Chromosome Microarray Testing (Non-Oncology Conditions)

Policy Number: 2020T0559R
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Instructions for Use

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Coverage Rationale

Genome-wide comparative genomic hybridization microarray testing or single nucleotide polymorphism (SNP) chromosomal microarray analysis is proven and medically necessary for the following:

- Evaluation of an embryo/fetus in the following cases:
  - Intrauterine Fetal Demise or Stillbirth
  - Testing the products of conception following pregnancy loss
  - Women undergoing invasive prenatal testing (i.e., amniocentesis, chorionic villus sampling or fetal tissue sampling)
- Evaluation of individuals with one or more of the following:
  - Autism spectrum disorder
  - Isolated severe congenital heart disease
  - Multiple anomalies not specific to a Well-Delineated Genetic Syndrome and cannot be identified by a clinical evaluation alone
  - Non-syndromic Developmental Delay/Intellectual Disability
- Evaluation of biological parent of a fetus or child with an equivocal chromosome microarray result

Genome-wide comparative genomic hybridization microarray testing or SNP chromosomal microarray analysis is unproven and not medically necessary for all other populations and conditions due to insufficient evidence of efficacy. This includes but is not limited to:

- Epilepsy

Note: Genome-wide comparative genomic hybridization microarray testing or SNP chromosomal microarray analysis for the following are addressed in other Medical Policies:

- The evaluation of cancer is addressed in the Medical Policy titled Molecular Oncology Testing for Cancer Diagnosis Prognosis, and Treatment Decisions.
- Preimplantation genetic testing (PGT) is addressed in the Medical Policy titled Preimplantation Genetic Testing.

Documentation Requirements

Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The documentation requirements outlined below are used to assess whether the member meets the clinical criteria for coverage but do not guarantee coverage of the service requested.

CPT/HCPCS Codes*	Required Clinical Information
Chromosome Microarray Testing (Non-Oncology Conditions)	
81228 81229 81479 0209U S3870	Medical notes documenting all of the following: • Personal history of the condition, if applicable, including age at diagnosis • Complete family history (usually three-generation pedigree) relevant to condition being tested • Genetic testing results of family member, if applicable, and reason for testing • Ethnicity/ancestry (e.g., Ashkenazi Jewish), if reason for testing • Any prior genetic testing results • How clinical management will be impacted based on results of genetic testing • Genetic counseling (if available)

**For code descriptions, see the Applicable Codes section.*

Definitions

Developmental Delay: Developmental Delay may be used to describe children younger than 5 years of age who present with delays in the attainment of developmental milestones at the expected age (Moeschler and Shevell, 2014).

Intellectual Disability: Intellectual Disability may be used to describe persons 5 years of age and older (when standardized measures of intelligence become reliable and valid) who exhibit deficits in intelligence (IQ), adaptive behavior, and systems of support (Moeschler and Shevell, 2014).

Intrauterine Fetal Demise or Stillbirth: Fetal death at or after 20 weeks' gestation (ACOG, 2009, reaffirmed 2016).

Prenatal Diagnosis: A laboratory test performed on fetal DNA or chromosomes before birth to determine if a fetus has a genetic or chromosomal disorder (American College of Obstetricians and Gynecologists, 2016a).

Well-Delineated Genetic Syndrome: A syndrome is a collection of recognizable traits or abnormalities that tend to occur together and are associated with a specific disease. Distinguishing characteristics, such as specific facial features or other physical traits, lab tests, or family history can be used to identify a genetic syndrome (Genetics Home Reference, National Library of Medicine, 2020; Genetics Glossary, National Genome Institute, 2019).

Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

CPT Code	Description
0156U	Copy number (e.g., intellectual disability, dysmorphology), sequence analysis
0209U	Cytogenomic constitutional (genome-wide) analysis, interrogation of genomic regions for copy number, structural changes and areas of homozygosity for chromosomal abnormalities

CPT Code	Description
81228	Cytogenomic constitutional (genome-wide) microarray analysis; interrogation of genomic regions for copy number variants (e.g., 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
81479	Unlisted molecular pathology procedure

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

Diagnosis Code	Description
F70	Mild intellectual disabilities
F71	Moderate intellectual disabilities
F72	Severe intellectual disabilities
F73	Profound intellectual disabilities
F78	Other intellectual disabilities
F79	Unspecified intellectual disabilities
F80.0	Phonological disorder
F80.1	Expressive language disorder
F80.2	Mixed receptive-expressive language disorder
F80.4	Speech and language development delay due to hearing loss
F80.81	Childhood onset fluency disorder
F80.82	Social pragmatic communication disorder
F80.89	Other developmental disorders of speech and language
F80.9	Developmental disorder of speech and language, unspecified
F81.0	Specific reading disorder
F81.2	Mathematics disorder
F81.81	Disorder of written expression
F81.89	Other developmental disorders of scholastic skills
F81.9	Developmental disorder of scholastic skills, unspecified
F82	Specific developmental disorder of motor function
F84.0	Autistic disorder
F84.3	Other childhood disintegrative disorder
F84.5	Asperger's syndrome
F84.8	Other pervasive developmental disorders
F84.9	Pervasive developmental disorder, unspecified
F88	Other disorders of psychological development
F89	Unspecified disorder of psychological development
H93.25	Central auditory processing disorder
N96	Recurrent pregnancy loss
O02.1	Missed abortion
O03.4	Incomplete spontaneous abortion without complication

Diagnosis Code	Description
O03.9	Complete or unspecified spontaneous abortion without complication
O09.511	Supervision of elderly primigravida, first trimester
O09.512	Supervision of elderly primigravida, second trimester
O09.513	Supervision of elderly primigravida, third trimester
O09.519	Supervision of elderly primigravida, unspecified trimester
O09.521	Supervision of elderly multigravida, first trimester
O09.522	Supervision of elderly multigravida, second trimester
O09.523	Supervision of elderly multigravida, third trimester
O09.529	Supervision of elderly multigravida, unspecified trimester
O26.20	Pregnancy care for patient with recurrent pregnancy loss, unspecified trimester
O26.21	Pregnancy care for patient with recurrent pregnancy loss, first trimester
O26.22	Pregnancy care for patient with recurrent pregnancy loss, second trimester
O26.23	Pregnancy care for patient with recurrent pregnancy loss, third trimester
O28.0	Abnormal hematological finding on antenatal screening of mother
O28.1	Abnormal biochemical finding on antenatal screening of mother
O28.2	Abnormal cytological finding on antenatal screening of mother
O28.3	Abnormal ultrasonic finding on antenatal screening of mother
O28.4	Abnormal radiological finding on antenatal screening of mother
O28.5	Abnormal chromosomal and genetic finding on antenatal screening of mother
O28.8	Other abnormal findings on antenatal screening of mother
O28.9	Unspecified abnormal findings on antenatal screening of mother
O35.0XX0	Maternal care for (suspected) central nervous system malformation in fetus, not applicable or unspecified
O35.0XX1	Maternal care for (suspected) central nervous system malformation in fetus, fetus 1
O35.0XX2	Maternal care for (suspected) central nervous system malformation in fetus, fetus 2
O35.0XX3	Maternal care for (suspected) central nervous system malformation in fetus, fetus 3
O35.0XX4	Maternal care for (suspected) central nervous system malformation in fetus, fetus 4
O35.0XX5	Maternal care for (suspected) central nervous system malformation in fetus, fetus 5
O35.0XX9	Maternal care for (suspected) central nervous system malformation in fetus, other fetus
O35.1XX0	Maternal care for (suspected) chromosomal abnormality in fetus, not applicable or unspecified
O35.1XX1	Maternal care for (suspected) chromosomal abnormality in fetus, fetus 1
O35.1XX2	Maternal care for (suspected) chromosomal abnormality in fetus, fetus 2
O35.1XX3	Maternal care for (suspected) chromosomal abnormality in fetus, fetus 3
O35.1XX4	Maternal care for (suspected) chromosomal abnormality in fetus, fetus 4
O35.1XX5	Maternal care for (suspected) chromosomal abnormality in fetus, fetus 5
O35.1XX9	Maternal care for (suspected) chromosomal abnormality in fetus, other fetus
O35.2XX0	Maternal care for (suspected) hereditary disease in fetus, not applicable or unspecified
O35.2XX1	Maternal care for (suspected) hereditary disease in fetus, fetus 1
O35.2XX2	Maternal care for (suspected) hereditary disease in fetus, fetus 2
O35.2XX3	Maternal care for (suspected) hereditary disease in fetus, fetus 3
O35.2XX4	Maternal care for (suspected) hereditary disease in fetus, fetus 4
O35.2XX5	Maternal care for (suspected) hereditary disease in fetus, fetus 5

Diagnosis Code	Description
O35.2XX9	Maternal care for (suspected) hereditary disease in fetus, other fetus
O35.8XX0	Maternal care for other (suspected) fetal abnormality and damage, not applicable or unspecified
O35.8XX1	Maternal care for other (suspected) fetal abnormality and damage, fetus 1
O35.8XX2	Maternal care for other (suspected) fetal abnormality and damage, fetus 2
O35.8XX3	Maternal care for other (suspected) fetal abnormality and damage, fetus 3
O35.8XX4	Maternal care for other (suspected) fetal abnormality and damage, fetus 4
O35.8XX5	Maternal care for other (suspected) fetal abnormality and damage, fetus 5
O35.8XX9	Maternal care for other (suspected) fetal abnormality and damage, other fetus
O36.4XX0	Maternal care for intrauterine death, not applicable or unspecified
O36.4XX1	Maternal care for intrauterine death, fetus 1
O36.4XX2	Maternal care for intrauterine death, fetus 2
O36.4XX3	Maternal care for intrauterine death, fetus 3
O36.4XX4	Maternal care for intrauterine death, fetus 4
O36.4XX5	Maternal care for intrauterine death, fetus 5
O36.4XX9	Maternal care for intrauterine death, other fetus
P02.9	Newborn affected by abnormality of membranes, unspecified
P95	Stillbirth
Q20.1	Double outlet right ventricle
Q20.2	Double outlet left ventricle
Q20.3	Discordant ventriculoarterial connection
Q20.4	Double inlet ventricle
Q20.5	Discordant atrioventricular connection
Q20.6	Isomerism of atrial appendages
Q20.8	Other congenital malformations of cardiac chambers and connections
Q20.9	Congenital malformation of cardiac chambers and connections, unspecified
Q21.0	Ventricular septal defect
Q21.1	Atrial septal defect
Q21.2	Atrioventricular septal defect
Q21.3	Tetralogy of Fallot
Q21.4	Aortopulmonary septal defect
Q21.8	Other congenital malformations of cardiac septa
Q21.9	Congenital malformation of cardiac septum, unspecified
Q22.0	Pulmonary valve atresia
Q22.1	Congenital pulmonary valve stenosis
Q22.2	Congenital pulmonary valve insufficiency
Q22.3	Other congenital malformations of pulmonary valve
Q22.4	Congenital tricuspid stenosis
Q22.5	Ebstein's anomaly
Q22.6	Hypoplastic right heart syndrome
Q22.8	Other congenital malformations of tricuspid valve
Q22.9	Congenital malformation of tricuspid valve, unspecified
Q23.0	Congenital stenosis of aortic valve

Diagnosis Code	Description
Q23.1	Congenital insufficiency of aortic valve
Q23.2	Congenital mitral stenosis
Q23.3	Congenital mitral insufficiency
Q23.4	Hypoplastic left heart syndrome
Q23.8	Other congenital malformations of aortic and mitral valves
Q23.9	Congenital malformation of aortic and mitral valves, unspecified
Q24.0	Dextrocardia
Q24.1	Levocardia
Q24.2	Cor triatriatum
Q24.3	Pulmonary infundibular stenosis
Q24.4	Congenital subaortic stenosis
Q24.5	Malformation of coronary vessels
Q24.6	Congenital heart block
Q24.8	Other specified congenital malformations of heart
Q24.9	Congenital malformation of heart, unspecified
Q89.7	Multiple congenital malformations, not elsewhere classified
Q89.8	Other specified congenital malformations
Q89.9	Congenital malformation, unspecified
Q90.0	Trisomy 21, nonmosaicism (meiotic nondisjunction)
Q90.1	Trisomy 21, mosaicism (mitotic nondisjunction)
Q90.2	Trisomy 21, translocation
Q90.9	Down syndrome, unspecified
Q91.0	Trisomy 18, nonmosaicism (meiotic nondisjunction)
Q91.1	Trisomy 18, mosaicism (mitotic nondisjunction)
Q91.2	Trisomy 18, translocation
Q91.3	Trisomy 18, unspecified
Q91.4	Trisomy 13, nonmosaicism (meiotic nondisjunction)
Q91.5	Trisomy 13, mosaicism (mitotic nondisjunction)
Q91.6	Trisomy 13, translocation
Q91.7	Trisomy 13, unspecified
Q92.0	Whole chromosome trisomy, nonmosaicism (meiotic nondisjunction)
Q92.1	Whole chromosome trisomy, mosaicism (mitotic nondisjunction)
Q92.2	Partial trisomy
Q92.5	Duplications with other complex rearrangements
Q92.61	Marker chromosomes in normal individual
Q92.62	Marker chromosomes in abnormal individual
Q92.7	Triploidy and polyploidy
Q92.8	Other specified trisomies and partial trisomies of autosomes
Q92.9	Trisomy and partial trisomy of autosomes, unspecified
Q93.0	Whole chromosome monosomy, nonmosaicism (meiotic nondisjunction)
Q93.1	Whole chromosome monosomy, mosaicism (mitotic nondisjunction)
Q93.2	Chromosome replaced with ring, dicentric or isochromosome

Diagnosis Code	Description
Q93.3	Deletion of short arm of chromosome 4
Q93.4	Deletion of short arm of chromosome 5
Q93.7	Deletions with other complex rearrangements
Q93.51	Angelman syndrome
Q93.59	Other deletions of part of a chromosome
Q93.81	Velo-cardio-facial syndrome
Q93.82	Williams syndrome
Q93.88	Other microdeletions
Q93.89	Other deletions from the autosomes
Q93.9	Deletion from autosomes, unspecified
Q95.2	Balanced autosomal rearrangement in abnormal individual
Q95.3	Balanced sex/autosomal rearrangement in abnormal individual
Q99.8	Other specified chromosome abnormalities
Q99.9	Chromosomal abnormality, unspecified
R48.0	Dyslexia and alexia
R62.0	Delayed milestone in childhood
R62.50	Unspecified lack of expected normal physiological development in childhood
R62.51	Failure to thrive (child)
R62.59	Other lack of expected normal physiological development in childhood
R89.8	Other abnormal findings in specimens from other organs, systems and tissues
Z14.1	Cystic fibrosis carrier
Z14.8	Genetic carrier of other disease
Z36.0	Encounter for antenatal screening for chromosomal anomalies
Z37.1	Single stillbirth
Z37.3	Twins, one liveborn and one stillborn
Z37.4	Twins, both stillborn
Z37.60	Multiple births, unspecified, some liveborn
Z37.61	Triplets, some liveborn
Z37.62	Quadruplets, some liveborn
Z37.63	Quintuplets, some liveborn
Z37.64	Sextuplets, some liveborn
Z37.69	Other multiple births, some liveborn
Z37.7	Other multiple births, all stillborn
Z87.74	Personal history of (corrected) congenital malformations of heart and circulatory system

Description of Services

Genetic counseling is strongly recommended prior to genome-wide comparative genomic hybridization microarray testing or SNP chromosomal microarray analysis in order to inform persons being tested about the advantages and limitations of the test as applied to their unique situation.

Chromosome abnormalities are a well-established cause of congenital anomalies, dysmorphic features, Developmental Delay, Intellectual Disability, and other neurodevelopmental disorders. Two chromosome microarray genetic tests that are being evaluated for detection of chromosomal abnormalities are array comparative genomic hybridization (CGH) and single

nucleotide polymorphism (SNP). These tests analyze multiple sequences of deoxyribonucleic acid (DNA) by identifying multiple deletions and duplications across the genome simultaneously. The microarray may be targeted in nature, assaying certain regions of the genome known to be associated with a specific syndrome or phenotype, or may be genome-wide (Shaffer et al., 2007). Currently, most clinical applications of chromosome microarray testing are being investigated for the diagnosis of chromosomal abnormalities in fetuses and newborns, and in children with developmental disorders. For prenatal testing, chromosome microarray testing requires an invasive procedure (e.g., amniocentesis or chorionic villous sampling) for the collection of fetal cells.

Chromosomal microarray analysis (CMA) includes both CGH and SNP 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. This method allows the detection of chromosome imbalances that can provide more information than detected by conventional chromosome analysis [e.g., standard karyotype or fluorescence in situ hybridization (FISH)]. The array CGH approach compares patient DNA extracted from skin, blood, or fetal cells to a control or reference DNA from a normal individual. These are labelled separately with different colored fluorescent dyes and then mixed together and allowed to combine or hybridize to an array containing known DNA sequences called probes. The amount of hybridization is measured by the amount and color of light emitted from each spot. Computer analysis of the fluorescent signals is used to read and interpret the findings. Areas of unequal hybridization, mostly large deletions and duplications, signify a DNA alteration. CNVs may be benign, with no effect on clinical phenotype, or may be pathogenic and result in a variety of phenotypic abnormalities (Kearney et al., 2011). If an unknown CNV is detected, a genomic database is used to determine if the abnormality has been previously reported and if it has been associated with a benign or proposed pathogenic condition. The disadvantages of array CGH testing include the detection of a large number of variants of unknown clinical significance, potential false positive results that will require further testing, and the inability to detect certain anomalies such as those with balanced rearrangements where there is no net gain or loss of the chromosomes (Fruhman and Van den Veyver, 2010; Bui et al., 2011).

SNP arrays are sequence variants in which a single base pair differs from a specified reference sequence. For each SNP, a person generally has two alleles, one inherited from each parent. The absence of one allele in multiple contiguous SNPs indicates the presence of a chromosomal deletion, while an increase in SNP copy number indicates the presence of a chromosomal duplication. SNP microarrays are being studied as a way to evaluate the pattern of SNPs in a particular individual. Particular patterns of SNPs can be used as markers for inherited disease susceptibility or for detecting loss of heterozygosity of particular genetic alleles in tumor DNA. Like aCGH, SNP microarrays offer a cytogenetic evaluation at a significantly higher resolution than a standard karyotype analysis, as well as the ability to look for genomic imbalances throughout the genome in a single assay. The main challenge with microarray testing, including SNP microarray analysis, is the identification of CNVs of unknown clinical significance.

Clinical Evidence

Use in Obstetrics

Routine chromosome analysis has been used historically to identify chromosome abnormalities during pregnancy when risk factors are present, such as advanced maternal age and chromosome abnormalities. Chromosome microarray analysis (CMA) does not require cell culture or dividing cells, so it provides an advantage in turn-around time for time sensitive analysis, as is often the case during pregnancy. In addition, CMA can identify smaller chromosomal abnormalities than a routine chromosome analysis, and is able to identify chromosomal breakpoints that are unbalanced, but may appear balanced on a conventional karyotype. CMA does have limitations, in that it cannot detect totally balanced chromosomal material or low level mosaicism. Some arrays may not detect triploidy. Clinicians may use CMA as a first line test, or only when fetal abnormalities are identified (Society for Maternal-Fetal Medicine, 2016).

Prenatal Diagnosis

Analytical Validity

Hay et al. (2018) evaluated the frequency of significant chromosome abnormalities that would not have been detected if patients had been offered the choice of CMA or karyotype and karyotype was ultimately chosen. A total of 3,223 CMA samples were evaluated by chorionic villus sampling (CVS) or amniocentesis and were divided into those that met ACOG guidelines for CMA and those that met ACOG guidelines for either CMA or karyotype. A total of 1,475/3,223 (45.8%) were offered CMA and

1,748 (54.2%) were offered CMA or karyotype. Two hundred fifty-seven patients had a significant chromosome abnormality in the CMA group; 177(12%) would be detectable by karyotype; ten (0.7%) would have been possibly detected by karyotype and 70 (4.7%) were classified as being undetectable by karyotype. In the CMA/karyotype group 156 significant chromosomal abnormalities were detected. One hundred twelve (6.4%) were detectable by karyotype; one (0.06%) was possibly detectable by karyotype; 43 (2.5%) had a chromosomal abnormality not detectable by karyotype. Micro-duplications and microdeletions were the most common reported abnormality detected by CMA for both groups; regions of homozygosity and uniparental disomy were also revealed as additional findings in several cases. The study showed that when given the choice of karyotype or microarray, 2.5% had a chromosome abnormality that would have gone undetected if only karyotype had been chosen. The authors concluded that a significant number of chromosome abnormalities would be missed if guidelines continue to suggest that CMA and karyotyping have equivalent diagnostic value for patients in the absence of a fetal anomaly.

Pauta et al. (2017) performed a systemic review of the literature and meta-analysis to determine the utility of CMA by either aCGH or SNP-microarray, when compared to traditional karyotyping in early pregnancy loss. In twenty-three studies, 5520 pregnancies losses up to 20 weeks gestational age were reviewed. CMA provided informative results on 95% of cases compared to 67% with karyotyping, and CMA provided a 2% greater yield of pathogenic CNV. The authors concluded that CMA resulted in diagnostic information in early pregnancy loss in significantly more cases when compared to conventional chromosome analysis.

Clinical Validity

In an attempt to identify possible miscarriage-associated submicroscopic CNVs, target regions of large CNV, as well as recognize miscarriage candidate genes, Wang et al. (2020) analyzed 5,180 products of conception (POC) samples by quantitative fluorescent-polymerase chain reaction (QF-PCR)/CNV-sequencing and CMA. Significant submicroscopic CNVs were determined by comparing the frequency of recurrent submicroscopic CNVs between cases and a published control cohort. Genes found within critical regions of miscarriage-associated CNVs were prioritized by integrating Residual Variance Intolerance Score and the human gene expression data for identification of possible miscarriage candidate genes. A total of 2,955/5,033 (59.1%) showed clinically significant chromosomal abnormalities. Three areas of recurring CNVs (microdeletions of 22q11.21, 2q37.3 and 9p24.3p24.2) were detected and considered to be associated with miscarriage. Forty-four critical regions of large CNV were noted which included 14 deletions and 30 duplications. A total of 209 genes were identified as possible miscarriage candidate genes.

In a review by Levy and Wapner (2018), a meta-analysis by Srebniak et al. (2017) was cited. A total of 10,614 fetal CMA were reviewed from ten large studies; 1/119 (0.84%) of cases referred for AMA and/or anxiety revealed a clinically significant CNV (95% CI). A subsequent meta-analysis from 8 large studies on 10,314 fetuses demonstrated CNV associated with early onset syndromes in 1/270 (0.37%) of pregnancies (95% CI). A total of 1/909 (0.11%) revealed late onset diseases and CNV susceptibility in 1/333 (0.3%). By combining the individual risk for CNVs with individual risk for chromosome abnormalities detectable by karyotype, the author reported an overall risk of greater than 1/180 for a significant cytogenetic abnormality. Because women less than 36 years of age have a higher risk for CNV than for Down syndrome, the authors surmised that all women should be advised of these overall individual risks and not just of individual trisomic risks.

In a large cohort study, Maya et al. (2018) evaluated the frequency of penetrance of copy number variations (CNVs) in low and high risk prenatal and postnatal samples. The cohort was grouped according to chromosome microarray analysis (CMA) indication with group I being low-risk, prenatal women as the control group; group II being high risk prenatal women with fetuses that had congenital malformations; and group III being post-natal individuals with a variety of genetic based conditions. Within this cohort, 21,594 CMAs were performed and the frequency of high penetrance CNVs was 0.1% in group I, 0.9% in group II, and 2.6% in group III. CNV frequency of moderate-penetrance was 0.3%, 0.6%, and 1.2%, respectively, and these differences were statistically significant. The frequency of low-penetrance CNVs was not significantly different among groups: 0.6%, 0.9%, and 1.0%, respectively. The study concluded that high penetrance CNVs may be a factor in heritability of various anomalies, however low penetrance CNVs do not seem to contribute.

Parchem et al. (2018) evaluated the association of CNVs with perinatal outcomes in fetuses that had sonographic abnormalities. This retrospective studied reviewed anomalous fetuses that had CMA testing. There were abnormal CMA results in 60 (21.4%) of the 280 fetuses in the study. Of these 60, 21 (35%) were considered to be pathogenic and 39 (65%) were variants of uncertain significance (VUS). Perinatal death was also studied as a part of this evaluation and among 212 (75.7%) of the continued pregnancies, abnormal CMA was not associated with increased risk of perinatal death.

Jin et al. (2018) investigated the use of CMA for prenatal diagnosis of orofacial clefts. The institution evaluated 143 fetuses with oral clefts that were detected by ultrasonography. The cases were separated into four groups: isolated cleft lip (CL) (CL only), isolated cleft palate (CP only), isolated cleft lip and palate (CLP) (CLP only), and syndromic CLP (combined with other malformations). CMA was performed for all cases and a total of 11 fetuses had pathogenic CNVs (7.7%), including isolated CP (1/143, 0.7%), isolated CLP (5/143, 3.5%), and syndromic CLP (5/143, 3.5%). Compared with the CMA results, five fetuses had an abnormal karyotype (5/139, 3.6%). The researchers concluded that CMA is a diagnostic tool for identification of chromosomal abnormalities in the prenatal diagnosis for oral clefts.

A French multicenter study by Egloff et al. (2018) evaluated CMA in a large cohort of fetuses with increased nuchal translucency thickness (NT). In this retrospective study, 720 fetuses were analyzed by rapid aneuploidy test and those identified as euploid underwent CMA. An aneuploidy involving chromosome 13, 18 or 21 was detected by rapid aneuploidy test in 121 (16.8%) fetuses. The remaining 599 fetuses were euploid. Of these 599 cases, 53 (8.8%) had a CNV detected by CMA: 16 (2.7%) had a pathogenic CNV (11 were considered cryptic or not visible by karyotyping); seven (1.2%) were CNVs that are known to predispose one to neurodevelopmental disorders; eight (1.3%) were VUS; 1 was unrelated or an incidental finding; and 21 were benign CNVs. This study demonstrated the benefit of CMA in the diagnosis of fetuses with isolated increased NT. An additional finding was that most (69%) pathogenic CNVs were cryptic.

A 2018 study evaluated CMA copy number variations (CNVs) and prenatal posterior fossa anomalies (PFAs), especially cerebellar hypoplasia (CH) (Zou et al., 2018). The researchers analyzed 77 pregnancies with PFAs who underwent CMA and also compared the data to karyotype analysis. Chromosomal aberrations (pathogenic and VUS) were detected in 31.2% (24/77) of all cases by CMA and in 18.5% (12/65) in fetuses with normal karyotypes. There was a high detection rate of clinically significant CNVs in this group of fetuses including those with CH (54.6%, 6/11), vermis hypoplasia (33.3%, 1/3), and Dandy-Walker malformation (25%, 3/12). The study also compared those fetuses with and without other anomalies and determined that cases with CH and additional malformations had a higher detection rate in CMA (33.3% compared to 88.9%). This analysis allowed the researchers to conclude that CMA detected the most frequent aberrations with CH.

A study by Sagi-Dain et al. (2018) examined CMA results in pregnancies with ultrasonographic abnormalities. A retrospective review was performed and CMA of amniocenteses performed as a result of fetal ultrasound anomalies. In an analysis of 5,750 pregnancies, clinically significant CMA aberrations were detected in 272 (4.7%). Of these 272 cases, 115 (2%) were karyotype detectable and 157 (2.7%) were submicroscopic. The most common CNV was detected in 22q11.21 deletion. This study demonstrated that the rate of abnormal results from CMA was twice that of karyotyping in this set of pregnancies with abnormal fetal ultrasound findings.

Prenatal diagnosis of congenital heart disease (CHD) was studied using CMA in a study by Wang et al. (2018). The aim of the study was to evaluate the clinical utility of this approach and the studied evaluated 602 prenatal cases of CHD. Using CMA, pathogenic abnormalities were identified in 125 (20.8%) of these cases of CHD and 52.0% of these were numerical chromosomal abnormalities. The detection rates of likely pathogenic copy number variations and variants of uncertain significance were 1.3% and 6.0%, respectively. The researchers concluded that CMA was a reliable technology for this type of prenatal diagnosis of CHD.

Peng et al. (2017) assessed chromosomal and subchromosomal anomalies in small for gestational age (SGA) fetuses with no additional anomalies. A retrospective review of 128 SGA fetuses had both karyotyping and CMA. Analysis was performed and anomalies were identified in 6 (4.7%) SGA fetuses and pathogenic subchromosomal anomalies in four (3.1%) by CMA. The researchers concluded that there was a 3.3% incremental yield of subchromosomal anomalies in CMA above karyotyping in SGA fetuses.

Gliem et al. (2017) studied the use of CMA for the testing of products of conception (POCs) to provide information about the cause of fetal loss. Using CMA may help determine the recurrence risk of future losses and chromosome abnormalities for subsequent pregnancies. This institution used fluorescent in situ hybridization (FISH) testing to identify specific chromosome aneuploidy in formalin-fixed paraffin-embedded (FFPE) samples. Twenty-five archived FFPE POC specimens were evaluated by CMA using the Affymetrix OncoScan FFPE Assay. The previous FISH results (five normal, 12 trisomy, six triploidy, two monosomy) were compared to the CMA results. Of the five normal samples, four had no clinically relevant CMA findings, and one sample was found to have trisomy 9, which was not detectable by the FISH test. Of the abnormal FISH results samples (n=20), the CMA detected all FISH reported abnormalities along with additional findings including additional trisomies in samples. This small study verified the performance characteristics of CMA on FFPE POC samples.

Srebniak et al. (2016) evaluated the diagnostic value of SNP array testing in 1033 fetuses with ultrasound anomalies by investigating the prevalence and genetic nature of pathogenic findings. Pathogenic findings were classified into three categories: causative findings; unexpected diagnoses (UD); and susceptibility loci (SL) for neurodevelopmental disorders. After exclusion of trisomy 13, 18, 21, sex-chromosomal aneuploidy and triploidies, in 76/1033 (7.4%) fetuses a pathogenic chromosome abnormality was detected by genomic SNP array: in 19/1033 cases (1.8%) a microscopically detectable abnormality was found and in 57/1033 (5.5%) fetuses a pathogenic submicroscopic chromosome abnormality was detected. 58% (n=44) of all these pathogenic chromosome abnormalities involved a causative finding, 35% (n=27) a SL for neurodevelopmental disorder, and 6% (n=5) a UD of an early-onset untreatable disease. In 0.3% of parental samples an incidental pathogenic finding was encountered. According to the authors, these results confirm that a genomic array should be the preferred first-tier technique in fetuses with ultrasound anomalies.

Rosenfeld et al. (2015) determined the frequency of clinically significant chromosomal abnormalities identified by chromosomal microarray in pregnancy losses at any gestational age and compared microarray performance with that of traditional cytogenetic analysis when testing pregnancy losses. Among 535 fetal demise specimens of any gestational age, clinical aCGH was performed successfully on 515, and a subset of 107 specimens underwent additional 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. The authors concluded that both the provision of results in cases in which karyotype fails and the detection of abnormalities in the presence of a normal karyotype demonstrate the increased diagnostic utility of microarray in pregnancy loss. According to the authors, chromosomal microarray testing is a preferable, robust method of analyzing cases of pregnancy loss to better delineate possible genetic etiologies, regardless of gestational age.

In a systematic review, Grande et al. (2015) estimated 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. Seventeen studies met the inclusion criteria for analysis. 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.

Papoulidis et al. (2015) evaluated 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%). The authors concluded that the 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.

Dhillon et al. (2014) evaluated whether CMA testing on the products of conception following miscarriage provides better diagnostic information compared with conventional karyotyping in a systematic review and meta-analysis that included 9 studies. There was agreement between CMA and karyotyping in 86.0% of cases. CMA detected 13% additional chromosome abnormalities over conventional full karyotyping. In addition, traditional, full karyotyping detected 3% additional abnormalities over CMA. The incidence of a variant of unknown significance (VOUS) being detected was 2%. The authors concluded that compared with karyotyping, there appears to be an increased detection rate of chromosomal abnormalities when CMA is used

to analyze the products of conception; however, some of these abnormalities are VOUS, and this information should be provided when counseling women following miscarriage and when taking consent for the analysis of miscarriage products by CMA.

de Wit et al. (2014) conducted a systematic review to evaluate the diagnostic and prognostic value of genomic array testing in pregnancies with fetuses with a structural ultrasound anomaly (restricted to one anatomical system) and a normal karyotype. Combined data of the reviewed studies (n = 18) indicated that fetuses with an ultrasound anomaly restricted to one anatomical system (n = 2220) had a 3.1-7.9% chance of carrying a causative submicroscopic CNV, depending on the anatomical system affected. This chance increased to 9.1% for fetuses with multiple ultrasound anomalies (n = 1139). According to the authors, this review indicates that 3.1-7.9% of fetuses with a structural ultrasound anomaly restricted to one anatomical system and a normal karyotype will show a submicroscopic CNV, which explains its phenotype and provides information for fetal prognosis. The authors concluded that microarray has considerable diagnostic and prognostic value in these pregnancies.

In a systematic review and meta-analysis, Hillman et al. (2011) evaluated whether array CGH testing in the prenatal population provides diagnostic information over that available from conventional karyotyping. Studies were selected if array CGH was used on prenatal samples or if array CGH was used on postnatal samples following termination of pregnancy for structural abnormalities that were detected on an ultrasound scan. Of the 135 potential articles, 10 were included in this systematic review and eight were included in the meta-analysis. The pooled rate of extra information detected by array CGH when the prenatal karyotype was normal was meta-analyzed using a random-effects model. The pooled rate of receiving an array CGH result of unknown significance was also meta-analyzed. Array CGH detected 3.6% additional genomic imbalances when conventional karyotyping was 'normal', regardless of referral indication. This increased to 5.2% more than karyotyping when the referral indication was a structural malformation on ultrasound. The authors concluded that there appears to be an increased detection rate of chromosomal imbalances, compared with conventional karyotyping, when array CGH techniques are employed in the prenatal population. However, some are copy number imbalances that are not clinically significant. Therefore, maternal anxiety may be generated by an abnormal test result that has little clinical significance.

Clinical Utility

Ni et al. (2019) evaluated 247 fetuses with increased nuchal translucency (NT) to establish the frequency of chromosome abnormalities and pregnancy outcomes. Fetuses with increased NT (>95 percentile) underwent CMA. One hundred sixty-eight cases were isolated increased NT; 20 cases had increased NT with cystic hygroma; 12 cases had increased NT with edema and 47 cases had increased NT with other anomalies. Couples were subsequently contacted for follow-up. A total of 78/247 (31.6%) had chromosome abnormalities; 66 were chromosomal aneuploidies and 12 had copy number variants (CNV). CNV were seen in 11/35 (31.4%) of total abnormalities in fetuses with isolated increased NT compared to 1/42 (2.3%) of the fetuses with non-isolated increased NT. Three fetuses with normal CMA results had intellectual and motor retardation; 2 of which had single gene disorders found by whole exome sequencing. The authors summarized that CMA has the potential to detect more chromosomal microdeletions/micro-duplications among fetuses with isolated increased NT.

Zhu et al. (2018) conducted a retrospective study to determine the impact of CMA for the management of couples who have undergone miscarriage and on products of conception (POC). Four hundred five POC were analyzed and 224 (55.3%) had pathogenic results. A total of 16/224 (7.1%) revealed copy number changes which would have been missed by karyotype analysis. No significant difference was noted between the rate of abnormalities seen in natural conceptions versus assisted reproductive conceptions. A total of 126/222 (56.8%) and 98/182 (53.6%) revealed abnormal results, respectively (p=0.645; OR = 1.110; CI 95%: 0.713-1.726). Of 141 POCs from mothers who had positive adverse pregnancy histories, 75 (53.2%) revealed abnormal results; 149/264 (56.4%) abnormal results were seen from mothers that had a negative adverse pregnancy history. The authors concluded that CMA should be offered to couples following their first miscarriage regardless of method of conception.

A retrospective study was performed to evaluate the use of CMA versus chromosome analysis for prenatal diagnosis of ventricular septal defects (VSDs) (Cai et al., 2018). The researchers analyzed 151 VSD cases (79 had an isolated defect and 72 had an additional anomaly) that were diagnosed by fetal ultrasonography. Chromosome karyotype testing identified 16 chromosomal abnormalities. CMA identified 14 cases that were consistent with the karyotype analysis and identified an additional 20 cases (13.2%) of abnormal copy number variations (CNVs), of which 13 were pathogenic CNVs, 5 were variations of uncertain significance (VUS) and 2 were benign CNVs. The detection rate of pathogenic CNVs was also compared between the two groups of VSD subjects. They determined that in non-isolated-VSDs this rate was significantly higher than that in isolated-VSDs (36.1% (26/72) vs. 1.3% (1/79)). The researchers concluded that CMA in combination with cytogenetics may be

effective in the identification of VSDs. In addition, the CMA results that indicated a pathogenic variant had an effect on obstetrical outcomes.

Another study also compared the utility of single-nucleotide polymorphism (SNP) arrays in fetuses with VSDs and normal karyotypes and with or without other structural anomalies (Fu et al., 2017). The researchers analyzed 144 fetuses with VSDs and normal karyotypes using Affymetrix CytoScan HD arrays. Twelve fetuses (8.3%) demonstrated clinically significant CNVs with the most common to be a 22q11.2 deletion (4/144; 2.8%). Other well-known microdeletion or microduplication syndromes were also identified in six cases. These researchers found no significant difference in pathogenic CNVs in fetuses with or without other structural anomalies. The conclusion was that high-resolution SNP arrays are valuable in identifying submicroscopic chromosomal abnormalities for prenatal VSD diagnosis.

Brady et al. (2013) evaluated the clinical utility of chromosomal microarrays for prenatal diagnosis by a prospective study of fetuses with abnormalities detected on ultrasound. Patients referred for prenatal diagnosis due to ultrasound anomalies underwent analysis by array comparative genomic hybridization as the first-tier diagnostic test. A total of 383 prenatal samples underwent analysis by array comparative genomic hybridization. Array analysis revealed causal imbalances in a total of 9.6% of patients (n = 37). Submicroscopic copy-number variations were detected in 2.6% of patients (n = 10/37), and arrays added valuable information over conventional karyotyping in 3.9% of patients (n = 15/37). Variants of uncertain significance were revealed in 1.6% of patients (n = 6/383). The authors concluded that there was added value of chromosomal microarrays for prenatal diagnosis in the presence of ultrasound anomalies.

Shaffer et al. (2012) evaluated the diagnostic utility of comparative genomic hybridization (CGH)-based microarrays for pregnancies with abnormal ultrasound findings. The authors conducted a retrospective analysis of 2858 pregnancies with abnormal ultrasounds and normal karyotypes (when performed) tested in their laboratory using CGH microarrays targeted to known chromosomal syndromes with later versions providing backbone coverage of the entire genome. Abnormalities were stratified according to organ system involvement. Detection rates for clinically significant findings among these categories were calculated. Clinically significant genomic alterations were identified in cases with a single ultrasound anomaly (n = 99/1773, 5.6%), anomalies in two or more organ systems (n = 77/808, 9.5%), isolated growth abnormalities (n = 2/76, 2.6%), and soft markers (n = 2/77, 2.6%). The following anomalies in isolation or with additional anomalies had particularly high detection rates: holoprosencephaly (n = 9/85, 10.6%), posterior fossa defects (n = 21/144, 14.6%), skeletal anomalies (n = 15/140, 10.7%), ventricular septal defect (n = 14/132, 10.6%), hypoplastic left heart (n = 11/68, 16.2%), and cleft lip/palate (n = 14/136, 10.3%). The authors concluded that microarray analysis identified clinically significant genomic alterations in 6.5% of cases with one or more abnormal ultrasound findings; the majority was below the resolution of karyotyping. The authors stated that for most informed medical management, pregnancies with ultrasound anomalies undergoing invasive testing should be tested by microarray to identify all clinically significant copy number alterations (CNAs).

Professional Societies

Society of Obstetricians and Gynaecologists of Canada (SOGC)/Canadian College of Medical Geneticists (CCMG)

A Joint Technical update for the SOGC and CCMG recommended offering chromosomal microarray (CMA) in cases of multiple congenital anomalies revealed on ultrasound (II-1A) or fetal MRI. In addition, CMA was also recommended when single congenital defects in conjunction with other findings (e.g. IUGR, oligohydramnios) are detected. Prenatal CMA should be considered for certain malformations that have a high association with abnormal results. CMA is not recommended for pregnancies that are at low risk for a structural anomaly (Audibert et al., 2017).

An SOGC/CCMG Practice Guideline for the use of chromosomal microarray analysis for prenatal diagnosis and assessment of fetal loss in Canada (Armour et al., 2018) replaced the former 2011 guideline.
Recommendations in the updated 2018 guideline included:

- Offering CMA following normal aneuploidy screen results when multiple fetal malformations are detected (II-1A) or NT ≥3.5MM (II-2B)
- Genetic counseling should be provided to obtain informed consent; parental decisions for reporting of incidental findings (II-2A); and for post-test results reporting counseling (III-A)
- CMA resolution should be similar to postnatal CMA panels for the detection of small pathogenic variants
- Variants of unknown significance (VOUS) smaller than 500 Kb deletion or 1 Mb duplication should not be reported in prenatal setting

- VOUS above such cut-offs should only be reported if there is significant evidence that deletion or duplication or the region may be pathogenic (III-B)
- Secondary findings associated with significant childhood onset conditions should be reported; variants associated with adult-onset conditions should only be reported if previously requested by parents or if disclosure could prevent harm to family members (III-A)

American College of Medical Genetics (ACMG)

ACMG (Cherry et al., 2017) published a practice resource guideline for laboratories for diagnostic testing following positive noninvasive prenatal screening (NIPS) recommending the following:

- CMA on CVS or amniocentesis may be used for confirmatory diagnosis for abnormal NIPS results or as a reflex to normal karyotype analysis.
- CMA testing should be utilized for follow-up when small copy number changes are reported as positive on NIPS.
- Testing of products of conception and/or fetus by karyotype of CMA should be considered on a case basis when prenatal diagnosis is not possible.
- For neonates with abnormal physical findings which are not suggestive of the trisomy suggested by original screening, CMA is recommended.
- CMA is recommended when NIPS sex determination is not concordant with physical examination or other clinical evidence reveals possible disorder of sexual differentiation.

American College of Obstetricians and Gynecologists (ACOG)

In a 2016 Committee Opinion on Microarrays and Next-Generation Sequencing Technology (American College of Obstetricians and Gynecologists, 2016a), ACOG and SMFM make the following recommendations and conclusions 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.
- 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.

In a 2016 Practice Bulletin (American College of Obstetricians and Gynecologists, 2016b) on prenatal diagnostic testing for genetic disorders, ACOG and the Society for Maternal-Fetal Medicine (SMFM) recommend the following based on good and consistent scientific evidence (Level A):

- Chromosome microarray analysis should be made available to any patient choosing to undergo invasive diagnostic testing.
- 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.

The 2016 Practice Bulletin further stated that prenatal diagnostic testing for genetic disorders makes the following recommendation based on limited or inconsistent scientific evidence (Level B):

- Chromosomal microarray analysis can be used to confirm an abnormal FISH test.

Society for Maternal-Fetal Medicine (SMFM)

In an SMFM Consult Series publication (2016) on the use of chromosomal microarray for prenatal diagnosis, SMFM makes the following recommendations:

- 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 (GRADE 1A)
- 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 (GRADE 1B)
- The use of CMA is not recommended as a first-line test to evaluate first trimester pregnancy losses due to limited data (GRADE 1C)
- 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 (Best practice).

Joint Committee on Genomics in Medicine (JCGM)

In 2015, the JCGM (Gardiner et al., 2015) recommended that chromosomal microarray be performed in prenatal cases with:
- One or more structural anomalies detected on ultrasound,
- Isolated nuchal translucency >3.5 mm, and
- In fetuses with sex chromosome abnormality detected by karyotype that is not likely associated with the ultrasound findings.

Use in Pediatrics

Developmental Disorders

Analytical Validity

Baldwin et al. (2008) described the validation of an oligonucleotide array with approximately 43,000 probes spaced an average of 75 kb across the genome, a resolution of 500 kb overall, and a resolution of 50 kb in targeted regions. Initially, ten patients with known chromosome abnormalities, including two supernumerary marker chromosomes, five telomere deletions, two unbalanced translocations, and a 15q11 to q13 microdeletion, were tested with the array. The array correctly identified all ten (100%) anomalies and identified additional complex rearrangements in two (20%) of the cases. Another 20 patient samples, including 14 cases with abnormalities and six with normal cytogenetic findings, were subsequently analyzed in a blinded manner. As with the previous group of samples, the concordance rate between the aCGH results and previous cytogenetic testing was 100%.

Clinical Validity

Fan et al. (2018) performed a retrospective review of CMA results from a Chinese population with developmental/ intellectual delays (DD/ID) in order to determine genotypes, diagnostic yields and phenotypes among a diverse group with varying manifestations. A total of 710 patients were evaluated and 247 copy number variants (CNV) were reported in 201 patients (28%). The authors reported that the diagnostic yields were significantly higher with co-existing congenital heart defects (CHD 55%), facial dysmorphism (39%), microcephaly (34%) or hypotonia (35%). Co-existing skeletal malformations (26%), brain malformations (24%) or epilepsy (24%) did not affect the diagnostic yield. ID severity correlated positively with CMA (mild: 19%, moderate: 22, severe: 33%); however the correlation was not statistically significant (p=0.08). Coexistence of CHD was the strongest phenotype associated with CNV (OR 5.52). The presence of facial dysmorphism with CHD increased the diagnostic yield to 62% (OR 10.81). The results showed that diagnostic yields vary based on phenotypic presentation. CHD, microcephaly, hypotonia and facial dysmorphism co-existing with DD/ID are associated with an increased likelihood of CNVs.

Geddes et al. (2017) evaluated a protocol to direct genetic testing, including karyotyping, 22q deletion analysis, and CMA, on infants with critical congenital heart disease. In a retrospective review of data of 733 infants prior to implementing the genetic testing protocol, 433 had at least one of included genetic tests. Sixty-six % of these patients had more than one genetic test, and the rate of diagnosis was 26%. A genetic testing protocol was identified that aligned genetic testing with clinical presentation. For example, infants that were likely to have Trisomy 21 or Turner syndrome were first tested with routine chromosome analysis. Conotruncal heart lesion patients were evaluated by 22q analysis, and all others had a chromosome microarray as a first test. The protocol was implemented in January 2015 and evaluated through June 2016. In the post protocol period, 158 patients were evaluated and 121 patients had at least one genetic test. The rate of genetic testing increased to 77%, and only 24% of patients had more than one genetic test. The rate of diagnosis was 36%. Overall, in the post-protocol period, infants were less likely to undergo multiple genetic tests, and were more likely to get a genetic diagnosis. Diagnostic yield varied between pre-and post-protocol tests as well. For karyotyping, the pre-protocol yield as 18%, and post-protocol was 76%. The 22q analysis pre-protocol diagnostic yield was 24% and 26% post-protocol. There was no significant difference in the

diagnostic yield of CMA at 22% pre-protocol and 22% post-protocol. There were no results in this cohort detected by karyotype or 22q deletion analysis that was not detectable by CMA.

McCormack et al. (2016) examined the utility of aCGH to replace karyotype in 5369 pre- and post-natal patients with an unexplained phenotype. In this cohort, 28% of those tested had a deletion or duplication. Ninety-seven percent of cases with a CNV that was less than five kilobases in size would not have been detected by routine chromosome analysis. Eight hundred and forty two (15.7%) had a variant of unknown significance. About 5% of the cohort met the criteria for a known syndrome. Using microarray as a primary analysis tool significantly increased the detection of CNV abnormalities, with one syndromic case identified per 20 referrals.

Szczaluba et al. (2016) studied the value of aCGH in newborns with multiple congenital anomalies. A group of 54 neonates with two or more birth defects were evaluated with an OGT Cytosure 8x60 K microarray. Ten newborns were found to have rearrangements detected by aCGH. One was a recurrent syndromic microdeletion, but the others were unique. Five could be seen on routine cytogenetics, but one was sub-microscopic. The other four were copy number variants that were likely pathogenic and could explain the phenotype.

Bartnik et al. (2014) evaluated the application of array CGH in clinical diagnostics of developmental delay/ intellectual disability in 112 children. The authors identified 37 copy number variants (CNVs) 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. According to the authors, 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.

Nicholl et al. (2014) prospectively 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 CGH platform, replacing conventional cytogenetic testing that would have been used in the past. 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. The authors stated that precise determination of any previously hidden molecular defect responsible for the patient's condition is translated to improved genetic counselling.

Battaglia et al. (2013) evaluated the usefulness of CMA as a first-tier tool in detecting the etiology of unexplained intellectual disability/autism spectrum disorders (ID/ASDs) associated with dysmorphic features in a large cohort of pediatric patients. The study included 349 individuals; 223 males, 126 females, aged 5 months-19 years. Blood samples were analyzed with CMA at a resolution ranging from 1 Mb to 40 Kb. The imbalance was confirmed by FISH or qPCR. CNVs were considered causative if the variant was responsible for a known syndrome, encompassed gene/s of known function, occurred de novo or, if inherited, the parent was variably affected, and/or the involved gene/s had been reported in association with ID/ASDs in dedicated databases. A total of 91 CNVs were detected in 77 (22.06%) patients: 5 (6.49%) of those presenting with borderline cognitive impairment, 54 (70.13%) with a variable degree of DD/ID, and 18/77 (23.38%) with ID of variable degree and ASDs. The CNVs caused the phenotype in 57/77 (74%) patients; 12/57 (21.05%) had ASDs/ID, and 45/57 (78.95%) had DD/ID. The authors concluded that this study provided further evidence of the high diagnostic yield of CMA for genetic testing in children with unexplained ID/ASDs who had dysmorphic features.

Miller et al. (2010) assessed the clinical validity of chromosomal microarray testing as a first-tier analysis in the evaluation of patients with unexplained DD, ID, ASD, and/or MCA (postnatal only). A review of 33 studies involving 21,698 patients was performed to evaluate the sensitivity of microarrays in the detection of deletions and duplications. The analysis of data from all 33 studies, including those that involved BAC or oligonucleotide microarrays (aCGH), showed that chromosomal microarray analysis in general had a diagnostic yield of approximately 15% to 20%. In addition, it was determined that, although balanced

rearrangements and low-level mosaicism were generally not detectable by microarray analysis, these anomalies were rare causes of DD/ID/MCA (< 1%). As a result, the ISCA stated that the evidence supports the use of chromosomal microarray testing as a first-tier test in the clinical evaluation of infants, children, or adults with DD, ID, ASD, and/or MCA.

Clinical Utility

A retrospective study conducted by Hureaux et al. (2019) suggested that the use of CMA can increase the genetic diagnostic yield for congenital heart defects (CHD) by 4-10%. CMA was performed for 239 isolated cases of CHD in France in 2015. Thirty-three copy number variants (CNV) were found; 19 were pathogenic, six were variants of unknown significance, and eight were non-pathogenic variants. The overall anomaly detection rate was 10.4%. Known CNVs included: ten 22q11.21 deletions; two 22q11.21 duplications; two 8p23 deletions; one Alagille syndrome deletion (20p12) and one Kleefstra syndrome (9q34.3 deletion). The authors concluded that the additional diagnostic yield was clinically significant (3.1%) and that patients with isolated CHDs and normal karyotype should be offered additional microarray testing to include other chromosome abnormalities in addition to 22q11.21 duplications and deletions.

Jang et al. (2019) studied the impact of CMA analysis on patient management by conducting a multicenter, prospective study in Korea on patients with developmental delay/intellectual delay (DD/ID), autism spectrum disorders (ASD), and multiple congenital anomalies (MCA). G-banding karyotype and CMA were both performed simultaneously on 617 patients in an attempt to determine if results affect treatment recommendations. 122/617 (19.8%) had abnormal CMA findings; 65 were pathogenic and 57 were variants of possible significance. Thirty-five known disorders were detected with the most common being 16p11.2 microdeletion, followed by 15q11-q13 duplication, Down syndrome, and Duchenne muscular dystrophy. Variants of unknown significance (VOUS) were seen in 51 (8.3%) of patients. CMA test results influenced clinical management decisions including: imaging studies, referrals to specialists, and laboratory testing recommendations in 71.4% of those tested. Clinical management was also impacted in 86%, 83.3%, 75% and 67.3% of patients that had variants of possible significance, pathogenic variants, VOUS, and benign variants, respectively. More than 1,500 new medical management protocols were recommended based on the CMA results with an average of 2.9 new recommendations per patient. The final conclusion by the authors was that CMA as a first-tier test improves diagnostic yields and the overall quality of clinical management in patients with DD/ID, ASD, and MCA.

CMA is well known as a first-tier test for developmental disabilities (DD) and congenital anomalies. One study of a Turkish population by Ozyilmaz et al. (2017) evaluated 971 patient and 301 parent samples. Of the 971 patient samples, 133 (13.6%) had pathogenic variants. These results lead the researchers to conclude that there is high potential for using CMA in single gene disorders or novel gene-phenotype associations and CNVs.

A pediatric CMA study was performed to identify recurrent pathogenic CNVs in patients with idiopathic short stature (Homma et al., 2018). The study researchers selected 229 children that did not have a well-recognized syndrome but had short stature and dysmorphic features, developmental delay, and/or intellectual disability. CMA was used for evaluation of the patients and the study targeted pathogenic CNVs that were associated with short stature. In the 229 patients, 32 pathogenic or likely pathogenic CNVs were identified. The study also reviewed the literature and selected additional cohorts of patients with short stature to create a larger cohort of 671 patients. In total, CNVs were identified in 87 (13%) of patients with seven recurrent CNVs (22q11.21, 15q26, 1p36.33, Xp22.33, 17p13.3, 1q21.1, 2q24.2) that were identified as responsible for 40% of all genomic imbalances in this population.

Sys et al. (2018) evaluated CMA as a diagnostic tool for patients with autism spectrum disorders (ASD) with a variety of clinical characteristics. The researchers stated that this tool may be restricted to patients that had specific characteristics or comorbidities. A retrospective review of the files of 311 children diagnosed with ASD was performed and the following clinical characteristics were captured: intellectual disability, major congenital anomalies, epilepsy, prematurity, familial history of ASD, electroencephalography, and brain MRI findings. Next, the results of any genetic analyses were evaluated in conjunction with the clinical data. CMA had been performed in 79 patients and was normal in 55 (group 1) and abnormal in 23 (group 2). There was no significant difference between the two groups regarding the presence of clinical characteristics. Additionally, the researchers determined that the diagnostic yield of CMA (8.9%) was higher than karyotyping (1.6%) and other genetic tests (3.8%).

A study by Cuccaro et al. (2018) evaluated CNVs and mutations in Alzheimer's disease (AD). The researchers used the NeuroArray which was a custom CMA for screening patients with confirmed or suspected AD. The study design evaluated 641

genes and 9,118 exons that have been linked to AD. The NeuroArray demonstrated the presence of amplifications in several AD associated genes. This study concluded that this approach may be a helpful tool in clinical diagnosis of AD.

Hussein et al. (2018) studied the role of CMA for diagnosis of congenital heart defects (CHDs) in neonates. It is known that chromosomal abnormalities or single-gene defects cause a small proportion of CHDs, however many CHDs are unable to be linked to genetic causes due to conventional techniques. The use of CMA can detect pathogenic CNVs or imbalances that other methods cannot. The researchers investigated 94 patients with CHDs that were associated with developmental delay or other malformations. They used a high-density array-CGH 2 x 400K for 41 patients and CGH/SNP microarray 2 x 400k for 53 patients. In certain cases, confirmation was performed using Fluorescent in situ hybridization or qPCR. In 21 of 94 patients (22%) using both conventional cytogenetics and CMA, abnormalities were detected in trisomy 18, 13, 21, microdeletions: del22q11.2, del7q11.23, del18 (p11.32; p11.21), tetrasomy 18p, trisomy 9p, del11q24-q25, add 15p, add (18) (q21.3), and der 9, 15 (q34.2; q11.2). In 15 of 73 cases (20.5%), cryptic chromosomal abnormalities and pathogenic variants were detected. CMA was able to detect loss of heterozygosity in chromosomes in 10 of 25 patients. Cryptic chromosomal anomalies and pathogenic variants were detected in 15/73 (20.5%) cases.

CMA and fragile X syndrome analysis is currently recommended as a first-tier approach for testing of males with intellectual disabilities/learning delay (ID/LD) and ASD (Weinstein et al., 2017). The study analyzed 310 male patients with ID/LD or ASD. Abnormalities were detected by CMA in 29% of males with ID/LD and 9% of males with ASD. The study concluded that this detection rate of CMA in males with ID/LD was higher than that reported in the literature (10-20%).

Grünblatt et al. (2017) evaluated the use of CMA in 121 pediatric obsessive-compulsive disorder (OCD) cases compared to 124 controls to help identify rare and small CNVs which may contribute to early onset OCD. After analysis, the researchers determined that the frequency and size of the observed rare CNVs did not differ statistically between the subject groups, however there was a significant higher frequency of rare CNVs that affect brain related genes in the patient group (OR=1.98). They also determined that there was a significant cluster of predefined genes that are involved in brain related functional pathways that existed in the patient group and not in the control group. The study was able to conclude that these small, rare CNVs may be seen as a susceptibility factor for pediatric OCD.

Bassett et al. (2017) studied genetic factors by CMA and schizophrenia. Schizophrenia has been associated with the 22q11.2 deletion syndrome (22q11.2DS). DNA samples were obtained from 329 psychiatrically phenotyped subjects with 22q11.2DS. CMA and other methods that asses CNV were used to compare the genome outside of the 22q11.2 deletion. Rare CNVs were found that overlapped genes. Six of 19 gene-sets were found in this group and showed interactions with the 22q11.2 deletion region. The results demonstrated that there are additional rare CNVs overlapping genes outside of the 22q11.2 deletion region that may contribute to schizophrenia risk in 22q11.2DS. This supports a multi-genic hypothesis for schizophrenia.

A study by Rambo-Martin et al. (2017) assessed Down syndrome (DS) patients with atrioventricular septal defect (AVSD) who were evaluated with CMA to determine CNV to better understand why AVSD has a higher incidence in this population. This study tested 198 case individuals with DS+AVSD, and 211 control individuals with DS and a normal heart, using a custom microarray with dense probes tiled on chromosome 21 for array CGH (aCGH). The researchers found that neither an individual chromosome 21 CNV nor any individual gene intersected by a CNV was associated with AVSD in DS. This added to the literature that AVSD in Down syndrome is heterogeneous.

Pfundt et al. (2016) assessed the diagnostic yield and potential clinical utility of a high-density chromosomal microarray (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. The authors concluded that the assay's diagnostic yields are similar to those found in other studies of CMAs.

Fry et al. (2016) evaluated 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. Seven (8.8%) of the patients had at least one rare CNV 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.

In a clinical guideline for the recognition, referral and diagnosis of children and young people with autism, the National Institute for Health and Care Excellence (NICE) 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 (NICE, 2011).

Professional Societies

American Academy of Pediatrics (AAP)

In a 2014 clinical report, the Committee on Genetics AAP stated 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. The authors recommend that chromosomal microarray should be performed in all children with intellectual disability (ID) or global developmental delays (GDDs) (Moeschler and Shevell, 2014).

In a guidance for the identification and evaluation of autism spectrum disorders (ASDs), the AAP stated that microarray aCGH is a promising tool that may become standard of care in the future, but this technique has not been evaluated systematically in children with ASDs (Johnson, et al. 2007, Reaffirmed September 2010).

American Academy of Neurology (AAN)

In a model coverage policy for chromosomal microarray analysis for intellectual disabilities, the AAN recommends the following inclusion criteria for microarray testing:

- 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 AAN model coverage policy states that the following circumstances limit the value of microarray testing:

- 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.
- Inadequacy of knowledge about the test and the actions required to address the results of the test.
- 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.
- 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 AAN model coverage policy indicates 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 (AAN, 2015).

The Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society systematically reviewed the evidence concerning the diagnostic yield of genetic and metabolic evaluation of

children with global developmental delay or intellectual disability (GDD/ID). Relevant literature was reviewed, abstracted, and classified according to the 4-tiered American Academy of Neurology classification of evidence scheme. The authors concluded that in patients with GDD/ID, microarray testing is diagnostic on average in 7.8% (Class III), G-banded karyotyping is abnormal in at least 4% (Class II and III), and subtelomeric fluorescence in situ hybridization is positive in 3.5% (Class I, II, and III). The authors state that currently, microarray testing can identify only unbalanced copy number changes and is insufficiently sensitive for detecting genetic disorders caused by inversions, balanced insertions, reciprocal translocations, polyploidy, low-level mosaicism (less than 20%–25%), rearrangements in repeat sequences, point mutations, or duplications/deletions that are undetectable at the test's resolution level. According to the authors, there is consensus among clinical geneticists that microarrays should be considered first-line cytogenetic tests, preferred over subtelomeric fluorescence in situ hybridization (StFISH) testing and karyotyping, with karyotyping reserved for patients having signs of a specific chromosomal syndrome (e.g., Down syndrome), a family history of a chromosomal rearrangement, or a parent with a history of multiple miscarriages. In recommendations for future research, the authors state that research is sorely lacking on the medical, social, and financial benefits of having an accurate etiologic diagnosis. It may be that testing for relatively rare in-born errors of metabolism has a more substantial impact on families and society than testing for genetic syndromes, given how often the diagnosis directly influences patient treatment and outcome. The authors state that the ability to rate diagnostic tests on the basis of factors other than diagnostic yield, such as the availability of effective treatment, would have a positive influence on clinical practice (Michelson et al., 2011).

American Academy of Child and Adolescent Psychiatry (AACAP)

The AACAP 2014 guideline on diagnosis and treatment of children and adolescents with autism spectrum disorder (ASD) recommends that all children with ASD have genetic testing as part of their medical management, specifically G-banded karyotyping, fragile X testing, and/or CMA (Volkmar et al., 2014).

American College of Medical Genetics (ACMG)

The 2013 ACMG guideline for identifying the etiology of autism spectrum disorders (ASDs) lists chromosomal microarray (array-comparative genomic hybridization or single-nucleotide polymorphism arrays) as a first tier diagnostic test for the evaluation of ASDs. According to the ACMG, many recognizable syndromes (i.e., Fragile X syndrome, Rett syndrome) have a firmly documented association with ASDs. For these conditions, further investigation into the etiology of the ASD is unnecessary (Schaefer, 2013).

The ACMG published a guideline in 2010 that focused on when CGH should be used. The specific recommendations listed in the 2010 guideline are as follows (Manning and Hudgins, 2010):

- Cytogenetic microarray (CMA) testing for copy number variation (CNV) is recommended as a first-line test in the initial postnatal evaluation of individuals with the following:
  - Multiple anomalies not specific to a well-delineated genetic syndrome
  - Apparently non-syndromic developmental delay/intellectual disability
  - Autism spectrum disorders
- 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 is recommended, particularly via prospective studies and aftermarket analysis.
- Appropriate follow up is recommended in cases of chromosome imbalance identified by CMA, to include cytogenetic/FISH (fluorescence in situ hybridization) studies of the patient, parental evaluation, and clinical genetic evaluation and counseling.

This guideline did not address testing for prenatal gene mutations. These guidelines also do not specify what type of microarray platform should be used (i.e., microarray-based CGH versus SNP microarray), although they do state that any ordering physician should be aware of the information generated and the limitations of the particular test performed.

ACMG Practice Guidelines regarding the interpretation and reporting of microarray results in postnatal clinical settings were published in 2011 and include recommendations regarding how to define the various types of CNVs (pathogenic versus benign versus uncertain significance), the confirmation of abnormal results, the information that should be included in laboratory reports, and how to handle unanticipated or ambiguous results. Of importance, it is noted that if a CMA is identified that has unknown clinical significance, the parents of the proband should be tested to determine if the copy number variant is de novo or inherited, which may allow the clinician to determine the clinical significance of the result (Kearney et al., 2011).

International Standards for Cytogenomic Array (ISCA) Consortium

The ISCA reviewed the literature and meta-analyses on the clinical indications and diagnostic utility of chromosomal microarray testing and issued a consensus statement recommending that CMA be the first-tier clinical diagnostic test for individuals with developmental disabilities or congenital anomalies, followed by specific gene testing for the suspected condition(s) if CMA results are negative (Miller et al., 2010).

Epilepsy

There is insufficient evidence to support the use CMA for the evaluation of patients with epilepsy without an approved co-morbid condition. Further studies with a larger number of patients and longer follow-up are needed to determine if CMA is an appropriate diagnostic tool for patients with only epilepsy.

Coppola et al. (2019) studied 1,255 epileptic patients that also had a comorbid condition, including intellectual disability, psychiatric symptoms, and other neuro/non-neurological symptoms. 10.9% were found to have at least one pathogenic copy number variant (CNV). 1.7% had at least one probable CNV; 1% had more than one probable pathogenic variant. Recently reported CNVs were seen in this study and novel epilepsy candidate genes were also detected. The phenotypic features of pathogenic CNV carriers and non-carriers were compared and patients with non-neurological features, especially dysmorphism, were more likely to have a pathogenic CNV (OR 4.09, CI 2.51-6.68; P=2.34 x $10^{-}9$). The authors concluded that patients who have epilepsy with additional symptoms indicative of a comorbid disorder be considered for CNV detection.

Berg et al. (2017) examined the utility of various genetic testing methodologies when used in children with early life epilepsy. The study took place at 17 US based pediatric hospitals from 2012-2015. 795 families were recruited, and 775 agreed to participate. The median age of onset of symptoms was 7.5 months, and there were 397 girls and 408 boys. Ninety-five had acquired brain injuries. Of the remaining 680 patients, 327 had various forms of genetic testing. 132 had pathogenic variants identified. Diagnostic yield was greatest for epilepsy gene panels (29%), whole exome sequencing (28%) and least for CMA (8%).

d'Orsi et al. (2017) retrospectively investigated 61 adult patients with epilepsy and intellectual disability or other neurodevelopmental disorders by CMA to determine pathogenic CNVs. High resolution CMA was analyzed to detect clinical relevant chromosomal microdeletions and microduplications. CMA identified CNVs in 33 patients analyzed: 11 had an established pathogenic microdeletion/microduplication and 22 were carriers of CNVs of unknown clinical significance. The researchers concluded that high resolution CMA should be evaluated in adult patients with intellectual disability and epilepsy with peculiar clinical features.

U.S. Food and Drug Administration (FDA)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

A search of the FDA website identified an approval (K042279) for the Affymetrix Genechip Microarray Instrumentation System on December 23, 2004. See the following website for more information: http://www.accessdata.fda.gov/cdrh_docs/pdf4/K042279.pdf. (Accessed March 2, 2020)

The CytoScan® DX Assay (Affymetrix, Inc.) was cleared for marketing under the FDA's 510(k) process in January 2014. The FDA classifies the devices a Type II postnatal chromosomal copy number variation detection system. According to documents filed with FDA, CytoScan Dx Assay is 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. The CytoScan DX Assay is a microarray that works with Affymetrix's existing GeneChip technology platform to perform comparative whole-genome hybridization. This device is not intended to be used for standalone diagnostic purposes, preimplantation or prenatal testing or screening, population screening, or for the detection of, or screening for, acquired or somatic genetic aberrations. The FDA's review of the CytoScan Dx Assay included an analytic evaluation of the test's ability to accurately detect numerous chromosomal variations of different types, sizes, and genome locations when compared with several analytically validated test methods. FDA found that the CytoScan Dx Assay could analyze a patient's entire genome and adequately detect chromosome variations in regions of the genome associated with intellectual and developmental disabilities. See the following websites for more information:

- http://www.accessdata.fda.gov/cdrh_docs/pdf13/K130313.pdf
- http://www.accessdata.fda.gov/cdrh_docs/reviews/k130313.pdf

(Accessed March 2, 2020)

Genetic tests are regulated under the Clinical Laboratory Improvement Amendments (CLIA) of 1988. All laboratories offering microarray testing have current CLIA certifications, including Ambry Genetics Corp., ARUP Laboratories, Baylor College of Medicine Medical Genetics Laboratories, GeneDx Inc., LabCorp, Quest Diagnostics Inc., and Signature Genomic Laboratories. See the following website for more information: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/IVDRegulatoryAssistance/ucm124105.htm. (Accessed March 2, 2020)

Additional Products

180K Oligo Array and SNP+CGH Array (Ambry Genetics Corp.); Cytogenomic SNP Microarray (2003414), Cytogenomic SNP Microarray, Prenatal (2002366), and Cytogenomic SNP Microarray, Products of Conception (2005633) (ARUP Laboratories); Chromosomal Microarray Analysis – HR (Test #8655), Chromosomal Microarray Analysis HR + SNP Screen (Test #8665), Chromosomal Microarray Analysis – CytoScan HD SNP Array – Non-Tumor (Test #8650), Targeted Chromosomal Microarray Analysis – Prenatal (Test #8656 [Amniocentesis] or #8657 [CVS]), and Expanded Chromosomal Microarray Analysis – Prenatal (Test #8670 [Amniocentesis] or #8671 [CVS]) (Baylor College of Medicine Medical Genetics Laboratories); Whole-Genome Chromosomal Microarray (GenomeDx), Whole-Genome Chromosomal Microarray, Prenatal, and Whole-Genome Chromosomal Microarray, Products of Conception (GeneDx Inc.); Reveal SNP Microarray- Pediatric; Reveal SNP Microarray – Prenatal, and Reveal SNP Microarray – POC (Integrated Genetics); Chromosomal Microarray, Postnatal, Clarisure Oligo-SNP (Test 16478), Chromosomal Microarray, Prenatal, Clarisure Oligo-SNP (Test 90927), and Chromosomal Microarray, POC, Clarisure Oligo-SNP (Test 90929) (Quest Diagnostics Inc.); Signature ChipOS, Signature ChipOS + SNP, Signature PrenatalChipOS, Signature PrenatalChipOS + SNP, Signature PrenatalChipTE, Signature PrenatalChipTE + SNP (Signature Genomic Laboratories LLC, and FirstStep PLUS® (Affymetrix).

Centers for Medicare and Medicaid Services (CMS)

Medicare does not have a National Coverage Determination (NCD) for chromosome microarray testing for non-oncology conditions. Local Coverage Determinations (LCDs) exist for CPT codes 81228 and 81229; see the LCDs for Biomarkers Overview, MolDX: Molecular Diagnostic Tests (MDT), Molecular Diagnostic Tests (MDT) and Molecular Pathology Procedures. (Accessed March 11, 2020)

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Policy History/Revision Information

Date	Summary of Changes
10/01/2020	**Documentation Requirements** • Updated list of CPT codes with associated documentation requirements to reflect quarterly edits; added 0209U **Applicable Codes** • Updated list of applicable CPT codes to reflect quarterly edits; added 0209U **Supporting Information** • Archived previous policy version 2020T0559Q

Instructions for Use

This Medical Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the member specific benefit plan document must be referenced as the terms of the member specific benefit plan may differ from the standard plan. In the event of a conflict, the member specific benefit plan document governs. Before using this policy, please check the member specific benefit plan document and any applicable federal or state mandates. UnitedHealthcare reserves the right to modify its Policies and Guidelines as necessary. This Medical Policy is provided for informational purposes. It does not constitute medical advice.

This Medical Policy may also be applied to Medicare Advantage plans in certain instances. In the absence of a Medicare National Coverage Determination (NCD), Local Coverage Determination (LCD), or other Medicare coverage guidance, CMS allows a Medicare Advantage Organization (MAO) to create its own coverage determinations, using objective evidence-based rationale relying on authoritative evidence (Medicare IOM Pub. No. 100-16, Ch. 4, §90.5).

UnitedHealthcare may also use tools developed by third parties, such as the MCG™ Care Guidelines, to assist us in administering health benefits. UnitedHealthcare Medical Policies are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.