended to proceed with the evaluation of recurrent pregnancy loss after two consecutive clinical pregnancy losses. This definition of recurrent pregnancy loss was reaffirmed in 2013. The recommended assessment of recurrent pregnancy loss included screening for genetic, hormonal and metabolic factors in addition to other factors. They have stated that “karyotypic analysis of products of conception may be useful in the setting of ongoing therapy for recurrent pregnancy loss.”

Society of Obstetricians and Gynaecologists of Canada (SOGC)-Canadian College of Medical Geneticists (CCMG) Joint Technical Update (2018)

The 2018 joint guideline (Armour et al., 2018) supersedes the 2011 iteration.

- “Offer of chromosomal microarray analysis (in addition to any other relevant diagnostic testing) is recommended in cases with multiple fetal anomalies identified by a comprehensive obstetric ultrasound (II-1A). Other diagnostic testing may include specific single gene, multigene panels or other genetic tests if the pattern of anomalies suggests a specific genetic condition not identified by array.”
- “Single structural defects in association with other abnormal ultrasound findings (eg, intrauterine growth restriction (IUGR), oligohydramnios) should not be considered isolated, and thus array should be offered if RAD is normal.”
- “In cases with a single fetal anomaly, prenatal CMA should be considered for those malformations associated with a high frequency of abnormal results. Its use in cases where the diagnostic yield is lower may be considered, if resources are available.”
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- “In fetuses with a nuchal translucency ≥3.5 mm, prenatal CMA should be offered.”
For “analysis of fetal loss prior to 20 weeks gestation”:
- “In cases of congenital anomalies and/or IUGR, in any fetal loss prior to 20 weeks gestation, if QF-PCR methodologies and/or other directed diagnostic inquiries do not provide a diagnosis and further cytogenetic analysis is intended, it is recommended that karyotype be replaced with chromosomal microarray analysis”.

For fetal deaths ≥20 weeks gestation:
- “Aneuploidy is the most common abnormal chromosomal finding in stillbirths. If RAD and/or other directed diagnostic inquiries are uninformative, it is recommended that in cases complicated by congenital anomalies and/or IUGR, karyotype be replaced with CMA when further cytogenetic analysis is desired.”
- “In stillbirths without structural fetal anomalies, CMA may be considered in the context of local resource availability and site-based postmortem protocol (whether complete, limited or external only)” (Armour et al., 2018).

**Billing/Coding/Physician Documentation Information**

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

*Applicable service codes: 81228, 81229, 81265, S3870, 96040, S0265*

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

**Scientific Background and Reference Sources**


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fetuses with ultrasound abnormalities and an exploration of a framework for reporting unclassified variants and risk factors. *Genetics in Medicine, 16*, 469-476. doi:10.1038/gim.2013.168


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**Policy Implementation/Update Information**

<table>
<thead>
<tr>
<th>Date</th>
<th>Update</th>
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<tbody>
<tr>
<td>1/1/19</td>
<td>New policy developed. BCBSNC will provide coverage for chromosomal microarray testing when it is determined to be medically necessary because the medical criteria and guidelines are met. Medical Director review 1/1/2019. Policy noticed 1/1/2019 for effective date 4/1/2019. (an)</td>
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<tr>
<td>9/10/19</td>
<td>Medical Director review 8/2019. Reviewed by Avalon 2nd Quarter 2019 CAB. References and policy guidelines updated. Coding table removed, added code 81265. For clarity, the term “Postnatal” was added to when not covered section so it now states that Postnatal chromosomal microarray testing. Maternal cell contamination (MCC) analysis performed in parallel with fetal</td>
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diagnostic testing is medically necessary (based on both AMP and ACMG guidelines). Added to when not covered section “except for microarray for neoplasia.” (eel)

10/29/19  Wording in the Policy, When Covered, and/or Not Covered section(s) changed from Medical Necessity to Reimbursement language, where needed. (gm)

3/31/20  Specialty Matched Consultant Advisory Panel 3/18/20. No change to policy statement. (eel)

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