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Corporate Medical Policy

Chromosomal Microarray AHS – M2033

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Description of Procedure or Service

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 or CNVs), similarity in single nucleotide sequences (homozygosity), and triploidy when chromosomal abnormality is suspected based on clinical presentation (Schrijver, Zehnder, & Cherry, 2019).

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

Chromosomal microarray (CMA) testing to detect copy number variations (CNVs), 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., 2010a; Schrijver et al., 2019). CMA is significantly more sensitive (10 to 100 kb) 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. This technique may be used for several different purposes, such as identifying a cause of pregnancy loss or identifying other aneuploid conditions, such as Down Syndrome (ACOG, 2016; Reddy, Page, & Saade, 2012).

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, for targeted analysis of known microdeletion/microduplication syndromes, and for 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 detect runs of homozygosity between the maternal and paternal copy of each chromosome, enabling diagnosis of triploidy, uniparental disomy, and consanguinity as well as improving the detection of low levels of mosaicism (D. Miller, 2017).

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).

Several commercial CMA tests are available including the GenomeDx CMA by GeneDx. The GenomeDx is able to confirm clinical diagnoses, differentiate between de novo and familial cases, and assist with prenatal diagnoses in at-risk pregnancies (GeneDx, 2018). This test has a three-week turnaround time and may utilize both blood (preferred) and buccal swabs (cheek swabs) as the tested specimen. The GenomeDx is a whole-genome CMA, containing 118,000 oligonucleotide probes that detect CNVs (GeneDx, 2018).

Quest Diagnostics has developed the ClariSure® Postnatal CMA Test; the ClariSure® consists of over 2.6 million probes that detect 1,900,000 CNVs and 750,000 SNPs (Quest, 2020). With a 10- to 15-day turnaround time, this test can help to determine the genetic cause of developmental delay or mental retardation. Blood is the preferred specimen for this test, but saliva may also be used.
LabCorp has developed Reveal®, an SNP microarray aimed for pediatric purposes. This test uses a blood or salivary sample to detect chromosomal abnormalities that may be associated with congenital anomalies or developmental delay (LabCorp, 2020). Results are provided in 14-17 days.

The FirstStep^{DX} PLUS®, developed by Lineagen (2019), is a CMA test that uses a buccal sample to identify developmental disabilities. Lineagen claims that cheek swabs are a more effective way to ensure accurate CMA results than blood-based samples, and that "mosaicism is better diagnosed through DNA collected by cheek swab than by blood draw" (Lineagen, 2019).

CMA and Seizures
A seizure occurs due to erroneous electrical activity in the brain and may strike for many reasons including a brain injury or infection, abnormal sodium or glucose levels in the blood, congenital brain defects, epilepsy, and electric shock.

Epilepsy is a neurological disorder associated with abnormal electrical brain activity. CMA is often the first genetic tool used to obtain more information about a patient's epilepsy (Poduri, Sheidley, Shostak, & Ottman, 2014) and has a diagnostic yield of approximately 8% with several studies reporting higher values (Dubbs, 2020). Testing a specific gene may be appropriate in some epileptic cases as more than 80 genes have been associated with epilepsy and hundreds more associated with disorders that are accompanied by seizures (Dubbs, 2020). However, if results are negative, CMA or gene testing should commence as this is likely more appropriate than testing several more genes individually (Mefford, 2015). If CMA testing is negative, gene panel and exome testing are appropriate.

Olson et al. (2014) have found that in many patients, CNVs identified through CMA were able to explain an epileptic phenotype. The authors concluded that "Because the diagnostic yield of CMA for epilepsy patients is similar to the yield in autism spectrum disorders and in prenatal diagnosis, for which published guidelines recommend testing with CMA, we recommend the implementation of CMA in the evaluation of unexplained epilepsy (Olson et al., 2014)."

CMA and Short Stature
Short stature is a general term used to describe individuals whose height is two standard deviations or more below the mean compared to peers of the same age and racial-ethnic group (Richmond & Rogol, 2020). The most common causes of short stature are genetic and delayed growth; these are considered normal or nonpathologic variants of growth (Richmond & Rogol, 2020).

Intrauterine growth restriction (IUGR) is a condition which describes when an unborn baby is growing abnormally slow in the womb; this could be due to either genetic or environmental factors and may cause significant morbidity and mortality in infants (Mandy, 2019). CMA has been used for diagnostic purposes in fetuses due to IUGR (Daum et al., 2019).

Idiopathic short stature (ISS) describes individuals whose height falls below two standard deviations of the mean for age, but no metabolic, endocrine, or other diagnosis has been identified to cause the height disorder (Richmond & Rogol, 2020). Regarding the genetic evaluation of short stature, some researchers suggest that for patients with ISS, patients born small for gestational age, or patients with growth hormone deficiency, "Targeted evaluation of a single gene or panels of genes is recommended... For

those patients who do not fit into a distinct subgroup or for whom initial genetic testing is inconclusive, we recommend consideration of genome-wide evaluation through exome sequencing and chromosomal microarray to detect both sequence variants and CNVs (Dauber, Rosenfeld, & Hirschhorn, 2014)." A significant association has been identified between CNVs and short stature (Yu et al., 2015), and many report that CMA is a promising tool to identify pathogenic CNVs in patients with ISS (Richmond & Rogol, 2020).

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., 2010a; Schrijver et al., 2019). D. T. Miller et al. (2010a) 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.

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 (developmental disability/intellectual disability) 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, which is about 10% more than karyotyping alone (D. T. Miller et al., 2010a).

Hillman et al. (2013) 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, Page, Saade, et al. (2012) compared the detection rates of microarray and traditional karyotyping. A total of 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).

Coulter et al. (2011) 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. (2013) performed a prospective study of fetuses with abnormalities detected on ultrasound. A total of 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, Grande, Pauta, Rodriguez-Revenga, and Figueras (2017) 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 et al., 2017).

Robson et al. (2017) 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)."

Li, Anderson, Ginns, and Devlin (2018) 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 et al., 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 [global developmental delay/intellectual disability] 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)."

Hydrops fetalis occurs when fluid accumulates in fetal serous cavities and soft tissues; nonimmune hydrops fetalis (NIHF) develops when red cell alloimmunization does not cause the hydrops fetalis case in question. A retrospective study of all prenatally diagnosed NIHF cases identified at the University of California, San Francisco from 2008 to 2018 were analyzed . A total of 131 cases were identified. The researchers found that "In 43/44 cases with a CMA performed, results were categorized as normal or likely benign. One case was found on CMA to have a large pathogenic duplication (Mardy et al., 2020)." This shows that CMA is not an effective diagnostic tool for NIHF.

Another study aimed to assess the diagnostic capabilities of CMA among pregnancies terminated due to fetal malformations identified with ultrasounds. CMA was performed on 71 pregnancies using fetal DNA or placental DNA. The authors noted that "Findings were abnormal in 17 cases (23.9%), of which 13 were detectable by karyotype. The incremental yield of CMA was 4/71 (5.6%); 1/32 (3.1%) for cases with an isolated anomaly and 3/39 (7.7%) for cases with nonisolated anomalies (Pasternak et al., 2020)." CMA identified more chromosomal abnormalities than karyotype and did not require dividing cells, making it a more practical option after termination.

Regulatory

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" (FDA, 2014).

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" (FDA, 2017).

Additionally, many labs have developed specific tests that they must validate and perform in house. These laboratory-developed tests (LDTs) are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA '88). As an LDT, the U. S. Food and Drug Administration has not approved or cleared this test; however, FDA clearance or approval is not currently required for clinical use.

******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, OR
    D. Sex determination by NIPS is discordant with physical examination, or clinical findings suggestive of a disorder of sexual differentiation, OR
    E. Proportionate short stature with other physical or structure defects.

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.

Low-pass whole genome sequencing (low-pass WGS) is considered investigational.

Note: For whole exon array testing, please see policy AHS – M2145 – General Genetic Testing, Germline Disorders.

Policy Guidelines

Guidelines and Recommendations

American College of Medical Genetics and Genomics (ACMG) (Cherry et al., 2017; Gregg et al., 2016; Manning & Hudgins, 2010; Seaver & Irons, 2009; Waggoner et al., 2018)

The 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 (Manning & Hudgins, 2010)."

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"
- "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 2008 ACMG *Standards and Guidelines for Clinical Genetics Laboratories* state, "The contamination of both direct and cultured cells from AF and CVS with maternal cells is well documented and therefore represents a potential source of error in prenatal diagnosis. Prenatal samples should be examined in parallel with a maternal sample to rule out error due to maternal cell contamination (MCC). Laboratories should understand how their testing methods are affected by the presence and the amount of MCC (ACMG, 2008)."

In 2018, the ACMG published a clinical practice report on genetic testing after CMA for the diagnosis of neurodevelopmental disability and congenital anomalies. These guidelines state that "Chromosomal microarray (CMA) is recommended as the first tier test in evaluation of individuals with neurodevelopmental disability and congenital anomalies. CMA may not detect balanced cytogenomic abnormalities or uniparental disomy (UPD), and deletion/duplications and regions of homozygosity may require additional testing to clarify the mechanism and inform accurate counseling (Waggoner et al., 2018)."

In 2009, the ACMG published guidelines on the genetic evaluation of short stature. These guidelines provide recommendations for genes associated with short stature and intrauterine growth restriction (IUGR) and state that high resolution chromosome analysis and/or array CGH can be used to evaluate IUGR (Seaver & Irons, 2009).

American Academy of Pediatrics (AAP) (Dubbs, 2020; Lipkin & Macias, 2020; Moeschler & Shevell, 2014)

The 2014 AAP 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."

Another clinical report published by the AAP on the identification of infants and young children with developmental disorders states that "The child with suspected global developmental delay or intellectual disability should have laboratory testing done, including chromosomal microarray and fragile X testing (Lipkin & Macias, 2020)." Further, the authors also note that "The initial genetic workup of the child with suspected ASD is evolving; current recommendations also include chromosomal microarray and fragile X testing (Lipkin & Macias, 2020)."

The AAP has an epilepsy webpage overview and states that "The genetic tests most commonly utilized in the evaluation of children with epilepsy include chromosomal microarray (CMA), epilepsy gene panels, and whole-exome sequencing (WES). Each test has its own specific benefits and limitations, and the diagnostic yield is variable. Currently, no specific guidelines exist to establish standards of practice for genetic testing in individuals with epilepsy and decisions regarding testing may be influenced by factors including clinical indication, turn-around time, insurance coverage, and cost. Although traditional practice often implements a stepwise approach consisting of chromosomal microarray, followed by epilepsy panel, followed by whole-exome sequencing,67 recent studies have suggested that this may not be the most-cost-effective approach (Dubbs, 2020)."

American Academy of Neurology (AAN) (Satya-Murti, 2015)

The AAN published coverage policies for chromosomal microarray analysis for intellectual disabilities in 2015 (Satya-Murti, 2015). 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, 2015):

- 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;
  AND
- 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, 2015).

American College of Obstetricians and Gynecologists (ACOG) and Society for Maternal-Fetal Medicine (SMFM) (ACOG, 2016; Gregg et al., 2016; Hay et al., 2018)

Originally published 2013 reaffirmed in 2016, the ACOG (ACOG, 2016) and SMFM (Gregg et al., 2016) issued joint guidelines recommending 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 (ACOG, 2016; Gregg et al., 2016)."

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)."

American Society for Reproductive Medicine (ASRM) (ASRM, 2012)

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 (ASRM, 2012)."

EUROPEAN SOCIETY OF HUMAN REPRODUCTION AND EMBRYOLOGY (ESHRE) (BENDER ATIK ET AL., 2018)

The ESHRE published guidelines on recurrent pregnancy loss and state that "For genetic analysis of the pregnancy tissue, array-based comparative genomic hybridization (array-CGH) is recommended based on a reduced maternal contamination effect (Bender Atik et al., 2018)."

Society of Obstetricians and Gynaecologists of Canada (SOGC)-Canadian College of Medical Geneticists (CCMG) Joint Technical Update (2018) (Armour et al., 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."
- "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).

Association for Molecular Pathology (AMP) (Nagan, Faulkner, Curtis, & Schrijver, 2011)

The MCC [maternal cell contamination] Guidelines Working Group of the AMP Clinical Practice Committee issued laboratory guidelines for detecting MCC in 2011. They state, "To determine the pure fetal origin of all prenatal specimens undergoing genetic analysis, it is recommended that MCC analysis be performed in parallel with diagnostic testing, regardless of the genetic disorder or its mode of inheritance (Nagan et al., 2011)."

Society for Maternal-Fetal Medicine (SMFM) (Fox, Monteagudo, Kuller, Craigo, & Norton, 2018)

The SMFM recommends chromosomal microarray for evaluation of mild fetal ventriculomegaly and nonimmune hydrops fetalis (Fox et al., 2018; Norton, Chauhan, & Dashe, 2015).

International Standard Cytogenomic Array (ISCA) Consortium (D. T. Miller et al., 2010a)

The ISCA (an international group of experts in the field) assembled to "address mutual concerns about standardization and collaboration for clinical CMA testing" (D. T. Miller et al., 2010b). After much research, the ISCA has stated that "Our recommendation based on current evidence is to offer CMA as the first-tier genetic test, in place of G-banded karyotype, for patients with unexplained DD/ID, ASD, or MCA [multiple congenital anomalies] (D. T. Miller et al., 2010b)."

International Society for Prenatal Diagnosis (ISPD), the Society for Maternal Fetal Medicine (SMFM), and the Perinatal Quality Foundation (PQF) (IPSD, 2018)

Joint guidelines on the use of genome-wide sequencing for fetal dianosis were published by the ISPD, SMFM and PQF. However, these guidelines also mention CMA quite frequently because "The use of diagnostic sequencing is currently being introduced for evaluation of fetuses for whom standard diagnostic genetic testing, such as chromosomal microarray analysis (CMA), has already been performed and is uninformative or is offered concurrently according to accepted practice guidelines, or for whom expert genetic opinion determines that standard genetic testing is less optimal than sequencing for the presenting fetal phenotype (IPSD, 2018)."

Fetal sequencing is recommended in several scenarios, including the following which also mention CMA:

- "A current pregnancy with a fetus with a single major anomaly or with multiple organ system anomalies that are suggestive of a possible genetic etiology, but no genetic diagnosis was found after CMA; or in select situations with no CMA result, following a multidisciplinary review and consensus, in which there is a fetus with a multiple anomaly 'pattern' that strongly suggests a single gene disorder.
- A personal (maternal or paternal) history of a prior undiagnosed fetus (or child) affected with a major single anomaly or multiple anomalies suggestive of a genetic etiology, and a recurrence of similar anomalies in the current pregnancy without a genetic diagnosis after karyotype or CMA
- In families with a history of recurrent stillbirths of unknown etiology after karyotype and/or CMA, where the fetus in the current pregnancy has a recurrent pattern of anomalies (IPSD, 2018)."

These recommendations show that CMA should be used as an initial strategy (before fetal sequencing) to determine the genetic causation during pregnancy of the aforementioned cases.

Autism Consortium Clinical Genetics/DNA Diagnostics Collaboration (Shen et al., 2010)

These guidelines focus on clinical genetic testing for patiets with autism spectrum disorders (ASDs). The authors note that "CMA had the highest detection rate among clinically available genetic tests for patients with ASD. Interpretation of microarray data is complicated by the presence of both novel and recurrent copy-number variants of unknown significance. Despite these limitations, CMA should be

considered as part of the initial diagnostic evaluation of patients with ASD (Shen et al., 2010).” Further, the guidelines later state that “our results suggest that CMA with whole genome coverage should be adopted as a national standard of care for genetic testing among patients with ASDs (Shen et al., 2010).”

Endocrine Society (ES) (Cohen et al., 2008)

The Endocrine Society published guidelines on the diagnosis and treatment of children with idiopathic short stature (ISS) in 2008. These guidelines state that “In situations where a specific genetic diagnosis associated with short stature is expected (such as Noonan syndrome or GH insensitivity syndrome), the genes of interest should be examined (Cohen et al., 2008).” These guidelines do not mention CMA.

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, 81479, 96040, 0209U, S0265, S3870

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.

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Specialty Matched Consultant Advisory Panel 3/2020

Policy Implementation/Update Information

1/1/19 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)

9/10/19 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 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)

7/28/20 Medical Director review 7/2020. Reviewed by Avalon 2nd Quarter CAB. Coding section updated with 81479. When Not Covered section clarified with low-pass investigational statement. Description, Policy Guidelines and Resources sections updated. When Covered section updated with item 4→E. No change to policy statement. (eel)

10/1/20 Coding section updated with new code 0209U effective 10/1/20. (eel)