

# Chromosome Microarray Testing (Non-Oncology Conditions)

Policy Number: LABORATORY 016.24  
Effective Date: January 1, 2023

[➔ Instructions for Use](#)

Table of Contents	Page
<a href="#">Coverage Rationale</a> .....	1
<a href="#">Documentation Requirements</a> .....	2
<a href="#">Definitions</a> .....	2
<a href="#">Applicable Codes</a> .....	2
<a href="#">Description of Services</a> .....	14
<a href="#">Clinical Evidence</a> .....	15
<a href="#">U.S. Food and Drug Administration</a> .....	28
<a href="#">References</a> .....	29
<a href="#">Policy History/Revision Information</a> .....	33
<a href="#">Instructions for Use</a> .....	34

## Related Policies

- [Molecular Oncology Testing for Cancer Diagnosis Prognosis, and Treatment Decisions](#)
- [Preimplantation Genetic Testing and Related Services](#)

## Coverage Rationale

[➔ See Benefit Considerations](#)

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 Clinical Policies:

- The evaluation of cancer is addressed in the Clinical Policy titled [Molecular Oncology Testing for Cancer Diagnosis Prognosis, and Treatment Decisions](#).

- Preimplantation genetic testing (PGT) is addressed in the Clinical Policy titled [Preimplantation Genetic Testing and Related Services](#).

## 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
<b>Chromosome Microarray Testing (Non-Oncology Conditions)</b>	
81228	Medical notes documenting all of the following: <ul style="list-style-type: none"> <li>• Personal history of the condition, if applicable, including age at diagnosis</li> <li>• Complete family history (usually three-generation pedigree) relevant to condition being tested</li> <li>• Genetic testing results of family member, if applicable, and reason for testing</li> <li>• Ethnicity/ancestry (e.g., Ashkenazi Jewish), if reason for testing</li> <li>• Any prior genetic testing results</li> <li>• How clinical management will be impacted based on results of genetic testing</li> <li>• Genetic counseling (if available)</li> </ul>
81229	
81349	
81479	
0209U	
S3870	

\*For code descriptions, refer to 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. (American College of Obstetricians and Gynecologists, Society of Maternal Fetal Medicine, 2020)

**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, 2021)

## 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, dysmorphism), sequence analysis

CPT Code	Description
0209U	Cytogenomic constitutional (genome-wide) analysis, interrogation of genomic regions for copy number, structural changes and areas of homozygosity for chromosomal abnormalities
81228	Cytogenomic (genome-wide) analysis for constitutional chromosomal abnormalities; interrogation of genomic regions for copy number variants, comparative genomic hybridization [CGH] microarray analysis
81229	Cytogenomic (genome-wide) analysis for constitutional chromosomal abnormalities; interrogation of genomic regions for copy number and single nucleotide polymorphism (SNP) variants, comparative genomic hybridization (CGH) microarray analysis
81349	Cytogenomic (genome-wide) analysis for constitutional chromosomal abnormalities; interrogation of genomic regions for copy number and loss-of-heterozygosity variants, low-pass sequencing analysis
81479	Unlisted molecular pathology procedure

*CPT® is a registered trademark of the American Medical Association*

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.A1	SYNGAP1-related intellectual disability
F78.A9	Other genetic related intellectual disability
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

Diagnosis Code	Description
F89	Unspecified disorder of psychological development
H93.25	Central auditory processing disorder
N96	Recurrent pregnancy loss
O02.1	Missed abortion
O02.89	Other abnormal products of conception
O03.4	Incomplete spontaneous abortion without complication
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
O35.00X0	Maternal care for (suspected) central nervous system malformation or damage in fetus, unspecified, not applicable or unspecified
O35.00X1	Maternal care for (suspected) central nervous system malformation or damage in fetus, unspecified, fetus 1
O35.00X2	Maternal care for (suspected) central nervous system malformation or damage in fetus, unspecified, fetus 2
O35.00X3	Maternal care for (suspected) central nervous system malformation or damage in fetus, unspecified, fetus 3
O35.00X4	Maternal care for (suspected) central nervous system malformation or damage in fetus, unspecified, fetus 4
O35.00X5	Maternal care for (suspected) central nervous system malformation or damage in fetus, unspecified, fetus 5
O35.00X9	Maternal care for (suspected) central nervous system malformation or damage in fetus, unspecified, other fetus
O35.01X0	Maternal care for (suspected) central nervous system malformation or damage in fetus, agenesis of the corpus callosum, not applicable or unspecified

Diagnosis Code	Description
O35.01X1	Maternal care for (suspected) central nervous system malformation or damage in fetus, agenesis of the corpus callosum, fetus 1
O35.01X2	Maternal care for (suspected) central nervous system malformation or damage in fetus, agenesis of the corpus callosum, fetus 2
O35.01X3	Maternal care for (suspected) central nervous system malformation or damage in fetus, agenesis of the corpus callosum, fetus 3
O35.01X4	Maternal care for (suspected) central nervous system malformation or damage in fetus, agenesis of the corpus callosum, fetus 4
O35.01X5	Maternal care for (suspected) central nervous system malformation or damage in fetus, agenesis of the corpus callosum, fetus 5
O35.01X9	Maternal care for (suspected) central nervous system malformation or damage in fetus, agenesis of the corpus callosum, other fetus
O35.02X0	Maternal care for (suspected) central nervous system malformation or damage in fetus, anencephaly, not applicable or unspecified
O35.02X1	Maternal care for (suspected) central nervous system malformation or damage in fetus, anencephaly, fetus 1
O35.02X2	Maternal care for (suspected) central nervous system malformation or damage in fetus, anencephaly, fetus 2
O35.02X3	Maternal care for (suspected) central nervous system malformation or damage in fetus, anencephaly, fetus 3
O35.02X4	Maternal care for (suspected) central nervous system malformation or damage in fetus, anencephaly, fetus 4
O35.02X5	Maternal care for (suspected) central nervous system malformation or damage in fetus, anencephaly, fetus 5
O35.02X9	Maternal care for (suspected) central nervous system malformation or damage in fetus, anencephaly, other fetus
O35.03X0	Maternal care for (suspected) central nervous system malformation or damage in fetus, choroid plexus cysts, not applicable or unspecified
O35.03X1	Maternal care for (suspected) central nervous system malformation or damage in fetus, choroid plexus cysts, fetus 1
O35.03X2	Maternal care for (suspected) central nervous system malformation or damage in fetus, choroid plexus cysts, fetus 2
O35.03X3	Maternal care for (suspected) central nervous system malformation or damage in fetus, choroid plexus cysts, fetus 3
O35.03X4	Maternal care for (suspected) central nervous system malformation or damage in fetus, choroid plexus cysts, fetus 4
O35.03X5	Maternal care for (suspected) central nervous system malformation or damage in fetus, choroid plexus cysts, fetus 5
O35.03X9	Maternal care for (suspected) central nervous system malformation or damage in fetus, choroid plexus cysts, other fetus
O35.04X0	Maternal care for (suspected) central nervous system malformation or damage in fetus, encephalocele, not applicable or unspecified
O35.04X1	Maternal care for (suspected) central nervous system malformation or damage in fetus, encephalocele, fetus 1
O35.04X2	Maternal care for (suspected) central nervous system malformation or damage in fetus, encephalocele, fetus 2

Diagnosis Code	Description
O35.04X3	Maternal care for (suspected) central nervous system malformation or damage in fetus, encephalocele, fetus 3
O35.04X4	Maternal care for (suspected) central nervous system malformation or damage in fetus, encephalocele, fetus 4
O35.04X5	Maternal care for (suspected) central nervous system malformation or damage in fetus, encephalocele, fetus 5
O35.04X9	Maternal care for (suspected) central nervous system malformation or damage in fetus, encephalocele, other fetus
O35.05X0	Maternal care for (suspected) central nervous system malformation or damage in fetus, holoprosencephaly, not applicable or unspecified
O35.05X1	Maternal care for (suspected) central nervous system malformation or damage in fetus, holoprosencephaly, fetus 1
O35.05X2	Maternal care for (suspected) central nervous system malformation or damage in fetus, holoprosencephaly, fetus 2
O35.05X3	Maternal care for (suspected) central nervous system malformation or damage in fetus, holoprosencephaly, fetus 3
O35.05X4	Maternal care for (suspected) central nervous system malformation or damage in fetus, holoprosencephaly, fetus 4
O35.05X5	Maternal care for (suspected) central nervous system malformation or damage in fetus, holoprosencephaly, fetus 5
O35.05X9	Maternal care for (suspected) central nervous system malformation or damage in fetus, holoprosencephaly, other fetus
O35.06X0	Maternal care for (suspected) central nervous system malformation or damage in fetus, hydrocephaly, not applicable or unspecified
O35.06X1	Maternal care for (suspected) central nervous system malformation or damage in fetus, hydrocephaly, fetus 1
O35.06X2	Maternal care for (suspected) central nervous system malformation or damage in fetus, hydrocephaly, fetus 2
O35.06X3	Maternal care for (suspected) central nervous system malformation or damage in fetus, hydrocephaly, fetus 3
O35.06X4	Maternal care for (suspected) central nervous system malformation or damage in fetus, hydrocephaly, fetus 4
O35.06X5	Maternal care for (suspected) central nervous system malformation or damage in fetus, hydrocephaly, fetus 5
O35.06X9	Maternal care for (suspected) central nervous system malformation or damage in fetus, hydrocephaly, other fetus
O35.07X0	Maternal care for (suspected) central nervous system malformation or damage in fetus, microcephaly, not applicable or unspecified
O35.07X1	Maternal care for (suspected) central nervous system malformation or damage in fetus, microcephaly, fetus 1
O35.07X2	Maternal care for (suspected) central nervous system malformation or damage in fetus, microcephaly, fetus 2
O35.07X3	Maternal care for (suspected) central nervous system malformation or damage in fetus, microcephaly, fetus 3
O35.07X4	Maternal care for (suspected) central nervous system malformation or damage in fetus, microcephaly, fetus 4

Diagnosis Code	Description
O35.07X5	Maternal care for (suspected) central nervous system malformation or damage in fetus, microcephaly, fetus 5
O35.07X9	Maternal care for (suspected) central nervous system malformation or damage in fetus, microcephaly, other fetus
O35.08X0	Maternal care for (suspected) central nervous system malformation or damage in fetus, spina bifida, not applicable or unspecified
O35.08X1	Maternal care for (suspected) central nervous system malformation or damage in fetus, spina bifida, fetus 1
O35.08X2	Maternal care for (suspected) central nervous system malformation or damage in fetus, spina bifida, fetus 2
O35.08X3	Maternal care for (suspected) central nervous system malformation or damage in fetus, spina bifida, fetus 3
O35.08X4	Maternal care for (suspected) central nervous system malformation or damage in fetus, spina bifida, fetus 4
O35.08X5	Maternal care for (suspected) central nervous system malformation or damage in fetus, spina bifida, fetus 5
O35.08X9	Maternal care for (suspected) central nervous system malformation or damage in fetus, spina bifida, other fetus
O35.09X0	Maternal care for (suspected) other central nervous system malformation or damage in fetus, not applicable or unspecified
O35.09X1	Maternal care for (suspected) other central nervous system malformation or damage in fetus, fetus 1
O35.09X2	Maternal care for (suspected) other central nervous system malformation or damage in fetus, fetus 2
O35.09X3	Maternal care for (suspected) other central nervous system malformation or damage in fetus, fetus 3
O35.09X4	Maternal care for (suspected) other central nervous system malformation or damage in fetus, fetus 4
O35.09X5	Maternal care for (suspected) other central nervous system malformation or damage in fetus, fetus 5
O35.09X9	Maternal care for (suspected) other central nervous system malformation or damage in fetus, other fetus
O35.10X0	Maternal care for (suspected) chromosomal abnormality in fetus, unspecified, not applicable or unspecified
O35.10X1	Maternal care for (suspected) chromosomal abnormality in fetus, unspecified, fetus 1
O35.10X2	Maternal care for (suspected) chromosomal abnormality in fetus, unspecified, fetus 2
O35.10X3	Maternal care for (suspected) chromosomal abnormality in fetus, unspecified, fetus 3
O35.10X4	Maternal care for (suspected) chromosomal abnormality in fetus, unspecified, fetus 4
O35.10X5	Maternal care for (suspected) chromosomal abnormality in fetus, unspecified, fetus 5
O35.10X9	Maternal care for (suspected) chromosomal abnormality in fetus, unspecified, other fetus
O35.11X0	Maternal care for (suspected) chromosomal abnormality in fetus, Trisomy 13, not applicable or unspecified
O35.11X1	Maternal care for (suspected) chromosomal abnormality in fetus, Trisomy 13, fetus 1
O35.11X2	Maternal care for (suspected) chromosomal abnormality in fetus, Trisomy 13, fetus 2
O35.11X3	Maternal care for (suspected) chromosomal abnormality in fetus, Trisomy 13, fetus 3
O35.11X4	Maternal care for (suspected) chromosomal abnormality in fetus, Trisomy 13, fetus 4
O35.11X5	Maternal care for (suspected) chromosomal abnormality in fetus, Trisomy 13, fetus 5
O35.11X9	Maternal care for (suspected) chromosomal abnormality in fetus, Trisomy 13, other fetus
O35.12X0	Maternal care for (suspected) chromosomal abnormality in fetus, Trisomy 18, not applicable or unspecified
O35.12X1	Maternal care for (suspected) chromosomal abnormality in fetus, Trisomy 18, fetus 1

Diagnosis Code	Description
O35.12X2	Maternal care for (suspected) chromosomal abnormality in fetus, Trisomy 18, fetus 2
O35.12X3	Maternal care for (suspected) chromosomal abnormality in fetus, Trisomy 18, fetus 3
O35.12X4	Maternal care for (suspected) chromosomal abnormality in fetus, Trisomy 18, fetus 4
O35.12X5	Maternal care for (suspected) chromosomal abnormality in fetus, Trisomy 18, fetus 5
O35.12X9	Maternal care for (suspected) chromosomal abnormality in fetus, Trisomy 18, other fetus
O35.13X0	Maternal care for (suspected) chromosomal abnormality in fetus, Trisomy 21, not applicable or unspecified
O35.13X1	Maternal care for (suspected) chromosomal abnormality in fetus, Trisomy 21, fetus 1
O35.13X2	Maternal care for (suspected) chromosomal abnormality in fetus, Trisomy 21, fetus 2
O35.13X3	Maternal care for (suspected) chromosomal abnormality in fetus, Trisomy 21, fetus 3
O35.13X4	Maternal care for (suspected) chromosomal abnormality in fetus, Trisomy 21, fetus 4
O35.13X5	Maternal care for (suspected) chromosomal abnormality in fetus, Trisomy 21, fetus 5
O35.13X9	Maternal care for (suspected) chromosomal abnormality in fetus, Trisomy 21, other fetus
O35.14X0	Maternal care for (suspected) chromosomal abnormality in fetus, Turner Syndrome, not applicable or unspecified
O35.14X1	Maternal care for (suspected) chromosomal abnormality in fetus, Turner Syndrome, fetus 1
O35.14X2	Maternal care for (suspected) chromosomal abnormality in fetus, Turner Syndrome, fetus 2
O35.14X3	Maternal care for (suspected) chromosomal abnormality in fetus, Turner Syndrome, fetus 3
O35.14X4	Maternal care for (suspected) chromosomal abnormality in fetus, Turner Syndrome, fetus 4
O35.14X5	Maternal care for (suspected) chromosomal abnormality in fetus, Turner Syndrome, fetus 5
O35.14X9	Maternal care for (suspected) chromosomal abnormality in fetus, Turner Syndrome, other fetus
O35.15X0	Maternal care for (suspected) chromosomal abnormality in fetus, sex chromosome abnormality, not applicable or unspecified
O35.15X1	Maternal care for (suspected) chromosomal abnormality in fetus, sex chromosome abnormality, fetus 1
O35.15X2	Maternal care for (suspected) chromosomal abnormality in fetus, sex chromosome abnormality, fetus 2
O35.15X3	Maternal care for (suspected) chromosomal abnormality in fetus, sex chromosome abnormality, fetus 3
O35.15X4	Maternal care for (suspected) chromosomal abnormality in fetus, sex chromosome abnormality, fetus 4
O35.15X5	Maternal care for (suspected) chromosomal abnormality in fetus, sex chromosome abnormality, fetus 5
O35.15X9	Maternal care for (suspected) chromosomal abnormality in fetus, sex chromosome abnormality, other fetus
O35.19X0	Maternal care for (suspected) chromosomal abnormality in fetus, other chromosomal abnormality, not applicable or unspecified
O35.19X1	Maternal care for (suspected) chromosomal abnormality in fetus, other chromosomal abnormality, fetus 1
O35.19X2	Maternal care for (suspected) chromosomal abnormality in fetus, other chromosomal abnormality, fetus 2
O35.19X3	Maternal care for (suspected) chromosomal abnormality in fetus, other chromosomal abnormality, fetus 3
O35.19X4	Maternal care for (suspected) chromosomal abnormality in fetus, other chromosomal abnormality, fetus 4
O35.19X5	Maternal care for (suspected) chromosomal abnormality in fetus, other chromosomal abnormality, fetus 5
O35.19X9	Maternal care for (suspected) chromosomal abnormality in fetus, other chromosomal abnormality, other fetus



Diagnosis Code	Description
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
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
O35.AXX0	Maternal care for other (suspected) fetal abnormality and damage, fetal facial anomalies, not applicable or unspecified
O35.AXX1	Maternal care for other (suspected) fetal abnormality and damage, fetal facial anomalies, fetus 1
O35.AXX2	Maternal care for other (suspected) fetal abnormality and damage, fetal facial anomalies, fetus 2
O35.AXX3	Maternal care for other (suspected) fetal abnormality and damage, fetal facial anomalies, fetus 3
O35.AXX4	Maternal care for other (suspected) fetal abnormality and damage, fetal facial anomalies, fetus 4
O35.AXX5	Maternal care for other (suspected) fetal abnormality and damage, fetal facial anomalies, fetus 5
O35.AXX9	Maternal care for other (suspected) fetal abnormality and damage, fetal facial anomalies, other fetus
O35.BXX0	Maternal care for other (suspected) fetal abnormality and damage, fetal cardiac anomalies, not applicable or unspecified
O35.BXX1	Maternal care for other (suspected) fetal abnormality and damage, fetal cardiac anomalies, fetus 1
O35.BXX2	Maternal care for other (suspected) fetal abnormality and damage, fetal cardiac anomalies, fetus 2
O35.BXX3	Maternal care for other (suspected) fetal abnormality and damage, fetal cardiac anomalies, fetus 3
O35.BXX4	Maternal care for other (suspected) fetal abnormality and damage, fetal cardiac anomalies, fetus 4
O35.BXX5	Maternal care for other (suspected) fetal abnormality and damage, fetal cardiac anomalies, fetus 5
O35.BXX9	Maternal care for other (suspected) fetal abnormality and damage, fetal cardiac anomalies, other fetus
O35.CXX0	Maternal care for other (suspected) fetal abnormality and damage, fetal pulmonary anomalies, not applicable or unspecified
O35.CXX1	Maternal care for other (suspected) fetal abnormality and damage, fetal pulmonary anomalies, fetus 1
O35.CXX2	Maternal care for other (suspected) fetal abnormality and damage, fetal pulmonary anomalies, fetus 2
O35.CXX3	Maternal care for other (suspected) fetal abnormality and damage, fetal pulmonary anomalies, fetus 3
O35.CXX4	Maternal care for other (suspected) fetal abnormality and damage, fetal pulmonary anomalies, fetus 4
O35.CXX5	Maternal care for other (suspected) fetal abnormality and damage, fetal pulmonary anomalies, fetus 5
O35.CXX9	Maternal care for other (suspected) fetal abnormality and damage, fetal pulmonary anomalies, other fetus
O35.DXX0	Maternal care for other (suspected) fetal abnormality and damage, fetal gastrointestinal anomalies, not applicable or unspecified
O35.DXX1	Maternal care for other (suspected) fetal abnormality and damage, fetal gastrointestinal anomalies, fetus 1

Diagnosis Code	Description
O35.DXX2	Maternal care for other (suspected) fetal abnormality and damage, fetal gastrointestinal anomalies, fetus 2
O35.DXX3	Maternal care for other (suspected) fetal abnormality and damage, fetal gastrointestinal anomalies, fetus 3
O35.DXX4	Maternal care for other (suspected) fetal abnormality and damage, fetal gastrointestinal anomalies, fetus 4
O35.DXX5	Maternal care for other (suspected) fetal abnormality and damage, fetal gastrointestinal anomalies, fetus 5
O35.DXX9	Maternal care for other (suspected) fetal abnormality and damage, fetal gastrointestinal anomalies, other fetus
O35.EXX0	Maternal care for other (suspected) fetal abnormality and damage, fetal genitourinary anomalies, not applicable or unspecified
O35.EXX1	Maternal care for other (suspected) fetal abnormality and damage, fetal genitourinary anomalies, fetus 1
O35.EXX2	Maternal care for other (suspected) fetal abnormality and damage, fetal genitourinary anomalies, fetus 2
O35.EXX3	Maternal care for other (suspected) fetal abnormality and damage, fetal genitourinary anomalies, fetus 3
O35.EXX4	Maternal care for other (suspected) fetal abnormality and damage, fetal genitourinary anomalies, fetus 4
O35.EXX5	Maternal care for other (suspected) fetal abnormality and damage, fetal genitourinary anomalies, fetus 5
O35.EXX9	Maternal care for other (suspected) fetal abnormality and damage, fetal genitourinary anomalies, other fetus
O35.FXX0	Maternal care for other (suspected) fetal abnormality and damage, fetal musculoskeletal anomalies of trunk, not applicable or unspecified
O35.FXX1	Maternal care for other (suspected) fetal abnormality and damage, fetal musculoskeletal anomalies of trunk, fetus 1
O35.FXX2	Maternal care for other (suspected) fetal abnormality and damage, fetal musculoskeletal anomalies of trunk, fetus 2
O35.FXX3	Maternal care for other (suspected) fetal abnormality and damage, fetal musculoskeletal anomalies of trunk, fetus 3
O35.FXX4	Maternal care for other (suspected) fetal abnormality and damage, fetal musculoskeletal anomalies of trunk, fetus 4
O35.FXX5	Maternal care for other (suspected) fetal abnormality and damage, fetal musculoskeletal anomalies of trunk, fetus 5
O35.FXX9	Maternal care for other (suspected) fetal abnormality and damage, fetal musculoskeletal anomalies of trunk, other fetus
O35.GXX0	Maternal care for other (suspected) fetal abnormality and damage, fetal upper extremities anomalies, not applicable or unspecified
O35.GXX1	Maternal care for other (suspected) fetal abnormality and damage, fetal upper extremities anomalies, fetus 1
O35.GXX2	Maternal care for other (suspected) fetal abnormality and damage, fetal upper extremities anomalies, fetus 2
O35.GXX3	Maternal care for other (suspected) fetal abnormality and damage, fetal upper extremities anomalies, fetus 3
O35.GXX4	Maternal care for other (suspected) fetal abnormality and damage, fetal upper extremities anomalies, fetus 4
O35.GXX5	Maternal care for other (suspected) fetal abnormality and damage, fetal upper extremities anomalies, fetus 5
O35.GXX9	Maternal care for other (suspected) fetal abnormality and damage, fetal upper extremities anomalies, other fetus

Diagnosis Code	Description
O35.HXX0	Maternal care for other (suspected) fetal abnormality and damage, fetal lower extremities anomalies, not applicable or unspecified
O35.HXX1	Maternal care for other (suspected) fetal abnormality and damage, fetal lower extremities anomalies, fetus 1
O35.HXX2	Maternal care for other (suspected) fetal abnormality and damage, fetal lower extremities anomalies, fetus 2
O35.HXX3	Maternal care for other (suspected) fetal abnormality and damage, fetal lower extremities anomalies, fetus 3
O35.HXX4	Maternal care for other (suspected) fetal abnormality and damage, fetal lower extremities anomalies, fetus 4
O35.HXX5	Maternal care for other (suspected) fetal abnormality and damage, fetal lower extremities anomalies, fetus 5
O35.HXX9	Maternal care for other (suspected) fetal abnormality and damage, fetal lower extremities anomalies, 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
Q21.10	Atrial septal defect, unspecified
Q21.11	Secundum atrial septal defect
Q21.12	Patent foramen ovale
Q21.13	Coronary sinus atrial septal defect
Q21.14	Superior sinus venosus atrial septal defect
Q21.15	Inferior sinus venosus atrial septal defect
Q21.16	Sinus venosus atrial septal defect, unspecified
Q21.19	Other specified atrial septal defect
Q21.20	Atrioventricular septal defect, unspecified as to partial or complete
Q21.21	Partial atrioventricular septal defect
Q21.22	Transitional atrioventricular septal defect
Q21.23	Complete atrioventricular septal defect

Diagnosis Code	Description
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
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)

Diagnosis Code	Description
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
Q93.3	Deletion of short arm of chromosome 4
Q93.4	Deletion of short arm of chromosome 5
Q93.51	Angelman syndrome
Q93.59	Other deletions of part of a chromosome
Q93.7	Deletions with other complex rearrangements
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	Triples, some liveborn

Diagnosis Code	Description
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.

## 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

Xia et al. (2020) examined the value of CMA in prenatal diagnosis by analyzing the results of chromosome karyotype analysis and CMA of 477 cases undergoing amniocentesis from January 2016 to December 2019. Results of the normal ultrasound group and the ultrasound abnormality group were compared separately. Within the ultrasound abnormality group, the results of three different groups, the structural malformation group, the soft index abnormality group, and other abnormality (including abnormal amniotic fluid volume and fetal growth restriction) group, were compared. Abnormal karyotype and CMA results were found in a total of 71 cases (15.88%, 71/447); 23 karyotype abnormalities (5.15%, 23/447), consisting of 18 cases of aneuploidy (4.03%, 18/447), 2 cases of unbalanced chromosome rearrangements (0.44%, 2/447), and 3 cases of chimerism (0.67%, 3/447); 17 cases with detection of pathogenic copy number variations (pCNVs) (3.80%, 17/447); and 31 cases of detection of clinical variants of unknown significance (VUS) (6.93%, 31/447). CMA detected 3.8% more genetic abnormalities than karyotype analysis. Between the normal ultrasound group and the ultrasound abnormality group, there was a significant difference in the detection rate of an abnormal chromosomal karyotype ( $P < 0.01$ ) and of VUS ( $P < 0.01$ ), but there was no significant difference in the detection rate of pCNV ( $P > 0.05$ ). Comparing the ultrasound structural malformation group, the ultrasound soft index abnormality group, and the other ultrasound abnormality group, there were no significant differences in the detection rate of abnormal chromosomal karyotypes ( $P > 0.05$ ), pCNV ( $P > 0.05$ ) or VUS ( $P > 0.05$ ). Among the single malformation group, the detection rate of pathogenic CNVs was highest in the cleft lip and palate group. The authors summarized that the detection rate of chromosomal karyotype abnormalities in prenatal diagnosis in cases with normal ultrasounds was higher. For cases with fetal ultrasound structural abnormalities, when compared with traditional karyotype analysis, CMA improved the detection rate of fetal genetic abnormalities. However, the normal ultrasound group also had a high VUS abnormality detection rate, so it is necessary to strictly define the CMA indications.

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 CNVs in low and high risk prenatal and postnatal samples. The cohort was grouped according to 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 postnatal 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 study 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 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; one 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 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 sub chromosomal 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 six (4.7%) SGA fetuses and pathogenic sub chromosomal anomalies in four (3.1%) by CMA. The researchers concluded that there was a 3.3% incremental yield of sub chromosomal anomalies in CMA above karyotyping in SGA fetuses.

Gliem et al. (2017) studied the use of CMA for the testing of 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 CMA 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, CMA 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 CNVs by genomic microarray over karyotyping in fetuses with increased 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 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 VUS 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 VUS 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 POC 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 VUS 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 VUS, 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

Geffen et al. (2020) examined the prevalence of pathogenic and likely-pathogenic variants detected by CMA in pregnancies with ultrasound findings of fetal short, long bones. The cohort included 66 cases of CMA performed nationwide with the indication of short, long bones; 6% (n = 4) cases had pathogenic/likely pathogenic results. Chromosome anomaly rates were significantly increased compared to the background risk for CNV in pregnancies with no ultrasound abnormalities (P < 0.001). The authors reported that the yield of CMA in their study was significantly higher for both isolated and non-isolated cases, for cases in which the lowest determined bone length percentile was over the 3<sup>rd</sup> percentile (below 5<sup>th</sup> percentile) and for cases diagnosed with short bones after 22 weeks but not after 24 weeks. It was concluded by the authors that CMA should be offered in pregnancies with fetal short, long bone diagnosis due to the significantly higher likelihood of CMA yield compared to background risk in pregnancies with no ultrasound findings.

The University of California-San Francisco performed a retrospective study of prenatally diagnosed non-immune hydrops fetalis (NIHF) from 2008-2018. Mardy et al. (2020) reported on the 131 cases which revealed 43/44 cases had CMA performed and results were categorized as normal or likely benign. One case had a large, pathogenic duplication. The authors stated that these results demonstrated the low diagnostic utility of CMA for NIHF.

Pasternak et al. (2020) analyzed the diagnostic yield of CMA among pregnancies terminated for fetal malformations detected on ultrasound. CMA was performed for 71 pregnancies using fetal or placental DNA. The authors reported that "Findings were abnormal in 17 cases (23.9%), 13 of which were detectable by karyotype. The incremental yield of CMA was 4/71 (5.6%); 1/32 (3.1%) for cases with an isolated anomaly and 3/39 (7.7%) for cases with non-isolated anomalies."

Song et al. (2020) conducted a retrospective study of the prenatal diagnosis and pregnancy outcomes of fetuses diagnosed with CNS anomalies and evaluated the clinical utility of CMA. At the Air Force Medical University from January 2015 to August 2018, 356 fetuses with CNS anomalies with or without additional ultrasound anomalies underwent prenatal genetic testing. Fetal karyotype and CMA were performed concurrently; 20 cases of diagnosed fetal aneuploidy were excluded. Pathogenic CNVs were identified by CMA in 27/336 (8.03%) fetuses; likely pathogenic variants were seen in 8/336 (2.38%), and variants of unknown significance were seen in 11/336 (3.27%) of fetuses. In 222 cases isolated CNS findings and the pathogenic copy number variant had a detection rate of 5.86% (13/222). One hundred fourteen cases with CNS anomalies included additional structural abnormalities, ultrasonographic soft markers and two or more CNS abnormalities; pathogenic CNV rate of 12.3% (14/114). Fetuses with CNS anomalies, the authors concluded, have an increased risk of chromosomal abnormalities and that CNV play a significant role in the etiology of such CNS anomalies. Utilization of CMA would increase the detection rate of pathogenic copy number variants leading to CNS anomalies.

Ni et al. (2019) evaluated 247 fetuses with increased 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 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; two 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 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 CNVs, of which 13 were pathogenic CNVs, five were VUS and two 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 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 CMA 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 CNVs 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). VUS were revealed in 1.6% of patients (n = 6/383). The authors concluded that there was added value of CMA 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).

### ***Clinical Practice Guidelines***

#### **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  $\geq$  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 of 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)

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

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 or 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)/Society for Maternal Fetal Medicine (SMFM)

In a 2020 Obstetric Care Consensus, ACOG and SMFM address microarray analysis as it relates to the management of stillbirth. Microarray analysis is noted to be the preferred method for evaluating stillbirth as it not only detects aneuploidy but correspondingly detects copy number variations that are not measurable by karyotype. Microarray analysis is also more likely to offer a genetic diagnosis due to its success with nonviable tissue, making it particularly valuable in analysis of stillbirths with congenital anomalies or when karyotype outcomes can't be obtained. The consensus document concludes that incorporating microarray analysis into stillbirth work up results in improvements in test success rates and detection of genetic anomalies compared with conventional testing with karyotype.

In a 2016 Committee Opinion on Microarrays and Next-Generation Sequencing Technology (American College of Obstetricians and Gynecologists, 2016a, reaffirmed 2020), 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)

SMFM Consult Series Number 52 (2020): Diagnosis and management of fetal growth restriction (replaces Clinical Guideline Number 3, 2012) recommends:

- Pregnant women should be offered fetal diagnostic testing, including chromosomal microarray (CMA), when fetal growth restriction (FGR) is detected and a fetal malformation, polyhydramnios, or both are present regardless of gestational age.
- Pregnant women should be offered prenatal diagnosis testing with CMA when unexplained isolated FGR is diagnosed < 32 weeks of gestation.

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 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 was 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 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.

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 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 DD, 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 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 CMA 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

Harris et al. (2020) reported on the diagnostic yield of genetic testing in toddlers with a Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition diagnosis of ASD. A retrospective chart review including 500 toddlers with ASD was conducted; genetic testing results were divided into normal and negative results, VUS, and pathogenic. 59.8% (n = 299) of subjects completed genetic testing and 12.0% (n = 36) had pathogenic results. No significant differences in Bayley Scales of Infant Development cognitive (P = .112), language (P = .898), or motor scores (P = .488) among toddlers with negative or normal findings compared to a variant of unknown significance versus pathogenic findings were reported. Medical recommendations following the genetic findings were made in 72.2% of those with pathogenic results. The authors concluded that these results confirm the importance of genetic testing in toddlers diagnosed with ASD due to the 12% yield and lack of phenotypic differences between subjects with and without pathogenic findings.

A retrospective study conducted by Hureau 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 Kleeftstra 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 DD/ID, 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. VUS 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 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 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 assess 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 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.

## ***Clinical Practice Guidelines***

### **American Academy of Pediatrics (AAP)**

A clinical report by Lipkin & Macias (2020) regarding the identification of infants/children with DD recommends that “A child with suspected global developmental delay or intellectual disability should have genetic testing including chromosomal microarray and Fragile-X...and the preliminary genetic work-up of such child should also include chromosomal microarray and Fragile-X testing.”

In 2020, the AAP (Hyman et al.) published a clinical report addressing the identification, evaluation, and management of children with autism spectrum disorder (ASD). The report indicates that in the last ten years the development of CMA and other technologies has led to evolution and understanding of the multifaceted genetics of ASD. The identification of genetic etiology provides clinicians additional evidence for families about the prognosis and recurring risk which contributes to identifying, treating, and avoiding co-occurring medical situations. Additionally, the genetic etiology identification permits clinicians the information to guide patients and families to disorder specific resources and supports and avoid the collection of unnecessary tests. CMA recognizes copy number variants (CNV), therefore, is the suggested testing if the etiology for developmental disability is unknown. The development of CMA and next-generation sequencing have given rise to identification of large-effect rare variants, including CNVs, that may be related to ASD.

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

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)

### 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)

### 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)

In a 2021 revision to the technical standard of the ACMG, Shao et al. state that chromosomal microarray technologies are well accepted and used in evaluation of both constitutional and neoplastic disorders. For chromosomal imbalances related to multiple congenital anomalies, autism, and/or intellectual disability, chromosomal microarray testing (including both array comparative genomic hybridization (CGH) and single nucleotide polymorphism array) are considered the first-tier test. In the case of individuals where ultrasound has identified major fetal structural abnormalities and invasive prenatal diagnostic testing will be performed, chromosome microarray is the recommended test. This is also true for further workup of intrauterine fetal demise or stillbirth when parents/providers make the decision to pursue potential genetic diagnosis.

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 & Mendelsohn, 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 of CMA for 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.

In a comprehensive 2022 systematic review and meta-analysis, Sheidley et al. evaluated the diagnostic yield of genetic tests commonly used for individuals with epilepsy as well as other, nonyield outcomes, including such items as changes in treatment or management, recurrence risk determination, prognostic information, and genetic counseling. One hundred fifty-four articles describing diagnostic yield for 39,094 individuals were included. Of those, 43 were used for assessment of outcomes other than yield. Overall, the diagnostic yield for all test types was 17%. Genome sequencing had the highest yield at 48%, followed by exome sequencing at 24%. Multigene panels had a yield of 19% and CMA had the lowest yield at 9%. Phenotypic factors that were significantly associated with increased yield included presence of developmental and epileptic encephalopathy and/or the presence of comorbid neurodevelopmental conditions. The authors call out the need for prospective evaluation of clinical utility of commonly used genetic tests for epilepsy to help to standardize reporting of patient characteristics and help support clinician decision making. (Publications by Coppola (2019), Berg (2017) and d'Orsi (2017) previously cited in this policy were included in the Sheidley (2022) systematic review and meta-analysis.

## 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. Refer to the following website for more information:

[http://www.accessdata.fda.gov/cdrh\\_docs/pdf4/K042279.pdf](http://www.accessdata.fda.gov/cdrh_docs/pdf4/K042279.pdf). (Accessed February 25, 2022)

The CytoScan® DX Assay (Affymetrix, Inc.) was cleared for marketing under the FDA's 510(k) process in January 2014. The FDA classifies the device 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. Refer to the following websites for more information:

- [http://www.accessdata.fda.gov/cdrh\\_docs/pdf13/K130313.pdf](http://www.accessdata.fda.gov/cdrh_docs/pdf13/K130313.pdf)
- [http://www.accessdata.fda.gov/cdrh\\_docs/reviews/k130313.pdf](http://www.accessdata.fda.gov/cdrh_docs/reviews/k130313.pdf)

(Accessed February 25, 2022)

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. Refer to the following website for more information:

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/IVDRegulatoryAssistance/ucm124105.htm>. (Accessed February 25, 2022)

## 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).

## References

The foregoing Oxford policy has been adapted from an existing UnitedHealthcare national policy that was researched, developed and approved by UnitedHealthcare Medical Technology Assessment Committee. [2022T0559V]

American Academy of Neurology (AAN). Model Coverage Policy. Chromosomal microarray analysis for intellectual disabilities. March 2015. Available at: [https://www.aan.com/siteassets/home-page/tools-and-resources/practicing-neurologist-administrators/billing-and-coding/model-coverage-policies/15microarrayanalysismodel\\_tr.pdf](https://www.aan.com/siteassets/home-page/tools-and-resources/practicing-neurologist-administrators/billing-and-coding/model-coverage-policies/15microarrayanalysismodel_tr.pdf). Accessed February 25, 2022.

American College of Obstetricians and Gynecologists (ACOG). ACOG Committee Opinion #682. Microarrays and next generation sequencing technology: the use of advanced genetic diagnostic tools in obstetrics and gynecology. December 2016a. Reaffirmed 2020. Available at [www.acog.org](http://www.acog.org). Accessed February 25, 2022.

American College of Obstetricians and Gynecologists; Society for Maternal-Fetal Medicine. Obstetric care consensus #10: management of stillbirth: (Replaces Practice Bulletin Number 102, March 2009). Am J Obstet Gynecol. 2020 Mar;222(3):B2-B20. Available at [www.acog.org](http://www.acog.org). Accessed February 25, 2022.

American College of Obstetricians and Gynecologists (ACOG). ACOG Practice Bulletin #162. Prenatal diagnostic testing for genetic disorders. May 2016b. Available at: [www.acog.org](http://www.acog.org). Accessed February 25, 2022.

Armour CM, Dougan SD, Brock JA, et al.; On-Behalf-Of the Canadian College of Medical Geneticists. Practice guideline: joint CCMG-SOGC recommendations for the use of chromosomal microarray analysis for prenatal diagnosis and assessment of fetal loss in Canada. *J Med Genet*. 2018 Apr;55(4):215-221.

Audibert F, De Bie I, Johnson JA, et al. No. 348-Joint SOGC-CCMG guideline: update on prenatal screening for fetal aneuploidy, fetal anomalies, and adverse pregnancy outcomes. *J Obstet Gynaecol Can*. 2017 Sep;39(9):805-817.

Baldwin EL, Lee JY, Blake DM, et al. Enhanced detection of clinically relevant genomic imbalances using a targeted plus whole genome oligonucleotide microarray. *Genet Med*. 2008;10(6):415-429.

Bartnik M, Wiśniowiecka-Kowalik B, Nowakowska B, et al. The usefulness of array comparative genomic hybridization in clinical diagnostics of intellectual disability in children. *Dev Period Med*. 2014 Jul-Sep;18(3):307-17.

Bassett AS, Lowther C, Merico D, et al. Rare genome-wide copy number variation and expression of Schizophrenia in 22q11.2 Deletion Syndrome. *Am J Psychiatry*. 2017;174(11):1054-1063.

Battaglia A, Doccini V, Bernardini L, et al. Confirmation of chromosomal microarray as a first-tier clinical diagnostic test for individuals with developmental delay, intellectual disability, autism spectrum disorders and dysmorphic features. *Eur J Paediatr Neurol*. 2013 Nov;17(6):589-99.

Berg AT, Coryell J, Saneto RP, et al. Early-life epilepsies and the emerging role of genetic testing. *JAMA Pediatr*. 2017 Sep 1;171(9):863-871.

Brady PD, Delle Chiaie B, Christenhusz G, et al. A prospective study of the clinical utility of prenatal chromosomal microarray analysis in fetuses with ultrasound abnormalities and an exploration of a framework for reporting unclassified variants and risk factors. *Genet Med*. 2014 Jun;16(6):469-76.

Bui TH, Vetro A, Zuffardi O, et al. Current controversies in prenatal diagnosis 3: is conventional chromosome analysis necessary in the post-array CGH era? *Prenat Diagn*. 2011 Mar;31(3):235-43.

Cai M, Huang H, Su L, et al. Chromosomal abnormalities and copy number variations in fetal ventricular septal defects. *Mol Cytogenet*. 2018 Nov 28;11:58.

Cherry A, Akkari Y, Barr K, et al. Diagnostic cytogenetic testing following positive noninvasive prenatal screening results: a clinical laboratory practice resource of the American College of Medical Genetics and Genomics (ACMG). *Genet Med*. 2017; 19(8): 845-850.

Coppola A, Cellini E, Stamberger H, et al. Diagnostic implications of genetic copy number variation in epilepsy plus. *Epilepsia*. 2019 Apr; 60(4):689-706.

Cuccaro D, Guarnaccia M, Iemolo R, et al. NeuroArray, A custom CGH microarray to decipher copy number variants in Alzheimer's Disease. *Curr Genomics*. 2018 Sep;19(6):499-504.

de Wit MC, Srebniak MI, Govaerts LC, et al. Additional value of prenatal genomic array testing in fetuses with isolated structural ultrasound abnormalities and a normal karyotype: a systematic review of the literature. *Ultrasound Obstet Gynecol*. 2014 Feb;43(2):139-46.

Dhillon R, Hillman S, Morris R, et al. Additional information from chromosomal microarray analysis (CMA) over conventional karyotyping when diagnosing chromosomal abnormalities in miscarriage: a systematic review and meta-analysis. *BJOG*. 2014 Jan;121(1):11-21.

d'Orsi G, Martino T, Palumbo O, et al. The epilepsy phenotype in adult patients with intellectual disability and pathogenic copy number variants. *Seizure*. 2017 Dec;53:86-93.

Dubbs H. American Academy of Pediatrics. National Coordinating Center for Epilepsy- Overview (2020). Available at: <https://www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/coordinating-center-on-epilepsy/pages/genetic-testing-for-epilepsy.aspx>. Accessed February 25, 2022.

Egloff M, Hervé B, Quibel T, et al. Diagnostic yield of chromosomal microarray analysis in fetuses with isolated increased nuchal translucency: a French multicenter study. *Ultrasound Obstet Gynecol*. 2018 Dec;52(6):715-721.

Fan Y, Wu Y, Wang L, et al. Chromosomal microarray analysis in developmental delay and intellectual disability with comorbid conditions. *BMC Med Genomics*. 2018 May 24;11(1):49.

Fruhman G, Van den Veyver IB. Applications of array comparative genomic hybridization in obstetrics. *Obstet Gynecol Clin North Am*. 2010 Mar;37(1):71-85.

Fu F, Deng Q, Lei TY, et al. Clinical application of SNP array analysis in fetuses with ventricular septal defects and normal karyotypes. *Arch Gynecol Obstet*. 2017 Nov;296(5):929-940.

Gardiner C, Wellesly D, Kilby MD, et al. Joint Committee on Genomics in Medicine (JCGM). Recommendations for the use of chromosome microarray in pregnancy. Royal College of Pathologists. 2015 Jun. Available at: <https://www.rcpath.org/uploads/assets/06664c28-0f90-4230-86158c91fea14be6/Recommendations-for-the-use-of-chromosome-microarray-in-pregnancy.pdf>. Accessed February 25, 2022.

Geddes GC, Basel D, Frommelt P, et al. Genetic testing protocol reduces costs and increases rate of genetic diagnosis in infants with congenital heart disease. *Pediatric Cardiology*. 2017;38(7):1465-1470.

Geffen K, Singer A, Maya I, et al. Chromosomal microarray should be performed for cases of fetal short long bones detected prenatally. *Arch Gynecol and Obstet*. 2020 Aug; 303: 85-92.

Genetics Glossary (Syndrome). National Genome Institute. 2021. Available at: <https://www.genome.gov/search?terms=syndrome>. Accessed February 25, 2022.

Genetics Home Reference, National Library of Medicine. How are Genetic Conditions Diagnosed? February 2020. Available at: [https://ghr.nlm.nih.gov/primer/consult/diagnosis?\\_ga=2.107334282.928673881.1559156694-1234460177.1559156694](https://ghr.nlm.nih.gov/primer/consult/diagnosis?_ga=2.107334282.928673881.1559156694-1234460177.1559156694). Accessed February 25, 2022.

Gliem TJ, Aypar U. Development of a chromosomal microarray test for the detection of abnormalities in formalin-fixed, paraffin-embedded products of conception specimens. *J Mol Diagn*. 2017 Nov;19(6):843-847.

Grande M, Jansen FA, Blumenfeld YJ, et al. Genomic microarray in fetuses with increased nuchal translucency and normal karyotype: a systematic review and meta-analysis. *Ultrasound Obstet Gynecol*. 2015 Dec;46(6):650-8.

Grünblatt E, Oneda B, Ekici AB, et al. High resolution chromosomal microarray analysis in paediatric obsessive-compulsive disorder. *BMC Med Genomics*. 2017;10(1):68.

Harris HK, Sideridis GD, Barbaresi WJ, et al. Pathogenic yield of genetic testing in autism spectrum disorder. *Pediatrics*. 2020 Oct;146(4):e20193211.

Hay S, Sahoo T, Travis M, et al. ACOG and SMFM guidelines for prenatal diagnosis: Is karyotyping really sufficient? *Prenat Diagn*. 2018 Feb. 38(3):184-189.

Hillman, SC, Pretlove, S, Coomarasamy, A, et al. Additional information from array comparative genomic hybridization technology over conventional karyotyping in prenatal diagnosis: a systematic review and meta-analysis. *Ultrasound Obstet Gynecol*. 2011;37(1):6-14.

Homma TK, Krepischi ACV, Furuya TK, et al. Recurrent copy number variants associated with syndromic short stature of unknown cause. *Horm Res Paediatr*. 2018;89(1):13-21.

Hureaux M, Guterman S, Herve B, et al. Chromosomal microarray analysis in fetuses with an isolated congenital heart defect: A retrospective, nationwide, multicenter study in France. *Prenat Diagn*. 2019 May; 39(6): 464-470.

Hussein IR, Bader RS, Chaudhary AG, et al. Identification of De Novo and rare inherited copy number variants in children with syndromic congenital heart defects. *Pediatr Cardiol*. 2018 Jun;39(5):924-940.

Hyman SL, Levy SE, Myers SM; COUNCIL ON CHILDREN WITH DISABILITIES, SECTION ON DEVELOPMENTAL AND BEHAVIORAL PEDIATRICS. Identification, evaluation, and management of children with autism spectrum disorder. *Pediatrics*. 2020 Jan;145(1):e20193447.

Jang W, Kim Y, Han E, et al. Chromosomal microarray analysis as a first-tier clinical diagnostic test in patients with developmental delay/intellectual disability, autism spectrum disorders, and multiple congenital anomalies: a prospective multicenter study in Korea. *Ann Lab Med*. 2019 May; 39(3):299-310.

Jin H, Yingqiu C, Zequn L, et al. Chromosomal microarray analysis in the prenatal diagnosis of orofacial clefts: Experience from a single medical center in mainland China. *Medicine (Baltimore)*. 2018;97(34):e12057.

Kearney HM, Thorland EC, Brown KK, et al. Working Group of the American College of Medical Genetics Laboratory Quality Assurance Committee. American College of Medical Genetics standards and guidelines for interpretation and reporting of postnatal constitutional copy number variants. *Genet Med*. 2011;13(7):680-685.

Levy B, Wapner R. Prenatal diagnosis by chromosomal microarray analysis. *Fertil Ster.* 2018 Feb; 109(2): 201-212.

Lipkin PH, Macias MM. Promoting optimal development: identifying infants and young children with developmental disorders through developmental surveillance and screening. *Pediatrics.* 2020 Jan;145(1):e20193449.

Manning M, Hudgins L; Professional Practice and Guidelines Committee. Array-based technology and recommendations for utilization in medical genetics practice for detection of chromosomal abnormalities. *Genet Med.* 2010 Nov;12(11):742-5.

Mardy A, Rangwala N, Hernandez-Cruz Y, et al. Utility of chromosomal microarray for diagnosis in cases of non-immune hydrops fetalis. *Prenatal Diagnosis* 2020; 40:492-496.

Martins J, Biggio J, Abuhamad A. Society for Maternal-Fetal Medicine (SMFM) Consult Series #52: Diagnosis and management of fetal growth restriction. 2020 Oct. Available at: [www.smfm.org](http://www.smfm.org). Accessed February 25, 2022.

Maya I, Davidov B, Gershovitz L, et al. Diagnostic utility of array-based comparative genomic hybridization (aCGH) in a prenatal setting. *Prenat Diagn.* 2010 Dec;30(12-13):1131-7.

McCormack A, Claxton K, Ashton F, et al. Microarray testing in clinical diagnosis: an analysis of 5,300 New Zealand patients. *Molecular Cytogenetics.* 2016;9:29.

Miller DT, Adam MP, Aradhya S, et al. Consensus statement: chromosomal microarray is a first-tier clinical diagnostic test for individuals with developmental disabilities or congenital anomalies. *Am J Hum Genet.* 2010;86(5):749-764.

Moeschler JB, Shevell M; Committee on Genetics. Comprehensive evaluation of the child with intellectual disability or global developmental delays. *Pediatrics.* 2014 Sep;134(3):e903-18.

Ni M, Li J, Zhu Y, et al. Application of chromosomal microarray analysis in prenatal diagnosis of fetuses with increased nuchal translucency. *Chinese Journ Med Gen.* 2019 Oct; 36(10): 970-974.

Nicholl J, Waters W, Mulley JC, et al. Array Referral Consortium, Friend K, Bain SM, Yu S. Cognitive deficit and autism spectrum disorders: prospective diagnosis by array CGH. *Pathology.* 2014 Jan;46(1):41-5.

Ozyilmaz B, Kirbiyik O, Koc A, et al. Experiences in microarray-based evaluation of developmental disabilities and congenital anomalies. *Clin Genet.* 2017 Oct;92(4):372-379.

Papoulidis I, Sotiriadis A, Siomou E, et al. Routine use of array comparative genomic hybridization (aCGH) as standard approach for prenatal diagnosis of chromosomal abnormalities. Clinical experience of 1763 prenatal cases. *Prenat Diagn.* 2015 Dec;35(13):1269-77.

Parchem JG, Sparks TN, Gosnell K, et al. Utility of chromosomal microarray in anomalous fetuses. *Prenat Diagn.* 2018 Jan;38(2):140-147.

Pasternak Y, Daykan Y, Tenne T, et al. The yield of chromosomal microarray analysis among pregnancies terminated due to fetal malformations. *J Matern Fetal Neonatal Med.* 2020 Jan 23:1-5.

Pauta M, Grande M, Rodriguez-Revenga L, et al. Added value of Chromosomal Microarray Analysis (CMA) over karyotyping in Early Pregnancy Loss - a Systematic Review and Meta-Analysis. *Ultrasound Obstet Gynecol.* 2017 Oct 21.

Peng R, Yang J, Xie HN, et al. Chromosomal and sub chromosomal anomalies associated too small for gestational age fetuses with no additional structural anomalies. *Prenat Diagn.* 2017 Dec;37(12):1219-1224.

Pfundt R, Kwiatkowski K, Roter A, et al. Clinical performance of the CytoScan Dx Assay in diagnosing developmental delay/intellectual disability. *Genet Med.* 2016 Feb;18(2):168-73.

Rambo-Martin BL, Mulle JG, Cutler DJ, et al. Analysis of copy number variants on chromosome 21 in Down Syndrome-associated congenital heart defects. *G3 (Bethesda).* 2017;8(1):105-111.

Rosenfeld JA, Tucker ME, Escobar LF, et al. Diagnostic utility of microarray testing in pregnancy loss. *Ultrasound Obstet Gynecol.* 2015 Oct;46(4):478-86.

Sagi-Dain L, Maya I, Reches A, et al. Chromosomal microarray analysis results from pregnancies with various ultrasonographic anomalies. *Obstet Gynecol.* 2018 Dec;132(6):1368-1375.

Schaefer GB, Mendelsohn NJ; Professional Practice and Guidelines Committee. Clinical genetics evaluation in identifying the etiology of autism spectrum disorders: 2013 guideline revisions. *Genet Med.* 2013 May;15(5):399-407.

Shaffer LG, Beaudet AL, Brothman AR, et al. Microarray analysis for constitutional cytogenetic abnormalities. *Genet Med.* 2007;9(9):654-662.



Shaffer LG, Rosenfeld JA, Dabell MP, et al. Detection rates of clinically significant genomic alterations by microarray analysis for specific anomalies detected by ultrasound. *Prenat Diagn.* 2012 Oct;32(10):986-95.

Shao L, Akkari Y, Cooley LD et al.; ACMG Laboratory Quality Assurance Committee. Chromosomal microarray analysis, including constitutional and neoplastic disease applications, 2021 revision: a technical standard of the American College of Medical Genetics and Genomics (ACMG). *Genet Med.* 2021 Oct;23(10):1818-1829.

Sheidley BR, Malinowski J, Bergner AL, et al. Genetic testing for the epilepsies: A systematic review. *Epilepsia.* 2022 Feb;63(2):375-387.

Society for Maternal-Fetal Medicine (SMFM). Dugoff L, Norton ME, Kuller JA. The use of chromosomal microarray for prenatal diagnosis. *Am J Obstet Gynecol.* 2016 Oct;215(4):B2-9.

Song T, Xu Y, Li Y, et al. Detection of submicroscopic chromosomal aberrations by chromosomal microarray analysis for the prenatal diagnosis of central nervous system abnormalities. *J Clin Lab Anal.* 2020 Oct;34(10):e23434.

Srebniak MI, Diderich KE, Joosten M, et al. Prenatal SNP array testing in 1000 fetuses with ultrasound anomalies: causative, unexpected and susceptibility CNVs. *Eur J Hum Genet.* 2016 May;24(5):645-51.

Srebniak MI, Joosten M, Knapen M, et al. Frequency of submicroscopic chromosome aberrations in pregnancies without increased risk for structural aberrations: a systematic review of literature and meta-analysis. *Ultrasound Obstet Gynecol.* 2017 Sept; 50(51):205-206.

Sys M, van den Bogaert A, Roosens B, et al. Can clinical characteristics be criteria to perform chromosomal microarray analysis in children and adolescents with autism spectrum disorders? *Minerva Pediatr.* 2018 Jun;70(3):225-232.

Volkmar F, Siegel M, Woodbury-Smith M, et al; American Academy of Child and Adolescent Psychiatry (AACAP) Committee on Quality Issues (CQI). Practice parameter for the assessment and treatment of children and adolescents with autism spectrum disorder. *J Am Acad Child Adolesc Psychiatry.* 2014 Feb;53(2):237-57.

Waggoner D, Wain K, Dubuc A, et al. Yield of additional genetic testing after chromosomal microarray for diagnosis of neurodevelopmental disability and congenital anomalies: a clinical practice resource of the American College of Medical Genetics and Genomics (ACMG). *Genetics in Medicine.* 2018 Oct;20(10):1105-1113.

Wang Y, Gao L, Liang D, et al. Prenatal chromosomal microarray analysis in fetuses with congenital heart disease: a prospective cohort study. *Am J Obstet Gynecol.* 2018 Feb;218(2):244.e1-244.e17.

Wang Y, Li Y, Chen Y, et al. Systematic analysis of copy-number variations associated with early pregnancy loss. *Ultrasound Obstet Gynecol.* 2020 Jan;55(1):96-104.

Weinstein V, Tanpaiboon P, Chapman KA, et al. Do the data really support ordering fragile X testing as a first-tier test without clinical features. *Genet Med.* 2017;19(12):1317-1322.

Xia M, Yang X, Fu J, et al. Application of chromosome microarray analysis in prenatal diagnosis. *BMC Pregnancy and Childbirth.* 2020 Nov 16;20(1):696.

Zhu X, Li J, Zhu Y, et al. Application of chromosomal microarray analysis in products of miscarriage. *Mol Cytogenet.* 2018 Aug 17;11:44.

Zou Z, Huang L, Lin S, et al. Prenatal diagnosis of posterior fossa anomalies: Additional value of chromosomal microarray analysis in fetuses with cerebellar hypoplasia. *Prenat Diagn.* 2018 Jan;38(2):91-98.

## Policy History/Revision Information

Date	Summary of Changes
01/01/2023	<p><b>Documentation Requirements</b></p> <ul style="list-style-type: none"> <li>Added list of applicable CPT/HCPCS codes</li> </ul> <p><b>Supporting Information</b></p> <ul style="list-style-type: none"> <li>Removed <i>Prior Authorization Requirements</i> section</li> <li>Archived previous policy version LABORATORY 016.23 T2</li> </ul>

## Instructions for Use

This Clinical Policy provides assistance in interpreting UnitedHealthcare Oxford 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 Oxford reserves the right to modify its Policies as necessary. This Clinical Policy is provided for informational purposes. It does not constitute medical advice.

The term Oxford includes Oxford Health Plans, LLC and all of its subsidiaries as appropriate for these policies. Unless otherwise stated, Oxford policies do not apply to Medicare Advantage members.

UnitedHealthcare may also use tools developed by third parties, such as the InterQual<sup>®</sup> criteria, to assist us in administering health benefits. UnitedHealthcare Oxford Clinical 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.