Chromosomal Microarray (CMA)/Comparative Genomic Hybridization (CGH) Testing for Developmental Delay and Fetal Demise

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Disclaimer:
1. Policies are subject to change without notice.
2. Policies outline coverage determinations for U of U Health Plans Commercial, and Healthy U (Medicaid) plans. Refer to the “Policy” section for more information.

Description:
Chromosomal microarray analysis (CMA) includes both CGH (comparative genomic hybridization) and SNP (single nucleotide polymorphism) arrays. CGH microarray testing, also known as array comparative genomic hybridization (aCGH) 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 (deoxyribonucleic acid). 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. 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. One of the main advantages of CGH/CMA is its use as a discovery tool, as it requires no prior knowledge of the chromosome imbalance that is involved.

Chromosomal microarray (CMA) testing for detection of genetic imbalances in infants or children with characteristics of global developmental delay (GDD), autism spectrum disorder (ASD), and/or congenital anomalies has increased the diagnostic yield over karyotyping in this population and may impact clinical management decisions. Next-generation sequencing (NGS) panel testing allows for simultaneous analysis of a large number of genes and has been suggested as a way to identify single-gene causes of syndromes that have autism as a significant clinical feature.

CMA testing of fetal tissue or placental tissue derived from the fetal genotype is another recommended technique to evaluate the cause of isolated and recurrent early pregnancy loss (miscarriages) and later pregnancy loss (intrauterine fetal demise [IUFD]). The evaluation of both recurrent and isolated miscarriages and IUFD may involve genetic testing of the products of conception. Such testing has typically been carried out through cell culture and karyotyping of cells in metaphase. However, this technique is limited by the need for fresh tissue, the potential for cell culture failure, and the potential for maternal cell contamination, limitations which may be addressed with CMA.

**Policy Statement and Criteria**

**1. Commercial Plans**

_U of U Health Plans covers genetic testing for clinical conditions presenting as developmental delay using Comparative Genomic Hybridization (CGH)/Chromosomal Microarray (CMA) testing in certain circumstances when the following criteria are met:_

A. The patient presents with a clinical diagnosis of developmental delay;

B. Thorough history and physical has failed to establish a definitive diagnosis other than developmental delay;

C. Chromosome analysis has failed to provide a definitive diagnose in patients presenting with dysmorphic features suggestive of specific chromosome abnormality (e.g. Down syndrome, Prader Willi syndrome);

D. Results of testing have been identified in a specific and meaningful manner to impact patient management.

_U of U Health Plans covers evaluation of pregnancy loss in patients with indications for genetic analysis of the embryo or fetal tissue* using Comparative Genomic Hybridization (CGH)/Chromosomal Microarray testing in certain circumstances when the following criteria are met:_

*Note: The criteria for genetic analysis of the embryo or fetal tissue during pregnancy loss may vary and should be discussed with a genetic counselor or healthcare provider.*
A. Pregnancy loss at less than or equal to 20 weeks of gestation when there is a maternal history of recurrent pregnancy loss, defined as having two or more consecutive clinical pregnancy losses; OR

B. All cases of pregnancy loss after 20 weeks of gestation.

*Fetal tissue may consist of: fetal tissue, a formed fetus, or placental tissue derived from the fetus, depending on the stage of pregnancy at the time of the fetal loss.

U of U Health Plans does NOT cover genetic testing using Comparative Genomic Hybridization (CGH)/Chromosomal Microarray technique for any other indication as it is considered investigational/experimental.

2. Medicaid Plans
Coverage is determined by the State of Utah Medicaid program; if Utah State Medicaid has no published coverage position and InterQual criteria are not available, the U of U Health Plans Commercial criteria will apply. For the most up-to-date Medicaid policies and coverage, please visit their website at http://health.utah.gov/medicaid/manuals/directory.php or the Utah Medicaid code Look-Up tool

Clinical Rationale
Children with signs of neurodevelopmental delays or disorders in the first few years of life may eventually be diagnosed with intellectual disability or autism syndromes, which are serious and lifelong conditions that present significant challenges to families and public health.

Intellectual disability (ID) is a lifelong disability diagnosed at or after 5 years of age when IQ testing is considered valid and reliable. The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V), of the American Psychiatric Association defined patients with ID as having onset during the developmental period, diagnoses based on the severity of deficits in general mental abilities that impact adaptive functioning in 3 areas or domains; Conceptual, Social, and Practical. The diagnosis of Global Developmental Delay (GDD) is reserved for children younger than 5 years of age when the clinical severity level cannot be reliably assessed during early childhood. GDD is diagnosed when an individual fails to meet expected developmental milestones in several areas of intellectual functioning and applies to individuals who are unable to undergo systematic assessments of intellectual functioning, including children who are too young to participate in standardized testing.

Developmental Delay
In 2011 the National Institute for Health and Care Excellence (NICE) set a clinical guideline for the recognition, referral and diagnosis of children and young people with autism. The guideline recommends that genetic tests only be done in patients who have either dysmorphic features and/or intellectual disability because these are the cases where the rate of genetic abnormalities are definitely increased above general population levels. According to the guideline, most research to date has focused on the rate and type of definite abnormalities rather than the impact of testing on children/young people with autism and their families. The authors of the guideline state that further research using CGH array would
lead to a stronger evidence base to inform key decision-makers as to whether wider use of genetic testing is appropriate or not when this guideline is updated. It would also alert practitioners to any negative consequences that might occur as a result of testing.

A 2014 cohort study (Bartnik et al) evaluated the application of array Comparative Genomic Hybridization (CGH) in clinical diagnostics of developmental delay/intellectual disability in 112 children. 37 copy number variants (CNVs) were identified with the size ranging from 40 kb to numerical chromosomal aberrations, including unbalanced translocations and chromosome Y disomy, receiving an overall diagnostic yield of 33%. Known pathogenic changes were identified in 21.4% of the cases. Among patients with pathogenic CNVs identified by array CGH, 41.7% had a previously normal karyotype analysis. This study provides more insight into the benefits derived by using chromosomal microarray analysis and demonstrates the usefulness of array CGH as a first-tier clinical setting test in patients with intellectual disability.

Another 2014 study (Nicholl et al), evaluated the frequency of pathogenic chromosomal microdeletions and microduplications in a large group of referred patients with developmental delay (DD), intellectual disability (ID) or autism spectrum disorders (ASD) within a genetic diagnostic service. First tier testing was applied using a standardized oligo-array comparative genomic hybridization (CGH) platform, replacing conventional cytogenetic testing that would have been used in the past. Copy number variants (CNVs) found to be responsible for the clinical condition on the request form could all be subdivided into 3 groups: well established pathogenic microdeletion/microduplication/aneuploidy syndromes, predicted pathogenic CNVs as interpreted by the laboratory, and recently established pathogenic disease susceptibility CNVs. Totaled from these three groups, with CNVs of uncertain significance excluded, detection rates were: DD (13.0%), ID (15.6%), ASD (2.3%), ASD with DD (8.2%), ASD with ID (12.7%) and unexplained epilepsy with DD, ID and ASD (10.9%). According to the authors, the greater diagnostic sensitivity arising from routine application of array CGH, compared with previously used conventional cytogenetics, outweighs the interpretative issues for the reporting laboratory and referring clinician arising from detection of CNVs of uncertain significance.

In a model coverage policy for chromosomal microarray analysis for intellectual disabilities, the American Academy of Neurology (AAN) in 2015 recommended the following inclusion criteria for microarray testing:

1. 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-V (DSM-V) criteria;
2. If warranted by the clinical situation, biochemical testing for metabolic diseases has been performed and is negative;
3. Targeted genetic testing, (for example: FMR1 gene analysis for Fragile X), if or when indicated by the clinical and family history, is negative;
4. The results for the testing have the potential to impact the clinical management of the patient;
5. 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 AAN also states that the following four circumstances limit the value of microarray testing:

1. Absence of an appropriate and informed consent from the patient, a parent (in case of minors) or a guardian (in persons with cognitive impairment) is necessary prior to testing.
2. Inadequacy of knowledge about the test and the actions required to address the results of the test.

3. A lack of clear value for chromosomal microarray analysis in all instances other than those delineated above. Under these circumstances the test is considered investigational.

4. Chromosomal microarray analysis would not be considered medically necessary when a diagnosis of a disorder or syndrome is readily apparent based on clinical evaluation alone. 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.

In a 2015 systematic review and meta-analysis (Grande et al), which included 17 studies that met criteria for analysis, approximated the incremental yield of detecting copy number variants (CNVs) by genomic microarray over karyotyping in fetuses with increased nuchal translucency (NT) diagnosed by first trimester ultrasound. Meta-analysis indicated an incremental yield of 5.0% for the detection of CNVs using microarray when pooling results. Stratified analysis of microarray results demonstrated a 4.0% incremental yield in cases of isolated NT and 7.0% when other malformations were present. The pooled prevalence for variants of uncertain significance was 1%. The authors concluded that the use of genomic microarray provides a 5.0% incremental yield of detecting CNVs in fetuses with increased NT and normal karyotype.

Another 2015 systematic review (Papoulidis et al) studied the diagnostic yield of comparative genomic hybridization microarrays (aCGH) and compare it with conventional karyotype analysis of standard >5-Mb resolution. A total of 1763 prenatal samples were analyzed by aCGH (CytoChip Focus Constitutional microarrays, BlueGnome, Cambridge). The diagnostic yield of chromosomal abnormalities detected by aCGH was assessed, compared with conventional karyotype analysis. The result was pathogenic/unknown penetrance in 125 cases (7.1%), and a variant of unknown significance (VOUS) was detected in 13 cases (0.7%). Out of the 125 cases with abnormal findings, 110 were also detected by conventional karyotype analysis. The aCGH increment in diagnostic yield was 0.9% (15/1763) and 1.6% when VOUS were included. Stratifying the sample according to indications for prenatal invasive testing, the highest values of diagnostic yield increment were observed for patients positive for second-trimester sonographic markers (1.5%) and for the presence of fetal structural anomalies (1.3%). In contrast, the incremental yield was marginal in patients with fetus with increased nuchal translucency (0.5%). In conclusion, routine implementation of aCGH offers an incremental yield over conventional karyotype analysis, which is also present in cases with 'milder' indications, further supporting its use as a first-tier test.

A 2016 controlled study (Ho et al) analyzed a series of 5487 patients during a 3 and a half year period, on the clinical performance of an ultrahigh resolution chromosomal microarray optimized for neurodevelopmental disorders, including developmental delay (DD), intellectual disability (ID), and autism spectrum disorder (ASD). A subset of 225 patients was comprised of adults over 18 years old, which were analyzed separately from the pediatric patients. In patients where the indication for testing was either ID (n=119) or multiple congenital anomalies (MCA) (n=35), the rate of pathogenic CNVs in adult patients tested were the highest of any age group, similar at levels similar to the first year of life: (16.8% and 20.0%, resp.). The authors note that this could be due to the relatively small size of this cohort, or alternatively, it may be more reflective of severity in that particular age group. The VUS rate in adults with ID was higher than any other age group analyzed (21.8%), but lower in adults with MCG (14.8%).
A 2016 randomized controlled trial (Lingen, et al), described the effect on parental quality of life of a diagnostic aCGH result in a child with unexplained DD/ID, with or without multiple congenital anomalies. The trial included parents and children evaluated at an interdisciplinary pediatric clinic. A validated metric constructed for the assessment of quality of life in parents of chronically ill children was obtained for parents of 65 children with no chromosomal imbalance detected on aCGH and for 34 children with a clear genetic diagnosis on aCGH. The interval between aCGH result and questionnaire ranged from 1 to 4 years. Quality of life scores were 20.17 percentile rank scales higher in mothers of children with diagnostic vs inconclusive aCGH results (effect size, 0.71). Interpretation of these results is limited by the retrospective nature of the study and the potential for response bias.

A 2016 study (Pfundt et al) evaluated the diagnostic yield and potential clinical utility of a high-density CMA of CytoScan Dx Assay in 960 patients with developmental delay or intellectual disability. Eighty-six percent of the subjects were assessed using a microarray as part of historical routine patient care (RPC). The rate of pathogenic findings was similar between RPC (13.3%) and the CytoScan Dx Assay (13.8%). Among the 138 patients who did not receive microarray as RPC, the diagnostic yield for CytoScan Dx Assay was 23.9% as compared with 14.5%, indicating a 9.4% improvement when using higher-resolution methods. Thirty-five percent of patients with abnormal findings had predicted clinical management implications that may improve health outcomes. In conclusion, the assay's diagnostic yields are similar to those found in other studies of CMAs.

Another study in 2016 (Fry et al) reported the range of rare Copy number variants (CNVs) found in 80 Welsh patients with intellectual disability (ID) or developmental delay (DD), and childhood-onset epilepsy. Molecular cytogenetic testing by single nucleotide polymorphism array or microarray-based comparative genome hybridization was performed. 8.8 % (7/80) of the patients had at least one rare CNVs that was considered to be pathogenic or likely pathogenic. The CNVs involved known disease genes (EHMT1, MBD5 and SCN1A) and imbalances in genomic regions associated with neurodevelopmental disorders (16p11.2, 16p13.11 and 2q13). Prompted by the observation of two deletions disrupting SCN1A the authors undertook further testing of this gene in selected patients. This led to the identification of four pathogenic SCN1A mutations in the cohort. Five rare de novo deletions were identified, and the authors confirmed the clinical utility of array analysis in patients with ID/DD and childhood-onset epilepsy.

CMA may also reveal a number of polymorphisms that are unrelated to the patient’s phenotype, but which must be considered nonetheless. From the current medical literature it appears array CGH and CMA have the ability to enhance diagnostic accuracy and expedite the testing process.

**Prenatal Testing for Fetal Demise**

The American College of Obstetricians and Gynecologists (ACOG) described comparative genomic hybridization (CGH) as an evolving method that identifies submicroscopic chromosomal deletions and duplications in a 2007 Practice Bulletin on invasive prenatal testing for aneuploidy. According to ACOG, Prenatal diagnosis of fetal chromosomal abnormalities is the most common indication for invasive prenatal testing. The prevalence of chromosomal abnormalities in clinically recognized early pregnancy loss is greater than 50%. Fetuses with aneuploidy account for 6-11% of all still births and neonatal deaths. Chromosomal abnormalities that are compatible with life but cause considerable morbidity occur in 0.65% of newborns, and structural chromosomal rearrangements that will eventually affect reproduction occur in 0.2% of newborns. The use of CGH in prenatal diagnosis, at present, is limited because of the difficulty in interpreting which DNA alterations revealed through CGH may be normal population variants. ACOG states that until there are more data available, use of CGH for routine prenatal diagnosis is not recommended.
A 2014 study (Mathur et al), assessed 58 women with 77 miscarriage specimens who were evaluated at a single recurrent pregnancy loss clinic for CMA testing results in preserved POC samples. All women had a history of recurrent pregnancy loss, defined as two or more ultrasound-documented miscarriages at less than 10 weeks of gestation. Samples were evaluated with CGH; if results were 46 XX, the genotype of the POC was compared with the maternal genotype at several highly polymorphic loci through microsatellite analysis (MSA) to determine if the 46 XX results were consistent with maternal cell contamination. Sixteen samples (21%) yielded uninformative results due to minimal pregnancy tissue (n=9), poor quality DNA (n=2), or confirmed maternal cell contamination (n=2). CGH was considered informative in 61 cases (79%), with 22 non-euploid and 39 euploid. Thirty-three of the euploid specimens were 46 XX, 11 of which were not sent for reflex MSA. The study concluded that CMA testing of preserved POC is technically feasible, including in cases where karyotyping had failed due to cell growth failure, which had occurred in eight samples evaluated.

A 2015 systematic review (Dahdouh et al) conducted randomized controlled trials on preimplantation genetic screening (PGS) using comprehensive chromosome screening (CCS) after blastocyst biopsy. Three trials met full inclusion criteria, comparing PGS using comprehensive chromosome screening after blastocyst biopsy and routine in vitro fertilization (IVF) care. PGS using comprehensive chromosome screening after blastocyst biopsy is associated with higher clinical implantation rates and higher ongoing pregnancy rates when the same number of embryos is transferred in both PGS and control groups. Additionally, PGS using comprehensive chromosome screening after blastocyst biopsy improves embryo selection in eSET practice, maintaining the same ongoing pregnancy rates between PGS and control groups, while sharply decreasing multiple pregnancy rates. These results stem from good prognosis patients undergoing IVF. Whether these findings can be extrapolated to poor-prognosis patients with decreased ovarian reserve remains to be determined. This systematic review combined data from the only three available RCTs. The first RCT was derived from a pilot study, and the two others were carried out in the same IVF unit having extensive experience with blastocyst culture and biopsy, and with the performance of CCS analysis with a highly validated in-house genetic platform. Additional results from well-conducted RCTs with larger sample sizes are encouraged.

A 2015 study (Rosenfeld et al) evaluated the frequency of clinically significant chromosomal abnormalities identified by CMA and compare its performance with that of traditional cytogenetic analysis in pregnancy losses at any gestational age. Among 535 fetal demise specimens of any gestational age, clinical microarray-based comparative genomic hybridization (aCGH) was performed successfully on 515, and a subset of 107 specimens underwent additional single nucleotide polymorphism (SNP) analysis. Overall, clinically significant abnormalities were identified in 12.8% (64/499) of specimens referred with normal or unknown karyotypes. Detection rates were significantly higher with earlier gestational age. In the subset with normal karyotype, clinically significant abnormalities were identified in 6.9% (20/288). This detection rate did not vary significantly with gestational age, suggesting that, unlike aneuploidy, the contribution of submicroscopic chromosomal abnormalities to fetal demise does not vary with gestational age. In the 107 specimens that underwent aCGH and SNP analysis, seven cases (6.5%) had abnormalities of potential clinical significance detected by the SNP component, including female triploidy. aCGH failed to yield fetal results in 8.3%, which is an improvement over traditional cytogenetic analysis of fetal demise specimens.

ACOG and the Society for Maternal Fetal Medicine (SMFM) published a Practice Bulletin in 2016 on prenatal diagnostic testing for genetic disorders, based on good and consistent scientific evidence, they recommend that “Chromosome microarray analysis should be made available to any patient choosing to undergo invasive diagnostic testing” and “Chromosome microarray analysis should be the primary test (replacing conventional karyotype) for patients undergoing prenatal diagnosis for the indication of a
fetal structural abnormality detected by ultrasound.” Another recommendation, “Chromosomal microarray analysis can be used to confirm an abnormal FISH test.” However, this recommendation is based on limited or inconsistent scientific evidence.

In a 2016 Joint Committee Opinion on Microarrays and Next-Generation Sequencing Technology, ACOG and SMFM concluded that "for the use of chromosomal microarray analysis and newer genetic technologies in prenatal diagnosis, most genetic changes identified by chromosomal microarray analysis that typically are not identified on standard karyotype are not associated with increasing maternal age; therefore, the use of this test can be considered for all women, regardless of age, who undergo prenatal diagnostic testing. Prenatal chromosomal microarray analysis is recommended for a patient with a fetus with one or more major structural abnormalities identified on ultrasonographic examination and who is undergoing invasive prenatal diagnosis. This test typically can replace the need for fetal karyotype. In a patient with a structurally normal fetus who is undergoing invasive prenatal diagnostic testing, either fetal karyotyping or a chromosomal microarray analysis can be performed. Chromosomal microarray analysis of fetal tissue (i.e., amniotic fluid, placenta, or products of conception) is recommended in the evaluation of intrauterine fetal death or stillbirth when further cytogenetic analysis is desired because of the test’s increased likelihood of obtaining results and improved detection of causative abnormalities. Also that comprehensive patient pretest and posttest genetic counseling from an obstetrician–gynecologist or other health care provider with genetics expertise regarding the benefits, limitations, and results of chromosomal microarray analysis is essential. Chromosomal microarray analysis should not be ordered without informed consent, which should include discussion of the potential to identify findings of uncertain significance, non-paternity, consanguinity, and adult-onset disease."

The following recommendations were made by a SMFM Consult Series publication in 2016 on the use of chromosomal microarray for prenatal diagnosis. First, chromosomal microarray analysis (CMA) should be offered when genetic analysis is performed in cases with fetal structural anomalies and/or stillbirth and replaces the need for fetal karyotype in these cases; Second, providers should discuss the benefits and limitations of CMA and conventional karyotype with patients who are considering amniocentesis and chorionic villus sampling (CVS) and that both options be available to women who choose to undergo diagnostic testing; Third the use of CMA is not recommended as a first-line test to evaluate first trimester pregnancy losses due to limited data; and finally Pre- and post-test counseling should be performed by trained genetic counselors, geneticists or other providers with expertise in the complexities of interpreting CMA results.

A 2016 retrospective study (Wou et al), evaluated a three-year study that analyzed tissue from products of conception and perinatal losses using QF-PCR and microarray. CMA was performed mostly in samples with normal QF-PCR results. Of the 1071 informative specimens analyzed, 30.8% (n = 330) were positive for chromosomal abnormalities, with 57.6% (n = 190) of the abnormalities being detected by QF-PCR and 42.4% (n = 140) by aCGH. In addition high-resolution aCGH enabled an additional diagnostic yield of 36 cases of microdeletions and/or microduplications (10.9%) in specimens found to be abnormal by QFPCR and 3.4% of all successfully analyzed specimens. Gestational age was known in 940 specimens. The study reported that the highest rate of chromosomal abnormalities (a combined analysis of QF-PCR and aCGH abnormalities) was observed in the first trimester (<12 weeks) with 67.6% being considered pathogenic. The difference in proportions of pathogenic findings across trimesters was statistically significant (p < 0.001) with the greater proportion of findings being in the first trimester.

In a 2018 UpToDate article (Miller et al), CMA is still the preferred option for further evaluation of fetuses after fetal demise. Especially when G-banding is not possible due to the failure of cell culture. In the prenatal setting, CMA testing has advantages over conventional G-banding such as faster turnaround time, higher diagnostic yield, and ability to perform the test without using a cell culture.
There is insufficient data regarding the clinical utility and analytical validity of microarray testing for preimplantation genetic diagnosis or screening in embryos. Comparative studies are needed to evaluate implantation and pregnancy rates after microarray analyses compared to conventional testing.

**Applicable Coding**

**CPT Codes**

81228  Cytogenomic constitutional (genome-wide) microarray analysis; interrogation of genomic regions for copy number variants (eg, bacterial artificial chromosome [BAC] or oligo-based comparative genomic hybridization [CGH] microarray analysis)

81229  Cytogenomic constitutional (genome-wide) microarray analysis; interrogation of genomic regions for copy number and single nucleotide polymorphism (SNP) variants for chromosomal abnormalities

**HCPCS Codes**

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

**References:**


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