Chromosome Microarray Testing (Non-Oncology Conditions)

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Instructions for Use

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Related Community Plan Policies

- Molecular Oncology Testing for Solid Tumor Cancer Diagnosis, Prognosis, and Treatment Decisions
- Preimplantation Genetic Testing and Related Services
- Whole Exome and Whole Genome Sequencing

Commercial Policy

- Chromosome Microarray Testing (Non-Oncology Conditions)

Medicare Advantage Coverage Summary

- Genetic Testing

Application

This Medical Policy does not apply to the states listed below; refer to the state-specific policy/guideline, if noted:

State	Policy/Guideline
Indiana	Chromosome Microarray Testing (Non-Oncology Conditions) (for Indiana Only)
Kentucky	Chromosome Microarray Testing (Non-Oncology Conditions) (for Kentucky Only)
Louisiana	None
Nebraska	Chromosome Microarray Testing (Non-Oncology Conditions) (for Nebraska Only)
New Jersey	Chromosome Microarray Testing (Non-Oncology Conditions) (for New Jersey Only)
North Carolina	Chromosome Microarray Testing (Non-Oncology Conditions) (for North Carolina Only)
Ohio	Chromosome Microarray Testing (Non-Oncology Conditions) (for Ohio Only)
Pennsylvania	Chromosome Microarray Testing (Non-Oncology Conditions) (for Pennsylvania Only)
Tennessee	Chromosome Microarray Testing (Non-Oncology Conditions) (for Tennessee Only)

Coverage Rationale

Pre-test genetic counseling is strongly recommended in order to inform persons being tested about the advantages and limitations of the test as applied to a unique person.

Chromosome microarray testing using array comparative genomic hybridization (aCGH) and/or single-nucleotide polymorphism (SNP) array is proven and medically necessary for the following:

- Evaluation of an embryo/fetus in the following cases:

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    - Intrauterine Fetal Demise or Stillbirth
    - Testing the products of conception following pregnancy loss
    - Individuals 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 that are not specific to a Well-Delineated Genetic Syndrome and cannot be identified by a clinical evaluation alone
    - Developmental Delay/Intellectual Disability where a specific syndrome is not suspected
- Evaluation of biological parent of a fetus or child with an abnormal or equivocal finding on chromosome microarray testing results

Chromosome microarray testing using aCGH or SNP array is unproven and not medically necessary for all other populations and conditions due to insufficient evidence of efficacy.

Note: Preimplantation genetic testing (PGT) is addressed in the Medical Policy titled Preimplantation Genetic Testing and Related Services.

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: A condition diagnosed before age 18 that includes below-average intellectual function and a lack of skills necessary for daily living (MedlinePlus, 2020).

Intrauterine Fetal Demise or Stillbirth: Fetal death at or after 20 weeks gestation [American College of Obstetricians and Gynecologists (ACOG), Society of Maternal Fetal Medicine (SMFM), 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 (ACOG, 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. (Talking Glossary of Genomic and Genetic Terms, National Human Genome Research Institute, 2023). Examples of Well-Delineated Genetic Syndromes include, but are not limited to: Down syndrome, Klinefelter syndrome, Marfan syndrome, neurofibromatosis type 1, osteogenesis imperfecta, Prader-Willi syndrome, Rett syndrome, trisomy 13 (Patau syndrome), trisomy 18 (Edwards syndrome), Turner syndrome, and Williams syndrome.

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 federal, state, or contractual requirements and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

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

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CPT Code	Description
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

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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
F89	Unspecified disorder of psychological development

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Diagnosis Code	Description
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
O35.01X1	Maternal care for (suspected) central nervous system malformation or damage in fetus, agenesis of the corpus callosum, fetus 1

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Diagnosis Code	Description
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
O35.04X3	Maternal care for (suspected) central nervous system malformation or damage in fetus, encephalocele, fetus 3

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Diagnosis Code	Description
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
O35.07X5	Maternal care for (suspected) central nervous system malformation or damage in fetus, microcephaly, fetus 5

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Diagnosis Code	Description
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
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

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Diagnosis Code	Description
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
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

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Diagnosis Code	Description
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
O35.DXX2	Maternal care for other (suspected) fetal abnormality and damage, fetal gastrointestinal anomalies, fetus 2

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Diagnosis Code	Description
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
O35.HXX0	Maternal care for other (suspected) fetal abnormality and damage, fetal lower extremities anomalies, not applicable or unspecified

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Diagnosis Code	Description
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
Q21.3	Tetralogy of Fallot

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Diagnosis Code	Description
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)
Q91.6	Trisomy 13, translocation

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

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Diagnosis Code	Description
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 chromosome microarray testing [also called chromosome microarray analysis (CMA)] in order to inform persons being tested about the advantages and limitations of the test as applied to their unique situation. CMA includes array comparative genomic hybridization (aCGH) and/or single-nucleotide polymorphism (SNP) array.

Chromosome abnormalities are a well-established cause of congenital anomalies, dysmorphic features, Developmental Delay (DD), Intellectual Disability (ID), and other neurodevelopmental disorders. There are two types of CMA that are used for the detection of chromosomal abnormalities: aCGH and SNP array. These tests analyze multiple sequences of deoxyribonucleic acid (DNA) by identifying deletions and duplications across the genome simultaneously. The chromosomal microarray may be targeted in nature, assaying certain regions of the genome known to be associated with a specific syndrome or phenotype and/or may be genome-wide (Shaffer et al., 2007). Currently, most clinical applications of CMA are being investigated for the diagnosis of chromosomal abnormalities in fetuses and newborns, and in children with developmental disorders. For diagnostic prenatal testing, CMA requires an invasive procedure (e.g., amniocentesis or chorionic villous sampling) for the collection of fetal cells.

SNP array testing and aCGH are 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 is detected by conventional chromosome analysis [e.g., standard karyotype or fluorescence in situ hybridization (FISH)]. The aCGH approach detects CNVs of a DNA sequence in an individual by comparing it to a control. The SNP array approach detects CNVs by using DNA probes that are specific to a single base pair site in the genome. The copy number is quantified by either hybridization of the individual's DNA and control DNA (aCGH) or comparison of the individual's DNA to a control reference DNA sequence (SNP array). Areas of unequal hybridization (aCGH) or differences between an individual and reference DNA (SNP array) signify a DNA alteration, such as large deletions or duplications. 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 a CNV of unknown clinical significance 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 CMA include the detection of variants of unknown clinical significance, false positive results that will require further testing, and the inability to detect certain chromosomal abnormalities such as balanced rearrangements where there is no net gain or loss of the chromosomal material (Fruhman and Van den Veyver, 2010; Bui et al., 2011).

Clinical Evidence

Use in Obstetrics

Routine chromosome analysis has been used historically to identify chromosome abnormalities during pregnancy when risk factors are present, such as advanced maternal age and chromosome abnormalities. Chromosome microarray analysis (CMA) does not require cell culture or dividing cells, so it provides an advantage in turn-around time for time sensitive analysis, as is often the case during pregnancy. In addition, CMA can identify smaller chromosomal abnormalities than a routine chromosome analysis and is able to identify chromosomal breakpoints that are unbalanced but may appear balanced on a conventional karyotype. CMA does have limitations; 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 (SMFM), 2016].

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Prenatal Diagnosis

In a 2022 systematic review, meta-analysis and case series, Mastromoro et al. studied diagnostic yields of genetic testing in cases where increased nuchal translucency (NT) was identified and compared these with results found in fetuses where cystic hygroma was detected, aiming to identify the differing chromosomal, genomic and monogenic conditions present in this phenotypic spectrum. In addition, a case series including dicentric fetal findings where karyotyping, CMA and RASopathy panel was performed was gathered. A cohort of 96 fetuses was evaluated. Fetuses with isolated NT of at least 2.5 mm were found to have karyotype anomalies in 22.76% of cases and an incremental detection rate of 2.35% was identified when CMA was used. Those fetuses having isolated NT ≥ 3 mm resulted in an aneuploidy in 14.36% of cases and an incremental detection rate of 3.89% with CMA. When isolated NT was ≥ 3.5 mm, diagnostic yield of the karyotype was 34.35% with an incremental detection rate for CMA of 4.1%. In this group, the RASopathy panel yielded an incremental diagnostic rate of 1.44% and exome sequencing yielded a 2.44% incremental detection rate. The most frequent finding across the group was karyotype abnormalities regardless of size of NT. CMA resulted in a substantial diagnostic yield in fetuses where NT was found to be at least 3.5 mm. The researchers recommend ongoing research to determine the diagnostic rate of CMA at all levels of increased NT with focus on analysis of monogenic conditions where NT measures between 2.5 and 2.9 mm or 2.5 and 3.4 mm in addition to studies which help define the best diagnostic algorithm which may include exome sequencing. Study by Eggloff et al. (2018), previously discussed in this policy, was included in the systematic review and meta-analysis described above.

Mastromoro et al. (2022) also performed a systematic review and meta-analysis focused on the incremental diagnostic yield of CMA in isolated cardiovascular abnormalities in fetuses and calculation of specific yield based on each category of heart disease. The end goal was to provide insight for genetic counseling for each subgroup of cardiovascular anomaly. Additionally, a comparison to the existing literature was performed with a group of fetuses (n = 59) who were found to have isolated cardiovascular malformations but a normal karyotype. After application of exclusion criteria, 18 articles were included in the analysis. The researchers found that in pooled cardiovascular anomalies, the diagnostic incremental yield of CMA was 5.79%; this is higher than the average for structural abnormalities, which verifies the importance of this type of testing. In conotruncal malformations, detection rate was highest at 15.93% and yields for ventricular septal defects and aberrant right subclavian artery were lowest at 2.64% and 0.66%, respectively. The majority of heart conditions evaluated yielded a detection rate in the rage of 4.42% to 6.67%, which did not vary greatly from the overall rate for cardiopathic disease. The highest detection rate (11.28%) was found in tetralogy of Fallot (TOF) which is likely due to the relationship with 22q11.2 deletion syndrome. In the group with cardiac anomalies and normal karyotypes, the diagnostic yield was consistent with the existing literature. The authors assert that CMA used to assess the cause of fetal cardiovascular anomalies in the prenatal setting is a helpful tool; information regarding unique risks associated with each type of cardiac malformation is highly valuable when customizing genetic counseling. Authors Hureaux et al. (2019), Fu et al. (2017), and Shaffer et al. (2012), previously discussed in this policy, were included in this systematic review.

In addition to the studies above, Mastromoro et al. (2022) performed another systematic review of the literature and meta-analysis, this time focused on examining the diagnostic yield and rates of variants of uncertain significance (VUSs) in a group of fetuses who had undergone non-targeted molecular diagnostic testing including CMA, whole exome sequencing (WES) or whole genome sequencing (WGS) related to findings on ultrasound evaluation. The researchers aimed to provide additional insights into the primary molecular testing modalities used in prenatal diagnostics and their use as part of a multidisciplinary evaluation. For CMA, the overall diagnostic yield for mixed anomalies was 5.72%. This included 2.15% for single soft markers (such as transient minor ultrasound findings), 3.44% for multiple soft markers, 3.66% for single structural anomalies and 8.57% for multiple structural anomalies. WES demonstrated a high incremental yield, with diagnostic rate of 19.47% including 27.47% for multiple structural abnormalities. Variability was seen related to the characteristics of participants, class of malformations and number of samples available. VUSs found for fetuses with structural abnormalities were 2.86% for CMA and 8.32% for WES. Existing data was not able to be used for meta-analysis in WGS. The authors assert that for structural anomalies in fetuses, CMA is considered a first-tier test and should be used in conjunction with parental segregation and karyotyping. They recommend considering findings of increased NT, short femur and mild ventriculomegaly to be similar to malformations, separate from other soft markers, and an indication for performing assessment with CMA. They further note that WES presents a very high incremental yield and a substantial VUS rate; as such the use of WES is recommended for selected cases. Further research focused on which findings should truly be considered “soft” markers is recommended in order to further refine testing recommendations. Authors Song et al. (2020), Xia et al. (2020), Hureaux et. al. (2019), Egloff et al. (2018), Sagi-Dain (2018), Wang et al. (2018), Peng et al. (2017), Papoulidis et al. (2015) and Shaffer et al. (2012), previously discussed in this policy, were included in this systematic review.

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In an attempt to identify possible miscarriage-associated submicroscopic copy number variations (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.

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 3rd percentile (below 5th 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.”

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 WES. The authors summarized that CMA has the potential to detect more chromosomal microdeletions/micro-duplications among fetuses with isolated increased NT.

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 advanced maternal age (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 post-natal individuals with a variety of genetic based conditions. Within this cohort, 21,594 CMAs were performed and the frequency of high penetrance CNVs was 0.1% in group I, 0.9% in group II, and 2.6% in group III. CNV frequency of moderate penetrance

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was 0.3%, 0.6%, and 1.2%, respectively, and these differences were statistically significant. The frequency of low-penetrance CNVs was not significantly different among groups: 0.6%, 0.9%, and 1.0%, respectively. The study concluded that high penetrance CNVs may be a factor in heritability of various anomalies, however low penetrance CNVs do not seem to contribute.

Parchem et al. (2018) evaluated the association of CNVs with perinatal outcomes in fetuses that had sonographic abnormalities. This retrospective studied reviewed anomalous fetuses that had CMA testing. There were abnormal CMA results in 60 (21.4%) of the 280 fetuses in the study. Of these 60, 21 (35%) were considered to be pathogenic and 39 (65%) were 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 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.

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.

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

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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, 5,520 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.

Srebniak et al. (2016) evaluated the diagnostic value of SNP array testing in 1,033 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 76/1,033 (7.4%) fetuses a pathogenic chromosome abnormality was detected by genomic SNP array: in 19/1,033 cases (1.8%) a microscopically detectable abnormality was found and in 57/1,033 (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 VUSs 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.

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 POC; 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.

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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 = 2,220) 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 = 1,139). 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.

Brady et al. (2014) 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 CGH as the first-tier diagnostic test. A total of 383 prenatal samples underwent analysis by array CGH. 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.

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 Practice Guidelines

American College of Medical Genetics and Genomics (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 POC and/or fetus by karyotype of CMA should be considered on a case basis when prenatal diagnosis is not possible.
- For neonates with abnormal physical findings which are not suggestive of the trisomy suggested by original screening, CMA is recommended.
- CMA is recommended when NIPS sex determination is not concordant with physical examination or other clinical evidence reveals possible disorder of sexual differentiation.

American College of Obstetricians and Gynecologists (ACOG)/Society for Maternal Fetal Medicine (SMFM)

In a 2020 (reaffirmed 2021) 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

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aneuploidy but correspondingly detects CNV 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 2023), 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 POC) 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):

- CMA should be made available to any patient choosing to undergo invasive diagnostic testing.
- CMA 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 (Martins et al., 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).

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- 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).

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

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

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

- Offering CMA following normal aneuploidy screen results when multiple fetal malformations are detected (II-1A) or NT ≥ 3.5 MM (II-2B).
- Genetic counseling should be provided to obtain informed consent; parental decisions for reporting of incidental findings (II-2A); and for post-test results reporting counseling (III-A).
- CMA resolution should be similar to postnatal CMA panels for the detection of small pathogenic variants.
- Variants of unknown significance (VOUS) smaller than 500 Kb deletion or 1 Mb duplication should not be reported in prenatal setting.
- VOUS above such cut-offs should only be reported if there is significant evidence that deletion or duplication or the region may be pathogenic (III-B).
- Secondary findings associated with significant childhood onset conditions should be reported; variants associated with adult-onset conditions should only be reported if previously requested by parents or if disclosure could prevent harm to family members (III-A).

Use in Pediatrics

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, non-yield 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 et al. (2019), Berg et al. (2017) and d'Orsi et al. (2017), previously cited in this policy, were included in the Sheidley (2022) systematic review and meta-analysis.

Miclea et al. (2022) sought to identify clinically relevant CNVs in children with a diagnosis of GDD/ID using CMA. The study included 189 Romanian children (3-18 years of age) who had been diagnosed with GDD/ID. The average age of participants was 11.17 years. A complete clinical evaluation was performed which included examination for dysmorphic and internal malformations, neuropsychological and psychiatric assessment, metabolic evaluation, standard karyotyping and genomic testing using CMA. Individuals determined to have trisomy 21 as confirmed by karyotype were excluded. Pathogenic findings, [which included pathogenic CNVs and uniparental disomy (UPD)] and VUSs were found in 28% of participants. Pathogenic CNVs/UPD were seen in 18.5% of the participants. UPD for chromosome 15 was found in two individuals, one of whom showed a clinical phenotype consistent with Prader-Willi syndrome and the other with clinical phenotype of Angleman syndrome. Recurrent CNVs were observed in 60% of participants. The authors concluded the high percentage of pathogenic structural variations found via CMA in children with GDD/ID lends support to the use of CMA in individuals with a non-specific phenotype.

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

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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.

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.

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, DD, and/or ID. 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: ID, 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 DD 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.

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Fan et al. (2018) performed a retrospective review of CMA results from a Chinese population with 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.

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

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

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

CMA and fragile X syndrome analysis is currently recommended as a first-tier approach for testing of males with ID and/or learning delay (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%).

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.

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

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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.

Pfundt et al. (2016) assessed the diagnostic yield and potential clinical utility of a high-density CMA CytoScan Dx Assay in 960 patients with DD or ID. 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.

McCormack et al. (2016) examined the utility of aCGH to replace karyotype in 5,369 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.

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.

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 Practice Guidelines

American Academy of Pediatrics (AAP)

The AAP National Coordinating Center for Epilepsy (2022) states that “the genetic tests most commonly used in the evaluation of children with epilepsy include CMA, epilepsy gene panels and whole-exome sequencing.” Individual test type have specific benefits and limitations, and the utility of various tests may be different depending on individual circumstances. Decisions regarding testing may be influenced by factors including symptoms, turn-around time, insurance coverage, and cost. Due to the complex nature of genetic testing and potential implications it may have (e.g., impact on eligibility for life insurance, reproductive decisions, medical decisions), incorporating genetic counseling is encouraged.

A clinical report by Lipkin & Macias (2020) regarding the identification of infants/children with DD recommends that “A child with suspected GDD or ID 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.”

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In 2020, the AAP (Hyman et al.) published a clinical report addressing the identification, evaluation, and management of children with 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.

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 sub telomere tests for the child with ID of unknown etiology. The authors recommend that chromosomal microarray should be performed in all children with ID or GDDs (Moeschler and Shevell, 2014).

American Academy of Neurology (AAN)

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

- In children with DD/ID or 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 further 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)

In a 2020 Practice Parameter, the American Academy of Child and Adolescent Psychiatry (Siegel et al.) presented a diagnostic genetic testing algorithm for youth with developmental disorders including ASD, ID, or GDD, indicating that if there is a recognized genetic syndrome (e.g., Fragile X syndrome, PTEN hamartoma syndrome, Rett syndrome, Tuberous sclerosis, Prader-Willi syndrome, Angelman syndrome, Down syndrome) after genetic counseling, specific and targeted testing for that syndrome is recommended first. If this testing does not yield a diagnosis, CMA and Fragile X testing are indicated. If findings remain unrevealing, additional testing including WES, karyotyping or mitochondrial DNA testing may be considered. The group states that “microarray is currently the genetic test with the highest diagnostic yield in children with unexplained ID/IDD, with an abnormal result reported in 7.8% of subjects with GDD/ID/IDD and in 10.6% of those with syndromic features, on average.”

American College of Medical Genetics and Genomics (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 ID, CMA (including both array CGH and single nucleotide polymorphism array)

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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 ASDs lists chromosomal microarray (array-CGH or SNP array) 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 resource 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, reaffirmed 2020):

- Cytogenetic microarray (CMA) testing for 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 DD/ID.
  - ASD.
- 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).

Canadian College of Medical Genetics (CCMG)

In a 2023 position statement, the CCMG recommends CMA as a first-tier test for individuals with GDD, ID or ASD. Fragile X testing is advised when family history or clinical symptoms are suggestive of this disorder. Further recommendations include the use of WES or comprehensive gene panels as second-tier testing for individuals with GDD/ID. The CCMG does not recommend genetic tests for individuals with neurodevelopmental disorders when GDD, ID or ASD is not present, unless the phenotype is suggestive of a syndromic etiology or an inherited metabolic disease (Carter et al., 2023).

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).

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. (Accessed March 20, 2023)

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The CytoScan® DX Assay (Affymetrix, Inc.) was cleared for marketing under the FDA's 510(k) process in January 2014. The FDA classifies the devices a Type II postnatal chromosomal copy number variation detection system. According to documents filed with FDA, CytoScan Dx Assay is a qualitative assay intended for the postnatal detection of copy number variations (CNV) in genomic DNA obtained from peripheral whole blood in patients referred for chromosomal testing based on clinical presentation. CytoScan Dx Assay is intended for the detection of CNVs associated with developmental delay, intellectual disability, congenital anomalies, or dysmorphic features. The CytoScan DX Assay is a microarray that works with Affymetrix's existing GeneChip technology platform to perform comparative whole-genome hybridization. This device is not intended to be used for standalone diagnostic purposes, preimplantation or prenatal testing or screening, population screening, or for the detection of, or screening for, acquired or somatic genetic aberrations. The FDA's review of the CytoScan Dx Assay included an analytic evaluation of the test's ability to accurately detect numerous chromosomal variations of different types, sizes, and genome locations when compared with several analytically validated test methods. FDA found that the CytoScan Dx Assay could analyze a patient's entire genome and adequately detect chromosome variations in regions of the genome associated with intellectual and developmental disabilities. 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/reviews/k130313.pdf
  (Accessed March 20, 2023)

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 March 20, 2023)

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).

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Policy History/Revision Information

Date	Summary of Changes
03/01/2024	**Related Policies** • Updated reference link to reflect current policy title for *Molecular Oncology Testing for Solid Tumor Cancer Diagnosis, Prognosis, and Treatment Decisions*
10/01/2023	**Related Policies** • Added reference link to the Medical Policy titled *Whole Exome and Whole Genome Sequencing* **Coverage Rationale** • Added language to indicate pre-test genetic counseling is strongly recommended in order to inform persons being tested about the advantages and limitations of the test as applied to a unique person • Replaced reference to "*genome-wide* comparative genomic hybridization/microarray testing or single-nucleotide polymorphism (SNP) chromosomal *microarray analysis*" with "chromosome microarray *testing using array* comparative genomic hybridization *(aCGH) and/*or single-nucleotide polymorphism (SNP) *array*" • Revised list of proven and medically necessary indications; replaced: ○ "Evaluation of an embryo/fetus in *women* undergoing invasive prenatal testing" with "evaluation of an embryo/fetus in *individuals* undergoing invasive prenatal testing" ○ "Evaluation of individuals with *non-syndromic* Developmental Delay/Intellectual Disability" with "evaluation of individuals with Developmental Delay/Intellectual Disability *where a specific syndrome is not suspected*" ○ "Evaluation of biological parent of a fetus or child with an equivocal chromosome microarray result" with "evaluation of biological parent of a fetus or child with an *abnormal or* equivocal *finding on* chromosome microarray *testing* results" • Removed list of examples of unproven and not medically necessary conditions • Removed reference link to the Medical Policy titled *Molecular Oncology Testing for Cancer Diagnosis Prognosis, and Treatment Decisions* for genome-wide comparative genomic hybridization microarray testing or SNP chromosomal microarray analysis for the evaluation of cancer **Definitions** • Updated definition of: ○ Intellectual Disability ○ Well-Delineated Genetic Syndrome **Supporting Information** • Updated *Description of Services*, *Clinical Evidence*, and *References* sections to reflect the most current information • Archived previous policy version CS017.W

Instructions for Use

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

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