Chromosome Microarray Testing (Non-Oncology Conditions)

Policy Number: 2026T0559GG
Effective Date: June 1, 2026

Instructions for Use

Table of Contents **Page**

Related Commercial/Individual Exchange Policies

- Genetic Testing for Cardiac Disease
- Molecular Oncology Testing for Solid Tumor Cancer Diagnosis, Prognosis, and Treatment Decisions
- Preimplantation Genetic Testing and Related Services
- Whole Exome and Whole Genome Sequencing (Non-Oncology Conditions)

Community Plan Policy

- Chromosome Microarray Testing (Non-Oncology Conditions)

Medicare Advantage Policy

- Molecular Pathology/Molecular Diagnostics/ Genetic Testing

Application

UnitedHealthcare Commercial

This Medical Policy applies to UnitedHealthcare Commercial benefit plans.

UnitedHealthcare Individual Exchange

This Medical Policy applies to Individual Exchange benefit plans.

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:
  - Intrauterine Fetal Demise or Stillbirth
  - Testing the products of conception following pregnancy loss
  - Individuals undergoing invasive prenatal testing (e.g., amniocentesis, chorionic villus sampling, fetal tissue sampling)
- Evaluation of individuals with one or more of the following:
  - Autism Spectrum Disorder
  - Isolated severe congenital heart disease
  - Multiple Congenital Anomalies that are not specific to a Well-Delineated Genetic Syndrome and cannot be identified by a clinical evaluation alone

- Global Developmental Delay/Intellectual Disability when a specific syndrome is not suspected
- Evaluation of biological parent or sibling 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 is addressed in the Medical Policy titled Preimplantation Genetic Testing and Related Services.

Medical Records Documentation Used for Reviews

Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. Medical records documentation may be required to assess whether the member meets the clinical criteria for coverage but does not guarantee coverage of the service requested; refer to the guidelines titled Medical Records Documentation Used for Reviews.

Definitions

Autism Spectrum Disorder: A condition marked by enduring problems communicating and interacting with others, along with restricted and repetitive behavior, interests, or activities and as listed in the current edition of the International Classification of Diseases section on Mental and Behavioral Disorders or the Diagnostic and Statistical Manual of Mental Disorders published by the American Psychiatric Association (UnitedHealthcare Insurance Company Generic Certificate of Coverage, 2026).

Congenital Anomaly: A physical developmental defect that is present at the time of birth and that is identified within the first twelve months of birth (UnitedHealthcare Insurance Company Generic Certificate of Coverage, 2026).

Global Developmental Delay: The failure to meet expected developmental milestones in several areas of intellectual functioning in an individual younger than 5 years of age (American Psychiatric Association, 2013).

Intellectual Disability: A neurodevelopmental disorder that begins in childhood, characterized by intellectual difficulties as well as difficulties in conceptual, social, and practical areas of living (American Psychiatric Association, 2013).

Intrauterine Fetal Demise or Stillbirth: Fetal death at or after 20 weeks' gestation (American College of Obstetricians and Gynecologists, Society of Maternal-Fetal Medicine, 2020; reaffirmed 2021).

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, laboratory tests, or family history, can be used to identify a genetic syndrome (Talking Glossary of Genomic and Genetic Terms, 2025).

Applicable Codes

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

CPT Code	Description
0156U	Copy number (e.g., intellectual disability, dysmorphology), sequence analysis
0209U	Cytogenomic constitutional (genome-wide) analysis, interrogation of genomic regions for copy number, structural changes and areas of homozygosity for chromosomal abnormalities
81228	Cytogenomic (genome-wide) analysis for constitutional chromosomal abnormalities; interrogation of genomic regions for copy number variants, comparative genomic hybridization [CGH] microarray analysis

CPT Code	Description
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

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
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

Diagnosis Code	Description
O03.9	Complete or unspecified spontaneous abortion without complication
O09.511	Supervision of elderly primigravida, first trimester
O09.512	Supervision of elderly primigravida, second trimester
O09.513	Supervision of elderly primigravida, third trimester
O09.519	Supervision of elderly primigravida, unspecified trimester
O09.521	Supervision of elderly multigravida, first trimester
O09.522	Supervision of elderly multigravida, second trimester
O09.523	Supervision of elderly multigravida, third trimester
O09.529	Supervision of elderly multigravida, unspecified trimester
O26.20	Pregnancy care for patient with recurrent pregnancy loss, unspecified trimester
O26.21	Pregnancy care for patient with recurrent pregnancy loss, first trimester
O26.22	Pregnancy care for patient with recurrent pregnancy loss, second trimester
O26.23	Pregnancy care for patient with recurrent pregnancy loss, third trimester
O28.0	Abnormal hematological finding on antenatal screening of mother
O28.1	Abnormal biochemical finding on antenatal screening of mother
O28.2	Abnormal cytological finding on antenatal screening of mother
O28.3	Abnormal ultrasonic finding on antenatal screening of mother
O28.4	Abnormal radiological finding on antenatal screening of mother
O28.5	Abnormal chromosomal and genetic finding on antenatal screening of mother
O28.8	Other abnormal findings on antenatal screening of mother
O28.9	Unspecified abnormal findings on antenatal screening of mother
O35.00X0	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
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

Diagnosis Code	Description
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
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

Diagnosis Code	Description
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
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

Diagnosis Code	Description
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
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

Diagnosis Code	Description
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
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

Diagnosis Code	Description
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
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

Diagnosis Code	Description
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
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

Diagnosis Code	Description
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
QA0.0159	Neurodevelopmental disorder, related to other genes associated with transcription and gene expression
QA0.8	Other neurodevelopmental disorders related to pathogenic variants in other specific genes
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
Q21.3	Tetralogy of Fallot
Q21.4	Aortopulmonary septal defect
Q21.8	Other congenital malformations of cardiac septa
Q21.9	Congenital malformation of cardiac septum, unspecified
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
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

Diagnosis Code	Description
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
Q23.81	Bicuspid aortic valve
Q23.82	Congenital mitral valve cleft leaflet
Q23.88	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
Q87.86	Kleefstra syndrome
Q89.7	Multiple congenital malformations, not elsewhere classified
Q89.89	Other specified congenital malformations
Q89.9	Congenital malformation, unspecified
Q90.0	Trisomy 21, nonmosaicism (meiotic nondisjunction)
Q90.1	Trisomy 21, mosaicism (mitotic nondisjunction)
Q90.2	Trisomy 21, translocation
Q90.9	Down syndrome, unspecified
Q91.0	Trisomy 18, nonmosaicism (meiotic nondisjunction)
Q91.1	Trisomy 18, mosaicism (mitotic nondisjunction)
Q91.2	Trisomy 18, translocation
Q91.3	Trisomy 18, unspecified
Q91.4	Trisomy 13, nonmosaicism (meiotic nondisjunction)
Q91.5	Trisomy 13, mosaicism (mitotic nondisjunction)
Q91.6	Trisomy 13, translocation
Q91.7	Trisomy 13, unspecified
Q92.0	Whole chromosome trisomy, nonmosaicism (meiotic nondisjunction)
Q92.1	Whole chromosome trisomy, mosaicism (mitotic nondisjunction)
Q92.2	Partial trisomy
Q92.5	Duplications with other complex rearrangements
Q92.61	Marker chromosomes in normal individual
Q92.62	Marker chromosomes in abnormal individual
Q92.7	Triploidy and polyploidy
Q92.8	Other specified trisomies and partial trisomies of autosomes
Q92.9	Trisomy and partial trisomy of autosomes, unspecified

Diagnosis Code	Description
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
Q93.52	Phelan-McDermid 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
Q99.89	Other specified chromosome abnormalities
Q99.9	Chromosomal abnormality, unspecified
R48.0	Dyslexia and alexia
R62.0	Delayed milestone in childhood
R62.50	Unspecified lack of expected normal physiological development in childhood
R62.51	Failure to thrive (child)
R62.59	Other lack of expected normal physiological development in childhood
R89.8	Other abnormal findings in specimens from other organs, systems and tissues
Z14.1	Cystic fibrosis carrier
Z14.8	Genetic carrier of other disease
Z36.0	Encounter for antenatal screening for chromosomal anomalies
Z37.1	Single stillbirth
Z37.3	Twins, one liveborn and one stillborn
Z37.4	Twins, both stillborn
Z37.60	Multiple births, unspecified, some liveborn
Z37.61	Triplets, some liveborn
Z37.62	Quadruplets, some liveborn
Z37.63	Quintuplets, some liveborn
Z37.64	Sextuplets, some liveborn
Z37.69	Other multiple births, some liveborn
Z37.7	Other multiple births, all stillborn
Z87.74	Personal history of (corrected) congenital malformations of heart and circulatory system

Description of Services

Chromosomal microarray (CMA) is a high-resolution molecular test used to detect chromosomal abnormalities, including copy number variants (CNVs) and other genomic alterations such as uniparental disomy. It is used in the evaluation of pregnancy loss, as well as for prenatal diagnosis via chorionic villus sampling or amniocentesis, to identify aneuploidies, polyploidies, and submicroscopic deletions or duplications. CMA, which includes array comparative genomic hybridization (aCGH) and single nucleotide polymorphism (SNP) arrays, offers greater sensitivity than traditional cytogenetic methods such as karyotype by detecting most abnormalities identified through conventional testing while providing superior

resolution. In neurodevelopmental conditions, CMA supports the diagnosis of genetic causes of Autism Spectrum Disorder, Global Developmental Delay, and Intellectual Disability (Awuah et al., 2025).

Clinical Evidence

Use in Obstetrics

The Sapantzoglou et al. (2026) systematic review and meta-analysis quantified the incremental diagnostic yield of CMA beyond conventional karyotyping in fetal growth restriction (FGR). Overall, 22 observational studies (19 retrospective cohorts, two prospective cohorts, and one retrospective case series), encompassing 2,275 fetuses, met the inclusion criteria; variants of uncertain significance (VUSs) were excluded. Incremental yield was defined as submicroscopic CNVs [< 10 megabases (Mb)] detected by CMA after a normal karyotype. The authors synthesized three predefined clinical strata: isolated FGR; nonmalformed FGR plus soft markers and/or amniotic fluid or Doppler abnormalities but no structural anomalies (FGR + US); and FGR plus structural malformations (FGR + SM). Pooled results showed a 3% incremental yield in isolated FGR (95% CI, 2%-5%; $I^2 = 0\%$), a 4% incremental yield in FGR + US (95% CI, 3%-5%; $I^2 = 0\%$), and a 10% incremental yield in FGR + SM (95% CI, 7%-13%; $I^2 = 0\%$), with individual study yields ranging from 0% to 17% in isolated and FGR + US groups and up to 21% in FGR + SM cases. The methodological quality [QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies)] frequently lacked consecutive enrollment and often conducted CMA concurrently with, rather than subsequent to, karyotyping, but concerns regarding applicability were consistently low; CMA was done after normal karyotype in five studies, after normal quantitative fluorescence polymerase chain reaction or fluorescence in situ hybridization (FISH) in four studies, and simultaneously with karyotype in 13 studies. The authors concluded that CMA provides a measurable additional diagnostic yield over karyotype in FGR, which is greatest when structural anomalies are present, and that these estimates can inform counseling and test selection. Key limitations of this meta-analysis include heterogeneity in FGR definitions (four diagnostic approaches across studies, with seven not reporting a definition); variability in inclusion criteria across isolated FGR, FGR + US, and FGR + SM cohorts; inconsistent testing workflows; differing CMA platforms; and an inability to stratify yield by early- vs late-onset FGR due to sparse and inconsistent reporting. The authors also noted potential selection bias arising from these sources of design heterogeneity. The study did not evaluate clinical utility, and demographic generalizability is unclear given the mix of single- and multicenter designs and variable recruitment approaches. Publications by Shaffer et al. (2012), Peng et al. (2017), Xia et al. (2020), and Nguyen et al. (2025), previously discussed in this policy, were included in this systematic review and meta-analysis.

The Matarrelli et al. (2025) systematic review and meta-analysis examined outcomes in fetuses with increased nuchal translucency measured before 11 weeks' gestation, who all had a crown-rump length of under 45 mm. The review included five cohort studies, two prospective and three retrospective, which encompassed 401 fetuses; the review pooled data from three of the studies, totaling 269 fetuses for the meta-analysis. The primary outcome was a composite of chromosomal, genetic, or structural anomalies or perinatal loss; the secondary outcomes included abnormal karyotype, CNVs on CMA, single-gene disorders on next-generation sequencing, structural anomalies, and perinatal loss, with subgroup analyses by persistence vs resolution of increased nuchal translucency at 11 to 14 weeks and by nuchal translucency thickness categories. Pooled estimates showed a composite adverse outcome in 42.0% of pregnancies, with chromosomal or genetic anomalies in 40.2%, abnormal karyotype in 33.3% overall, and CNVs detected in 4.3% of fetuses tested, highlighting incremental yield beyond karyotype. Single-gene disorders were identified in 17.6% of those in which next-generation sequencing was performed. Persistence of increased nuchal translucency at the 11- to 14-week scan was associated with a higher rate of composite adverse outcomes (64.2%) compared with cases in which nuchal translucency resolved (19.4%). Structural anomalies were identified in 5.9%, and perinatal loss occurred in 9.7%. The severity gradient by nuchal translucency thickness suggested higher adverse outcome rates with thicker nuchal translucency, although precision was limited. The authors concluded that increased nuchal translucency identified in the early first trimester is associated with elevated risks of chromosomal, genetic, and structural anomalies and perinatal loss, even when the nuchal translucency subsequently normalizes at 11 to 14 weeks; the authors advised referral to fetal medicine specialists on early detection and noted that routine early nuchal translucency measurement is not currently supported. Methodological constraints include small study sizes, heterogeneity in early nuchal translucency definitions and measurement standardization, and retrospective designs in most cohorts. None of the included studies used randomized or masked designs, and none incorporated formal comparison groups. Whether a study was single or multicenter varied across the included cohorts. Well-designed, comparative studies, with standardized early nuchal translucency protocols, are needed.

The Yin et al. (2025) retrospective cohort study evaluated 3,386 pregnant patients who underwent fetal echocardiography and amniocentesis between January 2020 and August 2022 at a single tertiary care facility. The objective was to assess the diagnostic contributions of fetal echocardiography, chromosomal karyotyping, and CMA in identifying congenital cardiac anomalies. The study group comprised 697 patients whose fetuses had cardiac abnormalities; 2,689 patients with

normal ultrasound findings served as the comparison group. No masking was implemented, and the study did not use randomization. All patients were recruited through routine prenatal care pathways, including referrals for high-risk factors such as advanced maternal age and abnormal noninvasive prenatal testing. All patients underwent echocardiography, and most underwent both genetic tests; however, not all patients completed each diagnostic modality. Follow-up was performed for pregnancy outcomes and postnatal echocardiography. Among the 697 fetuses with congenital heart disease (CHD), simple defects predominated (86.37%), with ventricular septal defects and isolated valve abnormalities being the most common. Complex CHD accounted for 9.9% and 3.73% involved extracardiac anomalies. Karyotyping identified chromosomal abnormalities in 6.52% (41 of 629) of evaluated CHD cases, with detection rates highest in those with extracardiac anomalies (23.08%) and complex heart disease (16.36%), compared with 4.71% in the comparison group. CMA detected pCNVs in 5.28% (34 of 644) of CHD cases and VUSs in 1.40%. The detection rate of pCNVs was higher in complex CHD and in cases with extracardiac anomalies (both 7.69%) than in the comparison group (1.38%). Among 588 CHD cases with a normal karyotype, CMA identified additional pCNVs in 4.42%, demonstrating incremental diagnostic yield. Follow-up data indicated high concordance between prenatal and postnatal diagnoses (99.2% among infants with prenatal CHD diagnoses) and low rates of missed CHD among patients with normal prenatal ultrasound findings (1.1%). The authors concluded that echocardiography is central to the prenatal detection of CHD and that combining karyotyping with CMA enhances detection of relevant genetic abnormalities, particularly in complex cases or when extracardiac anomalies are present. Limitations noted in the article include incomplete postnatal echocardiographic confirmation for all newborns, the restricted ability of CMA to detect certain mutation types, challenges in interpreting VUSs, and variability in follow-up duration. The findings are further constrained by the lack of randomization, single-center design, and incomplete genetic testing in a subset of patients. The findings are limited by the observational design; the analysis was descriptive and based on available data, with no intention-to-treat framework.

The Zheng et al. (2025) retrospective observational study from a single center examined 5,116 amniotic fluid samples collected between January 2022 and December 2024 to assess the diagnostic yield of SNP-based CMA in fetuses with ultrasound-detected CHD. Samples were grouped as isolated CHD (n = 237), CHD plus other structural malformations (CHD + SM; n = 136), non-CHD with other structural malformations (n = 1,632), and normal ultrasound (n = 3,111). All underwent karyotyping and SNP-based CMA, with classification of CNVs as pathogenic, likely pathogenic, or of uncertain significance. Aneuploidies were the most frequent finding overall (7.35%), with a substantially higher rate in the CHD + SM cohort than in isolated CHD (16.91% vs 3.8%; $p < 0.001$), driven by trisomy 21 (8.82% in CHD + SM vs 1.27% in isolated CHD and 3.57% in the normal group) and trisomy 18 (5.88% in CHD + SM vs 0.42% in isolated CHD and 0.55% in the normal group). The frequency of pCNVs was similar across groups, ranging from 2.11% to 3.68%. The authors reported no significant between-group differences in overall CNV size categories (< 1 Mb, 1-5 Mb, and ≥ 5 Mb) and concluded that SNP-based CMA (1) increases the detection of chromosomal etiologies in fetuses with CHD, (2) should be strongly recommended for CHD + SM, and (3) should be considered as a complementary test for isolated CHD. The study's limitations include its single-center, observational design; absence of randomization or masking; lack of intention-to-treat considerations; and no follow-up of pregnancy, neonatal, or infant outcomes, which precludes assessment of clinical utility and longer-term effects. Additional constraints include potential selection factors inherent to referral for amniocentesis and SNP-based testing and incomplete detail on how ultrasound phenotypes were linked to specific CNV findings beyond descriptive counts. Well-designed, comparative studies, with longitudinal outcomes, are needed.

The Li et al. (2025) single-center prospective cohort study explored the use of CMA to evaluate confirmed cases of FGR. Participants with singleton pregnancies and a diagnosis of FGR (n = 182) were enrolled from a medical center in China. The cohort was divided into three categories: isolated FGR (n = 94), FGR plus ultrasound soft marker anomalies (n = 67), and FGR + SM (n = 21). Amniocentesis and CMA were performed in all participants. In the FGR + SM group, the detection rate of pCNVs (19.0%; four of 21) was significantly higher than the detection rates in the group with FGR plus ultrasound soft marker anomalies (1.5%; one of 67) and the isolated FGR group (2.1%; two of 94) ($\chi^2 = 9.33$; $p = 0.005$). Fetuses in the FGR + SM group with multiple-system malformations had a significantly higher diagnostic rate of chromosomal variations than fetuses in the group with single-system malformations (60% vs 6.3%; $p = 0.028$). Notably, advanced maternal age, early-onset FGR, and FGR severity were not found to impact the diagnostic rate. Based on these results, the authors proposed that pregnancies affected by FGR plus structural anomalies may be associated with a significant risk of pCNV, especially if two or more organ systems are involved. They recommended standard genetic assessments in cases of FGR. The study is limited by its small sample size and single-facility design.

The Li et al. (2024) retrospective observational study evaluated 4,211 pregnant individuals who underwent invasive prenatal testing with CMA at a single medical center between 2016 and 2022. The study included individuals referred for advanced maternal age or for abnormal maternal serum screening, non-invasive prenatal testing, or ultrasound findings, and other high-risk indications, with samples obtained by CVS or amniocentesis following ultrasound-guided procedures. All analyses were conducted per protocol with complete follow-up reported for all 4,211 pregnancies. Across the cohort, chromosomal abnormalities were detected in 11.4% of fetuses, including 5.82% with ploidies and 5.58% with CNVs.

Clinically significant CNVs accounted for 3.78% of all cases. Detection rates varied by indication, from 6.42% for advanced maternal age to 39.09% for abnormal non-invasive prenatal testing, and 9.21% for abnormal ultrasound findings. Follow-up outcomes showed that 87.32% of pregnancies resulted in infants with normal findings after birth, while 10.97% of pregnancies were electively terminated and 1.21% resulted in live births with postnatal abnormalities. The authors concluded that CMA provided diagnostic value for identifying chromosomal abnormalities in this population. The findings were constrained by the absence of a comparison group, the single-center design, and the lack of randomization or masking. The study also reported limitations related to incomplete clinical information for some cases, challenges in interpreting VUSs, and limited parental testing, which restricted the assessment of inheritance patterns. The small number of cases within some subgroups, particularly those involving specific ultrasound phenotypes or rare CNVs, further limited interpretation.

The Olayiwola et al. (2024) single-center, retrospective, observational study analyzed 842 CMA tests performed from 2011 to 2020, including 523 prenatal specimens (predominantly cultured amniocytes) and 319 specimens of products of conception. The objective was to describe testing indications, diagnostic yield, and the spectrum of CNV findings. Patients undergoing testing were 15 to 44 years of age; among prenatal specimens, abnormal ultrasound findings were the most frequent indication (422 of 523; 80.7%). The overall diagnostic yield for clinically significant CNVs was 11.05% (93 of 842), comprising 7.8% of the prenatal samples (41 of 523) and 16.3% of the products of conception samples (52 of 319). Of the 422 prenatal cases with abnormal ultrasound, 8.3% (35 of 422) of the CNVs identified were pathogenic, most commonly involving cardiac and brain/central nervous system findings. Across all samples, recurrent aneuploidies included trisomy 21 (n = 7), monosomy X (n = 4), trisomy 18 (n = 4), and trisomy 13 (n = 2); among the products of conception samples with pathogenic results, 66.5% (33 of 52) were aneuploid or polyploid, including rare autosomal trisomies and triploidy incompatible with life. Mosaicism and classic microdeletion/duplication syndromes were observed, such as 1p36 deletion (n = 2), 22q11.2 deletion (n = 2), distal 22q11.2 deletion (n = 1), 22q11.2 microduplication (n = 2), 15q11.2 deletion (n = 6), and 16p11.2 deletion (n = 3). Among the 27 cases in which the CMA test was prompted by abnormal cell-free DNA screening, 11.1% (three of 27) yielded clinically significant findings, including monosomy X, 15q11.2 deletion, and an 18p deletion with 18q duplication consistent with a derivative 18. None of the 29 maternal serum screening–prompted cases had pathogenic findings on CMA. The authors concluded that this evidence supports the clinical utility of prenatal CMA for management decisions and for elucidating genetic etiologies in testing products of conception while also illustrating how indication patterns relate to yield in routine practice. The authors noted several limitations, including the single-center, observational design; lack of a comparison group; reliance on indications transcribed from requisitions; predominance of amniocentesis over chorionic villus sampling, which could miss confined placental mosaicism detectable by chorionic villus sampling; lack of detailed analyses of VUSs and potential for reclassification; and the fact that pathogenic CNVs may not fully explain fetal phenotypes, sometimes necessitating follow-up testing to reach a diagnosis. Analyses were not conducted on an intention-to-treat basis, given the laboratory cohort design. The authors emphasized that increasing uptake of next-generation sequencing in obstetric care may help resolve CMA-negative cases and recommended diagnostic confirmation of abnormal noninvasive screening results to guide decisions.

Lu et al. (2024) assessed the clinical utility of CMA in pregnancies in which fetal congenital heart defects were detected on routine ultrasound and subsequently confirmed by echocardiography (n = 642) over a 6-year time span. Both karyotyping and CMA were performed in all cases. The diagnostic yield of CMA was 15.3% (98 of 642), which was substantially higher than the diagnostic yield of karyotyping, which was 8.3% (53 of 642). Stratification demonstrated a significantly increased detection rate in pregnancies affected by congenital heart defects plus extracardiac structural anomalies compared with those affected by isolated congenital heart defects (33.1% vs 9.9%; $p < 0.0001$.) Based on their findings, the authors recommended CMA as a first-tier test for fetuses found to have congenital heart defects, with special consideration given to cases of congenital heart defects with additional structural abnormalities or soft markers. The study is limited by the need for participants to pay for invasive prenatal testing and the refusal of some participants to engage in further testing, leading to selection bias.

Ye et al. (2024) assessed the use of SNP-based CMA to identify genetic etiologies underlying fetal cardiac abnormalities detected on ultrasound. This study included 2,092 pregnant participants, who were grouped by the presence or absence of structural abnormalities and by the type of abnormality found. Each participant underwent prenatal invasive diagnostic testing. The authors found that fetuses with nonisolated CHD had the highest rate of chromosome abnormalities compared with those with isolated CHD, non-CHD abnormalities, or normal findings (42.6% vs 14.1%, 14.9%, and 9.4%, respectively). They suggested that SNP array–based CMA is effective for detecting abnormal CNVs in fetuses with CHD but also emphasized the complex etiologies of CHD and the need for further research.

Wang et al. (2023) performed a systematic review and meta-analysis of four prospective and 41 retrospective studies, which comprised a total of 16,484 fetuses affected by isolated CHD or CHD + SM, to assess the risk and prevalence of chromosomal abnormalities detectable by CMA, karyotype, and/or FISH. A meta-analysis revealed a pooled proportion of

23% (95% CI, 20%-26%) for overall chromosomal abnormalities, 19% (95% CI, 16%-22%) for aneuploidies, 2% (95% CI, 2%-3%) for 22q11 deletion, and 4% (95% CI, 3%-5%) for other CNVs. However, the included studies did not consistently evaluate outcomes and used differing test methodologies, which is a limitation that the authors recognized may have led to an underestimation of the pooled detection rate of 22q11 deletion. The pooled proportion of overall chromosome abnormalities was 16% (95% CI, 13%-20%) in isolated CHD and 37% (95% CI, 29%-44%) in CHD + SM, suggesting that fetuses with CHD + SM are at a higher risk of chromosome abnormalities. In addition, the incidence of chromosome abnormalities was higher in fetuses with a septal defect–related subtype of CHD than in those with CHD subtypes with conotruncal or other defects (odds ratio, 1.60 and 3.61, respectively). The authors indicated that their findings add to the evidence demonstrating relationships between CHD subtypes and chromosome abnormalities, which will lead to improvements in genetic counseling and clinical decision-making. They recommended CMA for CHD if karyotyping or FISH is normal, especially in cases of CHD + SM and CHD with septal defects, in which the incidence of chromosome abnormalities is higher. The heterogeneity of the included studies was high; however, interpretation processes were not described in most included studies, which limits the application of this meta-analysis. In addition, all but four of the studies were retrospective in design. Further large, high-quality, prospective studies focused on the specific pathogenicity of CNVs and VUSs in fetuses diagnosed with CHD are recommended. The publication by Sagi-Dain et al. (2018), previously discussed in this policy, was included in this systematic review and meta-analysis.

Mastromoro et al. (2022a) conducted a systematic review and meta-analysis evaluating the diagnostic yield of karyotyping and CMA in fetuses with increased nuchal translucency. Karyotyping detected chromosomal anomalies in 22.76% of fetuses with isolated nuchal translucency of ≥ 2.5 mm and had a 2.35% incremental detection rate with CMA. Karyotyping detected chromosomal anomalies in 14.36% of fetuses with isolated nuchal translucency of ≥ 3 mm and had a 3.89% incremental detection rate with CMA. Karyotyping detected chromosomal anomalies in 34.35% of fetuses with isolated nuchal translucency of ≥ 3.5 mm and had a 4.1% incremental detection rate with CMA. In this group, a comparison of the diagnostic yields of a RASopathy panel and exome sequencing demonstrated an incremental diagnostic rate of 1.44% with the panel and a 2.44% incremental detection rate with exome sequencing. The researchers recommended ongoing research to determine the diagnostic rate of CMA at all sizes of increased nuchal translucency, with a focus on analysis of monogenic conditions associated with increased nuchal translucency as well as development of a diagnostic algorithm, which may include exome sequencing following a negative CMA result. The publication by Egloff et al. (2018), previously discussed in this policy, was included in this systematic review and meta-analysis.

Mastromoro et al. (2022b) performed a systematic review and meta-analysis of 18 publications investigating the incremental diagnostic yield of CMA in isolated fetal CHD and fetal CHD subtypes. Additionally, the authors developed a comparison group of 59 fetuses described in the existing literature with isolated CHD but a known normal karyotype. In a pooled analysis, the diagnostic incremental yield of CMA over karyotyping was 5.79%. In CHD presenting with conotruncal malformations, the detection rate with CMA was 15.93%. Diagnostic yields for CHD with ventricular septal defects and aberrant right subclavian artery were 2.64% and 0.66%, respectively. Other CHD subtypes yielded CMA detection rates between 4.42% and 6.67%, consistent with the overall diagnostic rate for cardiopathies. Tetralogy of Fallot yielded the highest CMA detection rate, which was 11.28%. In the comparison group of fetuses with isolated CHD and a normal karyotype, the diagnostic yield was consistent with the existing literature. The authors asserted that CMA is a helpful tool for assessing the etiology of fetal CHD and that this etiologic information is highly valuable for customizing genetic counseling on each subtype's unique risks. Publications by Hureaux et al. (2019), Fu et al. (2017), and Shaffer et al. (2012), previously discussed in this policy, were included in this systematic review and meta-analysis.

Mastromoro et al. (2022c) performed a systematic review and meta-analysis examining the diagnostic yields and VUS rates of CMA and whole-exome sequencing (WES) in fetuses with anomalous findings (e.g., soft markers and/or structural malformations) detected on routine ultrasound evaluation. The pooled diagnostic yield of CMA was 5.72%, with subgroup analyses demonstrating yields of 2.15% for fetuses with single soft markers, 3.44% for multiple soft markers, 3.66% for single structural malformations, and 8.57% for multiple structural malformations. WES demonstrated a pooled diagnostic yield of 19.47% and a subgroup yield of 27.47% for multiple structural malformations. The VUS rates for fetuses with structural malformations were 2.86% with CMA and 8.32% with WES. The authors suggested that for fetal structural malformations, CMA may be considered a first-tier test used in conjunction with parental segregation and karyotyping. They further noted that WES presents a very high incremental yield but a substantial VUS rate; as such, the use of WES was recommended by the authors for use in select cases. Heterogeneity in the included studies was seen related to the characteristics of individuals, class of malformations, and number of samples available, presenting limitations to this meta-analysis. Publications by Song et al. (2020), Xia et al. (2020), Hureaux et al. (2019), Egloff et al. (2018), Sagi-Dain et al. (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.

Srebniak et al. (2018) performed a systematic review and meta-analysis to evaluate the use of CMA in pregnancies not at an increased risk for unbalanced chromosomal rearrangements. While 19 studies met the inclusion criteria, 10,614 fetal

CMA results from the 10 largest studies were evaluated in the overall meta-analysis; eight of these studies (10,314 fetuses) provided sufficient data to be included in a subanalysis of submicroscopic fetal findings. Across the 10 largest studies, 119 fetuses were referred for CMA due to advanced maternal age and/or parental anxiety. CMA identified a clinically significant CNV in 0.84% (95% CI, 0.55%-1.30%). In the eight-study subset, CMA identified a CNV associated with an early-onset syndromic disorder in 0.37% (95% CI, 0.27%-0.52%) and identified a CNV associated with a late-onset disease in 0.11% (95% CI, 0.05%-0.21%). The authors reported these findings as an overall risk of greater than one in 180 for a significant fetal cytogenetic abnormality. Because the background risk of Down syndrome in pregnant women under age 36 years is lower than their background risk of pathogenic CNVs, as reported here, the authors concluded that all women should be advised of their overall individual risk of chromosomal aberrations, rather than their risk of trisomies alone. Publications by Papoulidis et al. (2015) and Shaffer et al. (2012), previously discussed in this policy, were included in this systematic review and meta-analysis.

Pauta et al. (2017) performed a systemic review of the literature and meta-analysis to determine the utility of CMA compared with traditional karyotyping in early pregnancy loss. In 23 studies, 5,520 pregnancy losses up to 20 weeks' gestational age were reviewed. CMA provided informative results in 95% of cases compared to 67% with karyotyping. CMA provided a 2% greater yield for pCNVs. The authors concluded that CMA resulted in diagnostic information in early pregnancy loss in significantly more cases than conventional chromosome analysis.

Clinical Practice Guidelines

American College of Medical Genetics and Genomics (ACMG)

The ACMG (Cherry et al., 2017) published a practice resource guideline for laboratories, which addresses diagnostic testing following positive noninvasive prenatal screening (NIPS), and makes the following recommendations:

- CMA on chorionic villus sampling or amniocentesis may be used for confirmatory diagnosis for abnormal NIPS results or as a reflex to normal karyotype analysis.
- CMA testing should be used for follow-up when small copy number changes are reported as positive on NIPS.
- Testing of the products of conception and/or fetus by karyotype or CMA should be considered on a case-by-case basis when pregnancy loss has already occurred.
- For neonates with abnormal physical findings that are not consistent with the trisomy suggested by NIPS, CMA is recommended.
- CMA is recommended when NIPS sex determination is not concordant with the neonatal physical examination or when other clinical evidence reveals a possible disorder of sex differentiation.

American College of Obstetricians and Gynecologists (ACOG)

The ACOG recommendations for prenatal diagnostic testing for genetic disorders (2016b) include the following:

- CMA should be made available to any patient choosing to undergo invasive diagnostic testing (based on good/consistent scientific evidence: level A).
- 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 (based on good/consistent scientific evidence: level A).
- CMA may be used to confirm an abnormal FISH test (based on limited or inconsistent scientific evidence: level B).

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

The 2020 ACOG and SMFM joint consensus statement includes the following recommendations for the use of CMA in the management of stillbirth:

- CMA, incorporated into the stillbirth workup, improves the test success rate and the detection of genetic anomalies compared with conventional karyotyping (1A: strong recommendation, high-quality evidence).
- Genetic analyses are of sufficient yield that they should be performed in all cases of stillbirth after appropriate parental permission is obtained (1A: strong recommendation, high-quality evidence).

In a 2016 committee opinion on microarrays and next-generation sequencing technology, ACOG and the SMFM made the following recommendations for the prenatal use of CMA:

- Most genetic changes identified by CMA 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 CMA 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 CMA can be performed.
- CMA of fetal tissue (e.g., amniotic fluid, placenta, products of conception) is recommended in the evaluation of intrauterine fetal death or stillbirth when further cytogenetic analysis is desired because of the test's increased likelihood of obtaining results and improved detection of causative abnormalities.
- Comprehensive patient pretest and posttest genetic counseling, provided by an obstetrician-gynecologist or other health care provider with genetics expertise, regarding the benefits, limitations, and results of CMA is essential. CMA should not be ordered without informed consent, which should include discussion of the potential to identify findings of uncertain significance, nonpaternity, consanguinity, and adult-onset disease.

Society for Maternal-Fetal Medicine (SMFM)

The SMFM Consult Series number 52 (2020) on the diagnosis and management of FGR includes the following recommendations:

- Pregnant women should be offered fetal diagnostic testing, including CMA, when FGR is detected and a fetal malformation, polyhydramnios, or both are present, regardless of gestational age (1B: strong recommendation, moderate-quality evidence).
- Pregnant women should be offered prenatal diagnostic testing with CMA when unexplained isolated FGR is diagnosed at < 32 weeks of gestation (1C: strong recommendation, low-quality evidence).

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

- 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: strong recommendation, high-quality evidence).
- Providers should discuss the benefits and limitations of CMA and conventional karyotype with patients who are considering amniocentesis and chorionic villus sampling; both options should be available to women who choose to undergo diagnostic testing (GRADE 1B: strong recommendation, moderate-quality evidence).
- Pre- and posttest 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)

The SOGC addresses the use of CMA in their recommendations on FGR in singleton pregnancies (Kingdom et al., 2023). The SOGC indicates that genetic consultation and amniocentesis for CMA should be offered to patients with suspected early-onset FGR, especially in the presence of structural abnormalities, polyhydramnios, or multiple soft markers, and when there is no indication of a placental basis for FGR (strong recommendation; high quality of evidence).

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

An SOGC/CCMG practice guideline for the use of CMA for prenatal diagnosis and assessment of fetal loss (Armour et al., 2018) recommends the following:

- For samples obtained via invasive prenatal testing:
  - An offer of CMA is recommended in cases with multiple fetal anomalies identified by a comprehensive obstetric ultrasound (II-1A).
  - Single structural defects in association with other abnormal ultrasound findings (e.g., intrauterine growth restriction, oligohydramnios) should not be considered isolated; thus, CMA should be offered if rapid aneuploidy detection results are normal (III-B).
  - In cases with a single fetal anomaly, prenatal CMA should be considered for those malformations associated with a high frequency of abnormal results. Its use in cases in which the diagnostic yield is lower may be considered, if resources are available (III-B).
  - In fetuses with nuchal translucency of ≥ 3.5 mm, prenatal CMA should be offered (II-2B).
- For analysis of fetal loss prior to 20 weeks' gestation, in cases of congenital anomalies and/or intrauterine growth restriction, if quantitative fluorescence–polymerase chain reaction methodologies and/or other directed diagnostic inquiries do not provide a diagnosis and further cytogenetic analysis is intended, it is recommended that karyotype be replaced with CMA (III-B).
- For samples from stillbirths, that is, fetal deaths at ≥ 20 weeks' gestation:
  - If rapid aneuploidy detection results and/or other directed diagnostic inquiries are uninformative, it is recommended that in cases complicated by congenital anomalies and/or intrauterine growth restriction, karyotype be replaced with CMA when further cytogenetic analysis is desired (II-2B).

- In stillbirths without structural fetal anomalies, CMA may be considered in the context of local resource availability and site-based postmortem protocol (whether complete, limited, or external only) (II-2B).

Use in Pediatrics

The Shreeve et al. (2024) systematic review and meta-analysis, evaluated the incremental diagnostic yield of whole-genome sequencing (WGS) compared with that of WES and/or CMA in fetuses and infants with anomalies detectable or potentially detectable via prenatal ultrasound. The secondary outcomes included turnaround time and DNA quantity requirements. The review included 18 studies, encompassing 1,284 cases, with eight prenatal cohorts (754 cases) and 10 postmortem, neonatal, or infant cohorts with congenital structural abnormalities. WGS demonstrated a nonsignificant incremental yield of 1% over WES (95% CI, 0%-4%; I^2 = 47%). In contrast, WGS showed a significant incremental yield over quantitative fluorescence polymerase chain reaction/CMA: 26% overall (95% CI, 18%-36%; I^2 = 86%), 16% in prenatal cases (95% CI, 9%-24%; I^2 = 85%), and 39% in postnatal cases (95% CI, 27%-51%; I^2 = 53%). The pooled median turnaround time for WGS was 18 days. However, only one study reported turnaround time for CMA/WES, precluding comparison. Overall, WGS significantly improved diagnostic yield compared with CMA but not compared with WES. The authors concluded that current evidence is insufficient to support the routine use of WGS over CMA or WES. However, WGS may offer advantages in requiring less DNA and enabling faster turnaround times. Further research is recommended to validate these potential benefits.

In 2023, Hayes published a Clinical Utility Evaluation addressing the use of genetic testing (including CMA) to determine genetic etiology and to improve outcomes in individuals who have been clinically diagnosed with autism spectrum disorder (ASD) and/or their first-degree relatives. Hayes found insufficient evidence to support the clinical utility of genetic testing in this population, finding only three very poor-quality studies suggesting that CMA may lead to additional medical management in a subset of individuals. However, Hayes did not identify studies of long-term follow-up in individuals or their family members or studies that compared outcomes with those in a control group. Hayes concluded that there is weak support for genetic testing in individuals with clinically diagnosed ASD in clinical practice guidelines and position statements. During their 2024 and 2025 annual reviews of this topic, Hayes identified additional evidence that may have implications for the clinical utility of CMA in this population but did not publish any conclusions regarding the quality, strength, or direction of effects of the new evidence.

Landis et al. (2023) evaluated the association of detailed pediatric phenotypes with abnormal CMA findings using registry data from 1,363 children at nine pediatric cardiac centers in the U.S. Each individual had both a CHD diagnosis (per abnormal findings on echocardiogram) and abnormal CMA results. Cardiac phenotypes were classified and assessed for associations with abnormal CMA results. Genomic disorders with a well-known CHD association were identified in 28% of the study population; in 67%, CMA identified CNVs with a rare or novel CHD association, with submicroscopic CNV enrichment for more complex types of CHD. Overall, 5% were found to have only regions of homozygosity. The authors concluded that the detection of new candidate genes and genomic associations identified in this study, contributing to stratified phenotyping, is expected to support the interpretation of CMA results and clinical management of individuals with CHD.

Sheidley et al. (2022) conducted a systematic review and meta-analysis to evaluate the diagnostic yield of genetic tests commonly used in epilepsy, including genome sequencing, exome sequencing, multigene panels, and CMA. The analysis included 154 studies, which encompassed 39,094 individual outcomes through 2020. An additional 43 publications were reviewed to assess nondiagnostic outcomes such as treatment modifications, prognostic insights, recurrence risk, and the role of genetic counseling. The overall diagnostic yield across all test types was 17%. Genome sequencing had the highest yield at 48%, followed by exome sequencing at 24%, multigene panels at 19%, and CMA at 9%. Among phenotypic factors, only the presence of developmental and epileptic encephalopathy or neurodevelopmental comorbidities was significantly associated with higher diagnostic yield. Significant heterogeneity limited the analyses. Despite efforts to identify contributing variables, subgroup analyses did not meaningfully reduce heterogeneity, suggesting the presence of additional, unrecognized factors. While the study offers a comparative assessment of current genetic testing options, it also highlights the need for large, high-quality, prospective studies to explore variable interactions and assess the clinical utility of genetic evaluation in epilepsy. Publications by Jang et al. (2019), Coppola et al. (2019), Berg et al. (2017) and d'Orsi et al. (2017), previously discussed in this policy, were included in this systematic review and meta-analysis.

Miclea et al. (2022) sought to identify clinically relevant CNVs in children with a diagnosis of global developmental delay (GDD)/intellectual disability (ID) using CMA. The study included 189 Romanian children (3-18 years of age; average age, 11.17 years) who had been diagnosed with GDD/ID but who had not been diagnosed with karyotype-confirmed trisomy 21. A complete clinical evaluation was performed, which included examination for dysmorphic and internal malformations, neuropsychological and psychiatric assessment, metabolic evaluation, standard karyotyping, and CMA. Pathogenic CNVs and uniparental disomy were identified in 35 of the participants (18.5%); recurrent CNVs were observed in 21 of the 35

participants with pathogenic findings. The authors concluded that these results support the use of CMA in individuals affected by GDD/ID with a nonspecific phenotype.

Harris et al. (2020) conducted a retrospective chart review to evaluate the diagnostic yield of CMA in toddlers with a *Diagnostic and Statistical Manual of Mental Disorders* (Fifth Edition) diagnosis of ASD (n = 500); of them, 59.8% (n = 299) received CMA, with results stratification into three groups: normal/negative findings, VUS, and pathogenic variants. Pathogenic variants were identified in 9.0% (n = 27) of those tested. No significant differences in Bayley Scales of Infant Development cognitive (p = 0.112), language (p = 0.898), and motor scores (p = 0.488) were observed between the patients with various CMA results. Of the patients with pathogenic findings on CMA, 63% received further medical recommendations based on the testing. The authors concluded that these results confirm the clinical utility of genetic testing in toddlers diagnosed with ASD due to the relatively high yield and lack of distinguishable pretest phenotypic differences. (This study is included in the Clinical Utility Evaluation by Hayes, 2023, updated 2025.)

Clinical Practice Guidelines

American Academy of Pediatrics (AAP)

Rodan et al. (2025) reported the AAP recommendations for the genetic evaluation of GDD/ID, basing the recommendations on diagnostic yield and practical considerations for the general pediatrician such as test complexity and impact on management. The AAP continues to recommend CMA in the first-tier agnostic evaluation for GDD/ID, along with WES (sequential or concurrent). Depending on the situation, testing additional affected or unaffected family members for further segregation data may be useful. If WGS is initially performed, there is typically adequate evaluation of CNVs, so CMA can be deferred in most cases.

In 2020, the AAP (Hyman et al.) published a clinical report addressing the identification, evaluation, and management of children with ASD. The AAP recommends offering CMA and considering a referral to genetics for an etiologic investigation if a syndrome diagnosis or metabolic disorder is not suspected.

American College of Medical Genetics and Genomics (ACMG)

In 2023, the ACMG (Raca et al., 2023) published guidance in a points-to-consider document for clinical laboratory geneticists and other clinicians, advising on the detection of germline structural variants. Their recommendations include the following:

- Test selection should be based on the clinical phenotype, medical and family history, results of ancillary testing, and scope of the differential diagnosis. If the clinician suspects a particular disorder or if a patient presents with a phenotype known to be commonly caused by a specific set of genes, a targeted test may be more appropriate than a genome-wide assay.
- Nonspecific or overlapping presentations may call for broader testing strategies such as CMA, WES, or WGS.
- In the prenatal setting, for a fetus with imaging abnormalities and/or abnormal NIPS, standard CMA and karyotyping should be considered.

The 2013 ACMG guidelines for the clinical genetics evaluation of ASD (Schaefer and Mendelsohn, 2013) list CMA as the recommended first-tier diagnostic test, replacing karyotype, except in certain settings, such as a clinically suspected chromosome aneuploidy.

The ACMG published the following recommendations for the use of CMA (Manning and Hudgins, 2010; reaffirmed 2020):

- CMA testing for CNVs is recommended as a first-line test in the initial postnatal evaluation of patients with the following:
  - Multiple anomalies not specific to a well-delineated genetic syndrome.
  - Apparently nonsyndromic developmental delay/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 studies in the patient, parental evaluation, and clinical genetic evaluation and counseling.

This guideline does 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 comparative genomic hybridization vs 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.

Canadian College of Medical Geneticists (CCMG)

In a 2023 position statement (Carter et al.), the CCMG recommended CMA as a first-tier test for patients with GDD, ID, or ASD.

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.

Genetic tests are regulated under the Clinical Laboratory Improvement Amendments of 1988. Refer to the following website for more information: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/IVDRegulatoryAssistance/ucm124105.htm. (Accessed February 3, 2026)

Refer to the following website for a list of nucleic acid–based tests/platforms that have been cleared or approved by the FDA's Center for Devices and Radiological Heath: https://www.fda.gov/medical-devices/in-vitro-diagnostics/nucleic-acid-based-tests. (Accessed February 3, 2026)

References

American College of Obstetricians and Gynecologists and the Society for Maternal-Fetal Medicine. Management of stillbirth: obstetric care consensus no. 10. Obstet Gynecol. 2020 Mar;135(3):e110-e132. Erratum in: Obstet Gynecol. 2023 May 01;141(5):1030.

American College of Obstetricians and Gynecologists Committee on Genetics and the Society for Maternal-Fetal Medicine. Committee opinion no. 682: microarrays and next-generation sequencing technology: the use of advanced genetic diagnostic tools in obstetrics and gynecology. Obstet Gynecol. 2016a Dec;128(6):e262-e268.

American College of Obstetricians and Gynecologists. Practice bulletin no. 162: prenatal diagnostic testing for genetic disorders. May 2016b. Available at: https://www.acog.org/clinical/clinical-guidance/practice-bulletin/articles/2016/05/prenatal-diagnostic-testing-for-genetic-disorders. Accessed February 20, 2026.

American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 5th ed. Arlington, VA: American Psychiatric Association. 2013.

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

Awuah WA, Shah MH, Sanker V, et al. Advances in chromosomal microarray analysis: transforming neurology and neurosurgery. Brain Spine. 2025 Jan 25;5:104197.

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

Carter MT, Srour M, Au PB, et al. Genetic and metabolic investigations for neurodevelopmental disorders: position statement of the Canadian College of Medical Geneticists (CCMG). J Med Genet. 2023 Jun;60(6):523-532.

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

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

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

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

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

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

Hayes, Inc. Clinical Utility Evaluation. Genetic testing for patients with clinically diagnosed autism spectrum disorder. Hayes, Inc.; September 15, 2023. Updated September 11, 2025.

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

Hyman SL, Levy SE, Myers SM. Identification, evaluation, and management of children with autism spectrum disorder. Reaffirmed 2025. Pediatrics. 2020 Jan;145(1):e20193447.

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

Kingdom J, Ashwal E, Lausman A, et al. Guideline No. 442: fetal growth restriction: screening, diagnosis, and management in singleton pregnancies. J Obstet Gynaecol Can. 2023 Oct;45(10):102154.

Landis BJ, Helvaty LR, Geddes GC, et al. A multicenter analysis of abnormal chromosomal microarray findings in congenital heart disease. J Am Heart Assoc. 2023 Sep;12(18):e029340.

Li H, Hu J, Wu Q, et al. Chromosomal abnormalities detected by chromosomal microarray analysis and pregnancy outcomes of 4,211 fetuses with high-risk prenatal indications. Sci Rep. 2024 Jul 10;14(1):15920.

Li P, Wu W, Zhang X, et al. The assessing of clinical relevance of chromosomal microarray analysis in the prenatal diagnosis of fetal growth restriction. BMC Pregnancy Childbirth. 2025 Feb;25(1):198.

Lu Q, Luo L, Zeng B, et al. Prenatal chromosomal microarray analysis in a large Chinese cohort of fetuses with congenital heart defects: a single center study. Orphanet J Rare Dis. 2024 Aug;19(1):307.

Manning M and Hudgins L. Array–based technology and recommendations for utilization in medical genetics practice for detection of chromosomal abnormalities. Genet Med. 2010 Nov;12(11):742-745. Erratum in: Genet Med. 2020 Dec;22(12):2126.

Mastromoro G, Guadagnolo D, Hashemian NK, et al. A pain in the neck: lessons learnt from genetic testing in fetuses detected with nuchal fluid collections, increased nuchal translucency versus cystic hygroma: systematic review of the literature, meta-analysis and case series. Diagnostics (Basel). 2022a Dec;13(1):48.

Mastromoro G, Guadagnolo D, Hashemian NK, et al. Molecular approaches in fetal malformations, dynamic anomalies and soft markers: diagnostic rates and challenges: systematic review of the literature and meta-analysis. Diagnostics (Basel). 2022c Feb;12(3):575.

Mastromoro G, Hashemian NK, Guadagnolo D, et al. Chromosomal microarray analysis in fetuses detected with isolated cardiovascular malformation: a multicenter study, systematic review of the literature and meta-analysis. Diagnostics (Basel). 2022b May;12(6):1328.

Matarrelli B, Khalil A, Bernassola M, et al. Outcome of fetuses with early increased nuchal translucency: systematic review and meta-analysis. Ultrasound Obstet Gynecol. 2025 Aug;66(2):147-154.

Miclea D, Osan S, Bucerzan S, et al. Copy number variation analysis in 189 Romanian patients with global developmental delay/intellectual disability. Ital J Pediatr. 2022 Dec;48(1):207.

Nguyen PT, Hoang TNL, Tran DC, et al. The yield of using single-nucleotide polymorphism–based chromosomal microarray analysis in diagnosis the genetic etiology of fetal growth restriction. Clin Ter. 2025 Jan-Feb;176(1):60-66.

Olayiwola JO, Marhabaie M, Koboldt D, et al. Clinically significant findings in a decade-long retrospective study of prenatal chromosomal microarray testing. Mol Genet Genomic Med. 2024 Mar;12(3):e2349.

Papoulidis I, Sotiriadis A, Siomou E, et al. Routine use of array comparative genomic hybridization (aCGH) as standard approach for prenatal diagnosis of chromosomal abnormalities: clinical experience of 1,763 prenatal cases. Prenat Diagn. 2015 Dec;35(13):1269-1277.

Pauta M, Grande M, Rodriguez-Revenga L, et al. Added value of chromosomal microarray analysis (CMA) over karyotyping in early pregnancy loss: a systematic review and meta-analysis. Ultrasound Obstet Gynecol. 2018 Apr;51(4):453-462.

Peng R, Yang J, Xie HN, et al. Chromosomal and subchromosomal anomalies associated to small for gestational age fetuses with no additional structural anomalies. Prenat Diagn. 2017 Dec;37(12):1219-1224. Erratum in: Prenat Diagn. 2018 Feb;38(3):224.

Raca G, Astbury C, Behlmann A, et al. Points to consider in the detection of germline structural variants using next-generation sequencing: a statement of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2023 Feb;25(2):100316.

Rodan LH, Stoler J, Chen E, et al. Genetic evaluation of the child with intellectual disability or global developmental delay: clinical report. Pediatrics. 2025 Jul 1;156(1):e2025072219.

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

Sapantzoglou I, Kontogeorgi E, Pergialiotis V, et al. The incremental yield of CMA over karyotype in fetal growth restriction: a systematic review and meta-analysis. Prenat Diagn. 2026 Jan;46(1):56-74.

Schaefer GB and Mendelsohn NJ. Clinical genetics evaluation in identifying the etiology of autism spectrum disorders: 2013 guideline revisions. Genet Med. 2013 May;15(5):399-407.Erratum in: Genet Med. 2013 Aug;15(8):669.

Shaffer LG, Rosenfeld JA, Dabell MP, et al. Detection rates of clinically significant genomic alterations by microarray analysis for specific anomalies detected by ultrasound. Prenat Diagn. 2012 Oct;32(10):986-995.

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

Shreeve N, Sproule C, Choy KW, et al. Incremental yield of whole-genome sequencing over chromosomal microarray analysis and exome sequencing for congenital anomalies in prenatal period and infancy: systematic review and meta-analysis. Ultrasound Obstet Gynecol. 2024 Jan;63(1):15-23.

Society for Maternal-Fetal Medicine (SMFM). The use of chromosomal microarray for prenatal diagnosis. Am J Obstet Gynecol. 2016 Oct;215(4):B2-B9. Erratum in: Am J Obstet Gynecol. 2017 Feb;216(2):180.

Society for Maternal-Fetal Medicine. Consult series #52: diagnosis and management of fetal growth restriction. Am J Obstet Gynecol. 2020 Oct;223(4):B2-B17.

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

Srebniak MI, Joosten M, Knapen MFCM, et al. Frequency of submicrosomic chromosomal aberrations in pregnancies without increased risk for structural chromosomal aberrations: systematic review and meta-analysis. Ultrasound Obstet Gynecol. 2018 Apr;51(4):445-452.

Talking Glossary of Genetic and Genomic Terms [Internet]. Bethesda (MD): National Human Genome Research Institute (US); Updated February 2025. Available from https://www.genome.gov/genetics-glossary. Accessed February 3, 2026.

Wang H, Lin X, Lyu G, et al. Chromosomal abnormalities in fetuses with congenital heart disease: a meta-analysis. Arch Gynecol Obstet. 2023 Sep;308(3):797-811.

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

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

Ye F, Xu X, Wang Y, et al. The yield of SNP microarray analysis for fetal ultrasound cardiac abnormalities. BMC Pregnancy Childbirth. 2024 Apr;24(1):244.

Yin J, Zhang X, Wang Q, et al. Complementary role of echocardiography, karyotyping, and chromosomal microarray in congenital cardiac anomalies. Front Med (Lausanne). 2025 Aug;12:1586161.

Zheng Y, Xue S, Ding G, et al. Clinical study of single nucleotide polymorphism–based chromosome microarray analysis in the etiological diagnosis of fetal congenital heart disease. Sci Rep. 2025 Nov;15(1):39970.

Policy History/Revision Information

Date	Summary of Changes

06/01/2026	**Related Policies**
	• Added reference link to the Medical Policy titled *Genetic Testing for Cardiac Disease*
	• Removed reference link to the Medical Policy titled:
	  ○ *FDA Cleared or Approved Companion Diagnostic Testing*
	  ○ *Molecular Oncology Testing for Hematologic Cancer Diagnosis, Prognosis, and Treatment Decisions*
	Coverage Rationale
	• Replaced reference to:
	  ○ "Multiple anomalies" with "multiple *Congenital* Anomalies"
	  ○ "Developmental Delay" with "*Global* Developmental Delay"

Date	Summary of Changes

	Definitions
	• Added definition of:
	  ○ Autism Spectrum Disorder
	  ○ Congenital Anomaly
	• Removed definition of "Prenatal Diagnosis"
	• Updated definition of:
	  ○ Global Developmental Delay
	  ○ 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 2026T0559FF

Instructions for Use

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

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

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