Chromosomal Microarray and Low-pass Whole Genome Sequencing

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POLICY DESCRIPTION | RELATED POLICIES | INDICATIONS AND/OR LIMITATIONS OF COVERAGE | TABLE OF TERMINOLOGY | SCIENTIFIC BACKGROUND | GUIDELINES AND RECOMMENDATIONS | APPLICABLE STATE AND FEDERAL REGULATIONS | APPLICABLE CPT/HCPCS PROCEDURE CODES | EVIDENCE-BASED SCIENTIFIC REFERENCES | REVISION HISTORY

I. Policy Description

Chromosomal microarray (CMA) testing refers to the use of comparative genomic hybridization (CGH) arrays to detect small (10 to 100kb) duplications or deletions of chromosomal DNA (copy number variants or CNVs), similarity in single nucleotide sequences (homozygosity), and triploidy when chromosomal abnormality is suspected based on clinical presentation.[1] Genetic counseling is strongly recommended for individuals being considered for chromosomal microarray testing. Low-pass whole genome sequencing (low-pass WGS) is a method of WGS that is less expensive and has lower coverage than standard WGS. Low-pass WGS maintains a high accuracy for detecting single nucleotide sequences by using imputation algorithms.[2]

For guidance on exome sequencing, please see AHS-M2032-Genome and Exome Sequencing.

II. Related Policies

Policy Number	Policy Title
AHS-G2055	Prenatal Screening for Fetal Aneuploidy
AHS-M2032	Genome and Exome Sequencing
AHS-M2075	Genetic Testing for Epilepsy
AHS-M2176	Testing for Developmental Delay
AHS-M2179	Prenatal Screening (Genetic)

III. Indications and/or Limitations of Coverage

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request. Specifications pertaining to Medicare and Medicaid can be found in the "Applicable State and Federal Regulations" section of this policy document.

1) To evaluate any second-trimester or later pregnancy loss **or** the second consecutive first-trimester

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pregnancy loss, chromosomal microarray (CMA) testing **or** low-pass whole genome sequencing (low-pass WGS) of the products of conception (e.g., fetal tissue and/or the fetus) **MEETS COVERAGE CRITERIA**.

2) Prenatal CMA testing **or** low-pass WGS **MEETS COVERAGE CRITERIA** when **any** of the following conditions are met:
   a) When diagnostic testing for fetal aneuploidy is needed for pregnant individuals undergoing invasive prenatal testing (i.e., amniocentesis, chorionic villus sampling, or fetal tissue sampling).
   b) When non- invasive prenatal screening (NIPS) results require confirmation.
   c) As a follow-up test for any smaller copy-number changes that were reported as positive by NIPS.
   d) When ultrasound examination reveals one or more structural abnormalities.
   e) When, regardless of gestational age, fetal growth restriction is detected and a fetal malformation or polyhydramnios (or both) are also present.
   f) When unexplained isolated fetal growth restriction is diagnosed at <32 weeks of gestation.
   ~~g) When there is intrauterine fetal demise or stillbirth in the third trimester and CMA is indicated to determine the potential cause.~~
   ~~h)~~g) When the fetus is at high risk for a chromosome abnormality detectable by CMA, based on family history.
3) Evaluation with CMA testing **or** low-pass WGS **MEETS COVERAGE CRITERIA** for **any** of the following situations:
   a) For individuals with multiple congenital anomalies that are not specific to a well-delineated genetic condition and cannot be identified based on clinical evaluation alone.
   b) For individuals with non-syndromic developmental delay/intellectual delay.
   c) For individuals with autism spectrum disorder.
   d) For individuals with a suspected inherited seizure disorder.
   e) When sex determination by NIPS is discordant with physical examination or clinical findings are suggestive of a disorder of sexual differentiation.
   f) For individuals with proportionate short stature with other physical or structure defects.
4) When performed in parallel with fetal diagnostic testing, maternal cell contamination (MCC) analysis **MEETS COVERAGE CRITERIA**.
5) For central nervous system (CNS) tumors and pediatric solid and soft tissue tumors, CMA testing **MEETS COVERAGE CRITERIA.**
6) When a chromosomal trisomy is suspected, postnatal CMA testing **DOES NOT MEET COVERAGE CRITERIA**.
7) Co-testing CMA and low-pass WGS **DOES NOT MEET COVERAGE CRITERIA**.

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The following does not meet coverage criteria due to a lack of available published scientific literature confirming that the test(s) is/are required and beneficial for the diagnosis and treatment of an individual's illness.

8) For all other situations not described above, CMA testing **DOES NOT MEET COVERAGE CRITERIA**.

IV. Table Of Terminology

Term	Definition
AAN	American Academy of Neurology
AAP	American Academy of Paediatrics
ACMG	American College of Medical Genetics and Genomics
ACOG	American College of Obstetricians and Gynaecologists
AMP	Association For Molecular Pathology
ASD	Autism Spectrum Disorder
ASRM	American Society for Reproductive Medicine
CCMG	Canadian College of Medical Geneticists
CGH	Comparative genomic hybridization
CLIA	Clinical Laboratory Improvement Amendments
CM	Chromosomal mosaicism
CMA	Chromosomal microarray analysis
CMS	Centers for Medicare and Medicaid
cnLOH	Copy-neutral loss of heterozygosity
CNS	Central nervous system
CNVs	Copy number variants
CSCA	Chromosomal abnormalities
CVS	Chorionic villi sampling
DD	Developmental delay
DD/ID	Developmental disability/Intellectual disability
ES	Endocrine Society
FGR	Fetal growth restriction
GDD/ID	Global developmental delay
ID	Intellectual disability
ISCA	International standard cytogenetic array
ISPD	International Society for Prenatal Diagnosis
ISS	Idiopathic short stature
IUGR	Intrauterine growth restriction
LDTs	Laboratory developed Tests
LOH	Loss/Absence of Heterozygosity
LP-GS	Low-pass genome sequencing

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MCC	Maternal cell contamination
NIHF	Non-immune hydrops fetalis
NIPS	Non- invasive prenatal screening
POC	Products of conception
PQF	Perinatal Quality Foundation
QF-PCR	Quantitative fluorescent polymerase chain reaction
RAD	Restriction-site associated DNA sequencing
SMFM	Society for Maternal-Fetal Medicine
SNP	Single nucleotide polymorphism
SOGC	Society of Obstetricians and Gynaecologists of Canada
STR	Short tandem repeat
UPD	Uniparental isodisomy
VOUS/VUS	Variant of unknown significance
VPS	Variant of possible significance
WES	Whole exome sequencing
WGS	Whole genome sequencing

V. Scientific Background

Chromosomal abnormalities are associated with a variety of disorders including developmental delay (DD), intellectual disability (ID), and congenital anomalies, as well as pregnancy loss.[3,4]

Chromosomal microarray (CMA) testing to detect copy number variations (CNVs), homozygosity, and triploidy has replaced karyotyping as the first-tier diagnostic tool for many cases where chromosomal abnormality is suspected.[1,4] CMA is significantly more sensitive (10 to 100 kb) than traditional karyotyping (5 to 10 Mb); additionally, CMA does not require cell culture, which reduces the turnaround time for results.[4] and provides an alternative to karyotyping when dividing cells are not available for analysis. This technique may be used for several different purposes, such as identifying a cause of pregnancy loss or identifying other aneuploid conditions, such as Down Syndrome.[5,6] **"**Emerging studies suggest that low-pass genome sequencing (GS) provides additional diagnostic yield of clinically significant copy-number variants (CNVs) compared with chromosomal microarray analysis (CMA). However, a prospective back-to-back comparison evaluating accuracy, efficacy, and incremental yield of low-pass GS compared with CMA is warranted."[7]

Chromosomal microarray (CMA) uses comparative genomic hybridization (CGH) to compare the DNA of a patient with a normal control using standard sets of DNA probes immobilized on a glass slide or glass beads.[8] CGH arrays have been designed to cover the entire genome, for targeted analysis of known microdeletion/microduplication syndromes, and for known loci of inherited mutations.[1] Array sensitivity varies based on the size and type of probes used. Oligonucleotide probes (~60 base pairs) or single nucleotide polymorphism (SNP) probes (32-40 base pairs) are most common. Oligonucleotide probes can be used to cover the entire genome at an average resolution of about 35 kb. Current arrays generally use a combination of copy number probes (oligonucleotide) to detect copy gains and losses and single nucleotide polymorphism (SNP) probes to detect similarity in single nucleotide sequences

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(homozygosity). The combination of probes detect runs of homozygosity between the maternal and paternal copy of each chromosome, enabling diagnosis of triploidy, uniparental disomy, and consanguinity as well as improving the detection of low levels of mosaicism.[4]

Chromosomal microarray (CMA), as all genetic tests, can have variable clinical sensitivity due to the numerous types of genetic abnormalities that can impact gene expression. Some genetic conditions are caused by a change in copy number and/or a sequence change in the gene that is undetectable by CMA. If a genetic condition in which a subset of cases are caused by sequence changes, then other testing should be considered either in place of, or in addition to, CMA.[4]

Low-pass WGS is a less expensive but lower coverage method of standard WGS. Low-pass WGS typically has less than 1x coverage, while standard WGS has a depth of 30x to 50x.[9] Alternatively, compared to traditional low-cost microarrays, low-pass WGS results have over ten times the amount of information. Low-pass WGS maintains accuracy with reduced coverage by using imputation algorithms, a statistical analysis method that assigns values to missing data based on known information. With imputation algorithms, the low-pass WGS method uses known genetic variants within a representative population to genotype an individual without measurements from every locus.[2]

CMA and Seizures

A seizure occurs due to erroneous electrical activity in the brain and may strike for many reasons including a brain injury or infection, abnormal sodium or glucose levels in the blood, congenital brain defects, epilepsy, and electric shock.

Epilepsy is a neurological disorder associated with abnormal electrical brain activity. CMA is often the first genetic tool used to obtain more information about a patient's epilepsy and has a diagnostic yield of approximately 8% with several studies reporting higher values.[10,11] Testing a specific gene may be appropriate in some epileptic cases as more than 80 genes have been associated with epilepsy and hundreds more associated with disorders that are accompanied by seizures.[10] However, if results are negative, CMA or gene testing should commence as this is likely more appropriate than testing several more genes individually.[12] If CMA testing is negative, gene panel and exome testing are appropriate.

Olson, et al. (2014)have found that in many patients, CNVs identified through CMA were able to explain an epileptic phenotype. The authors concluded that "Because the diagnostic yield of CMA for epilepsy patients is similar to the yield in autism spectrum disorders and in prenatal diagnosis, for which published guidelines recommend testing with CMA, we recommend the implementation of CMA in the evaluation of unexplained epilepsy."[13]

CMA and Short Stature

Short stature is a general term used to describe individuals whose height is two standard deviations or more below the mean compared to peers of the same age and racial-ethnic group.[14] The most common causes of short stature are genetic and delayed growth; these are considered normal or nonpathologic variants of growth.[14]

Intrauterine growth restriction (IUGR) is a condition which describes when an unborn baby is growing abnormally slow in the womb; this could be due to either genetic or environmental factors and may

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cause significant morbidity and mortality in infants.[3] CMA has been used for diagnostic purposes in fetuses due to IUGR.[14]

Idiopathic short stature (ISS) describes individuals whose height falls below two standard deviations of the mean for age, but no metabolic, endocrine, or other diagnosis has been identified to cause the height disorder.[14] Regarding the genetic evaluation of short stature, some researchers suggest that for patients with ISS, patients born small for gestational age, or patients with growth hormone deficiency, "Targeted evaluation of a single gene or panels of genes is recommended... For those patients who do not fit into a distinct subgroup or for whom initial genetic testing is inconclusive, we recommend consideration of genome-wide evaluation through exome sequencing and chromosomal microarray to detect both sequence variants and CNVs."[15] An association has been identified between CNVs and short stature, and many report that CMA is a promising tool to identify pathogenic CNVs in patients with ISS.[16]

Proprietary Testing

The only FDA-approved commercial CMA test is CytoScan® by ThermoFisher. This test helps identify the underlying genetic causes of developmental delay, intellectual disability, congenital anomalies, or dysmorphic features in children. CytoScan® detects chromosomal CNVs in genomic DNA from peripheral whole blood.[17]

Several other commercial CMA tests are available including the GenomeDx CMA by GeneDx. The GenomeDx is able to confirm clinical diagnoses, differentiate between de novo and familial cases, and assist with prenatal diagnoses in at-risk pregnancies.[18] This test has a three-week turnaround time and may utilize both blood (preferred) and buccal swabs (cheek swabs) as the tested specimen. The GenomeDx is a whole-genome CMA, containing 118,000 oligonucleotide probes that detect CNVs.[18]

Quest Diagnostics has developed the ClariSure® Postnatal CMA Test; the ClariSure® consists of over 2.6 million probes that detect 1,900,000 CNVs and 750,000 SNPs.[19] With a 10- to 15-day turnaround time, this test can help to determine the genetic cause of developmental delay or mental retardation. Blood is the preferred specimen for this test, but saliva may also be used.[19]

LabCorp has developed Reveal®, an SNP microarray aimed for pediatric purposes. This test uses a blood or salivary sample to detect chromosomal abnormalities that may be associated with congenital anomalies or developmental delay. Results are provided in 14-17 days.[20]

The Invitae Chromosomal Microarray Analysis test is used too diagnosis chromosomal abnormalities associated with developmental disorders, multiple congenital anomalies, dysmorphic features, autism spectrum disorders, seizures, and epilepsy. The turnaround time is 10-12 days and samples can include whole blood or post birth cord blood. This test can detect whole and segmental aneuploidies, submicroscopic copy CNVs that cannot be detected by conventional karyotype, size and gene content of CNVs, regions of homozygosity, and uniparental isodisomy.[21]

Analytical Validity

Although chromosomal microarray testing can vary widely in technology, resolution, and the likelihood of producing results of unknown significance, studies have demonstrated that CMA provides chromosomal evaluation at a much higher resolution than karyotyping.[1,22] Miller, et al. (2010) noted that

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most clinical CMA platforms available in 2010 could detect copy number changes at a resolution of 400 kb; this was considered at least a "10-fold" improvement over G-banded karyotyping.[22]

In a retrospective study, Zhu, et al. (2021) compared the utility of non-invasive prenatal screening (NIPS) with chromosomal microarray analysis (CMA) for the detection of chromosomal abnormalities in high-risk pregnancies. Of the 774 high risk pregnancies, 550 (71.1%) had a positive NIPS result, while 308 (39.8%) had a positive CMA result. The rate of full or partial concordance was 82.2% between NIPS and CMA. CNV's were more often detected by CMA, with an incidence of 7.9% by CMA and 3.1% by NIPS. In addition, a genetic aberration was detected by CMA in 1 in 17 high risk pregnancies that had a negative NIPS result. Overall, the authors conclude that "CMA should be offered instead of expanded NIPS for high-risk pregnancies."[23]

Chaubey, et al. (2020) compared the diagnostic utility of low-pass genome sequencing (LP-GS) to chromosomal microarrays (CMAs) in its ability to detect copy number variants (CNVs). 409 DNA samples were studied for CNV accuracy, precision, specificity, and sensitivity using both techniques. The LP-GS test accurately detected 40 positive control samples with clinically relevant CNVs, absence of heterozygosity, deletions and duplications, and translocations and accurately reported 38 control samples without any clinically significant CNVs. In addition, 331 clinical specimens were tested for developmental delay, autism, intellectual disability, congenital anomalies, and dysmorphic features. Of the 331 cases, pathogenic CNVs were detected in 57 cases relating to microdeletion/microduplication syndromes, intragenic deletions and intragenic duplications, uniparental isodisomy, triploidy, and whole chromosome aneuploidies. The other cases were classified as variants of unknown significance or did not have a reportable CNV finding. The authors conclude that "LP-GS was able to reliably detect absence of heterozygosity, microdeletion/microduplication syndromes, and intragenic CNVs with higher coverage and resolution over the genome."[24]

Mazzonetto, et al. (2024) preformed a study evaluating the performance of low-pass whole genome sequencing (LP-WGS) to detect copy number variants (CNVs) in clinical cytogenetics. The DNA samples selected for this study were obtained from 44 unrelated individuals previously referred to molecular investigation in clinical cytogenetics. The patients were investigated by CMA (either array-CGH or SNP-array), currently considered the gold standard diagnostic test for CNV analysis DNA panel, with 12 prenatal and 32 postnatal samples, comprising a total of 55 genomic imbalances. The CNVs were chosen to represent a wide range of clinically relevant CNVs detected by CMA in diagnostic routine, being the vast majority of them associated with intellectual disability or recognizable syndromes. The selected CNVs contained at least one coding sequence. They were mapped to a variety of chromosomes ranging in copy number state from zero to 3/4, and ranging in genomic size from 75 kb to 90.3 Mb, including aneuploidies and two mosaic cases. Particularly, for methodology evaluation and quality control metrics, we used DNA extracted from several types of biological samples. The data shows "the potential use of LP-WGS to detect CNVs in clinical diagnosis and confirm the method as an alternative for chromosome imbalances detection."[25]

Clinical Utility and Validity

A review of 33 studies, comparing traditional karyotyping to CMA, has shown that CMA increases the detection rate for chromosomal abnormalities in individuals with DD/ID (developmental disability/intellectual disability) or autism spectrum disorder (ASD). CMA detected pathogenic genomic

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imbalances with an average diagnostic yield of 12.2% across all studies in this patient population, which is about 10% more than karyotyping alone.[22]

Hillman, et al. (2013) performed both a meta-analysis and cohort study evaluating CMA's detection rate of chromosomal abnormalities. The authors investigated 243 pregnant individuals who had both a CMA and karyotype performed, and the meta-analysis included 25 primary studies. Overall, CMA was found to detect 4.1% more abnormalities compared to karyotyping in the cohort study and 10% more in the meta-analysis.[26]

Reddy, et al. (2012) compared the detection rates of microarray and traditional karyotyping. A total of 532 stillbirths were examined. The authors found that microarrays provided more results than karyotyping (87.4% compared to 70.5%) and identified more genetic abnormalities (8.3% vs 5.8%). Microarray analysis also found more genetic abnormalities among 443 antepartum stillbirths (8.8% vs 6.5%) and among 67 stillbirths with congenital abnormalities (29.9% vs 19.4%). Overall, microarray analysis provided a relative increase in the diagnosis of genetic abnormalities of 41.9% in all stillbirths, 34.5% in antepartum stillbirths, and 53.8% in stillbirths with anomalies compared to karyotyping.[5]

Coulter, et al. (2011) assessed impact of CMA results on clinical decision making. A total of 1792 patients were examined, and 235 of them had either an "abnormal" result (n = 131) or a "variant of possible significance" (VPS) (n = 104). Clinical action was recommended for 54% of the patients in the "abnormal" cohort and 34% of the patients in the VPS cohort.[27]

Brady, et al. (2013) performed a prospective study of fetuses with abnormalities detected on ultrasound. A total of 383 prenatal samples were examined. Causal imbalances were found in 37 samples, submicroscopic CNVs were found in ten of the 37 samples, and arrays added "valuable information" over conventional karyotyping in 15 of 37 samples. The authors concluded that there was added value of chromosomal microarrays for prenatal diagnosis in the presence of ultrasound anomalies.[28]

Borrell, et al. (2017) performed a meta-analysis of literature to estimate the incremental yield of CMA over karyotyping in fetal growth restriction (FGR). The authors identified ten studies and found a 4% incremental yield of CMA over karyotyping in "nonmalformed growth-restricted fetuses" and a 10% incremental yield in FGR when associated with fetal malformations.[29]

Robson, et al. (2017) compared karyotyping and CMA in fetuses with ultrasound anomalies. Out of 629 cases with structural anomalies, CMA detected copy number variants (CNVs) and more pathogenic CNVs than karyotyping. CMA was also found to have a turnaround time of five days quicker than karyotyping. Finally, CMA was found to be £113 more expensive per patient than karyotyping. The authors conclude, "CMA is a robust, acceptable and probably cost-effective method to detect more clinically significant chromosomal imbalances in the anomalous fetus. The results suggest that CMA should replace karyotyping in these care pathways."[30]

Li, et al. (2018) performed a study investigating the cost effectiveness of karyotyping, CMA, and NGS in genetic diagnosis of unexplained global developmental delay. The authors found that: "CMA testing results in more genetic diagnoses at an incremental cost of US $2692 per additional diagnosis compared with karyotyping, which has an average cost per diagnosis of US $11,033."[31] The authors also found that performing both tests sequentially result in the same number of diagnoses but costs less

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when CMA testing is done first and karyotyping second. The authors also analyzed the cost-effectiveness of a variant of unknown significance. When CMA testing yields a variant of unknown significance, additional genetic diagnoses can be obtained "at an incremental cost of US $4220 by CMA testing of both parents, and when parents are not available or the patient had a normal CMA result, targeted NGS of the patient can add diagnoses at a further incremental cost of US $12,295." The authors concluded that "These results provide a cost effectiveness rationale for the use of CMA as the first-tier test for the genetic diagnosis of unexplained GDD/ID [global developmental delay/intellectual disability] and further indicate that testing of both parents may be cost effective when a variant of unknown significance is detected in the patient."[31]

Hydrops fetalis occurs when fluid accumulates in fetal serous cavities and soft tissues; nonimmune hydrops fetalis (NIHF) develops when red cell alloimmunization does not cause the hydrops fetalis case in question. A retrospective study by Mardy, et al. (2020) looked at prenatally diagnosed NIHF cases identified at the University of California, San Francisco from 2008 to 2018 was performed. A total of 131 cases were identified. The researchers found that "In 43/44 cases with a CMA performed, results were categorized as normal or likely benign. One case was found on CMA to have a large pathogenic duplication."[32] This shows that CMA is not an effective diagnostic tool for NIHF.

Pasternak, et al. (2020) aimed to assess the diagnostic capabilities of CMA among pregnancies terminated due to fetal malformations identified with ultrasounds. CMA was performed on 71 pregnancies using fetal DNA or placental DNA. The authors noted that "Findings were abnormal in 17 cases (23.9%), of which 13 were detectable by karyotype. The incremental yield of CMA was 4/71 (5.6%); 1/32 (3.1%) for cases with an isolated anomaly and 3/39 (7.7%) for cases with nonisolated anomalies." CMA identified more chromosomal abnormalities than karyotype and did not require dividing cells, making it a more practical option after termination.[33]

Rodriguez-Revenga, et al. (2020) studied the diagnostic yield of CMA in prenatal diagnosis where 2905 prenatal samples with a normal rapid aneuploidy detection test were referred for CMA testing. The study revealed pathogenic CNVs associated with syndromic disorders in 4.8% of the 2905 cases, adding a 2.8% diagnostic value of CMA over karyotyping. This study shows that "CMA increases 2-fold the diagnostic yield achieved by conventional karyotyping." Therefore, "chromosome microarray analysis should be offered to all invasive prenatal diagnostic testing following a normal rapid aneuploidy test result."[34]

Bajaj Lall, et al. (2021) evaluated the diagnostic yield and clinical utility of CMA by comparing it to karyotyping results. CMA and karyotyping were performed on consecutive referrals of 370 prenatal samples of amniotic fluid (n = 274) and chorionic villi (n = 96) from Indian pregnant individuals with high maternal age (n = 23), biochemical screen positive (n = 61), previous child abnormal (n = 59), abnormal fetal ultrasound (n = 205) and heterozygous parents (n = 22). The overall diagnostic yield of abnormal results was higher via CMA than by karyotyping (9.18% vs. 5.40%, respectively). As such, the authors argue that "CMA must be used as the first tier test in all cases with abnormal fetal ultrasound and if cost is not an issue, it can be offered to all pregnant [individuals] undergoing the invasive test, as the test results are faster and the diagnostic yield is higher by CMA than by karyotyping even in other groups."[35]

Monier, et al. (2021) evaluated the use of chromosomal microarray analysis as compared to karyotyping in these cases of isolated fetal growth restriction. Both karyotyping and chromosomal microarray

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analysis were performed in 146 fetuses, and the researchers found that the detection rate of genetic abnormalities by CMA was 7.5%, with an incremental yield of 3.6% as compared to karyotyping. Moreover, CMA was able to identify a variant of unknown significance in three fetuses boasting normal karyotypes. Consequently, the level of granularity of CMA in "these results support the use of chromosomal microarray analysis in addition to karyotype for isolated fetal growth restriction."[36]

Zhang, et al. (2021) investigated the incidence and clinical significance of chromosomal mosaicism (CM) in a single-center retrospective study of invasive prenatal diagnosis of CM. From a sample of 5758 G-band karyotyping results and 6066 CMA results, the authors deduced that their findings "demonstrate that increased risk in genetic counselling is due to discordant CM from different specimens or testing methods" and so "It is highly recommended to use more comprehensive assays such as a combination of CMA, FISH [fluorescence in situ hybridization analysis] and karyotyping to detect mosaicism in AF [amniotic fluid] and CB [cord blood] before any irreversible decision is made in regard to the pregnancy.[37]

Chau, et al. (2020) conducted a retrospective back-to-back comparison study of "low-pass GS versus routine CMA for 532 prenatal, miscarriage, and postnatal cases, the overall diagnostic yield was 22.4% (119/532) for CMA and 23.1% (123/532) for low-pass GS. Thus, the overall relative improvement of the diagnostic yield by low-pass GS versus CMA was ~ 3.4% (4/119). Identification of cryptic and clinically significant CNVs among prenatal, miscarriage, and postnatal cases demonstrated that CNV detection at higher resolutions is warranted for clinical diagnosis regardless of referral indications. Overall, [the] study supports low-pass GS as the first-tier genetic test for molecular cytogenetic testing."~~39~~38

VI. Guidelines and Recommendations

American College of Medical Genetics and Genomics (ACMG)

In the Clinical Practice Resource for Array-based technology and recommendations for utilization in medical genetics practice for detection of chromosomal abnormalities, the ACMG recommends CMA testing "as a first-line test in the initial postnatal evaluation of individuals with the following:

A. "Multiple anomalies not specific to a well-delineated genetic syndrome."
B. "Apparently nonsyndromic DD/ID."
C. "Autism spectrum disorders."~~40~~39

The ACMG also recommends "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…, particularly by prospective studies and after- market analysis." Additionally, ACMG recommends "appropriate follow-up … in cases of chromosome imbalance identified by CMA, to include cytogenetic/FISH studies of the patient, parental evaluation, and clinical genetic evaluation and counseling."~~40~~39 These statements were reaffirmed in 2020 by the ACMG Board of Directors.

An update from ACMG states that a stepwise or tiered approach to the clinical genetic diagnostic evaluation of autism spectrum disorder is recommended, with the recommendation being for first tier to include fragile X syndrome and chromosomal microarray analysis (CMA).

In 2017 the ACMG published a laboratory practice resource outlining an algorithm for diagnostic cytogenetic testing following positive noninvasive prenatal screening results which recommends:

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- "CMA testing on either CVS or amniotic fluid may be used as confirmatory diagnostic testing in cases with positive NIPS results, or as reflex testing in cases with initial normal results from chromosome analysis."
- CMA is recommended as follow-up testing for any smaller copy-number changes that are reported as positive by NIPS.
- They also suggest that when "prenatal diagnostic testing may not be performed due to loss of the pregnancy before testing is possible. In such instances, testing of the products of conception and/or the fetus by either chromosome analysis or CMA should be considered on a case-by-case basis."~~41~~40
- In newborns for whom the screen is suggestive of aneuploidy, but further testing is declined a genetics consultation with physical examination is sufficient for neonates, however, "if the neonate has an abnormal physical examination that is not suggestive of the trisomy in question, CMA is recommended."~~41~~40

CMA is also recommended when the sex determination by NIPS is discordant with physical examination, or clinical findings suggestive of a disorder of sexual differentiation. Following a Systematic Evidence Review in 2023, the ACMG now recommends "ACMG strongly recommends NIPS over traditional screening methods for all pregnant patients with singleton and twin gestations for fetal trisomies 21, 18, and 13 and strongly recommends NIPS be offered to patients to screen for fetal sex chromosome aneuploidy."~~42~~41

In 2009, the ACMG published guidelines on the genetic evaluation of short stature. These guidelines provide recommendations for genes associated with short stature and intrauterine growth restriction (IUGR) and state that high resolution chromosome analysis and/or array CGH can be used to evaluate IUGR.~~43~~42

In 2018, the ACMG published a clinical practice report on genetic testing after CMA for the diagnosis of neurodevelopmental disability and congenital anomalies. These guidelines state that "CMA may not detect balanced cytogenomic abnormalities or uniparental disomy (UPD), and deletion/duplications and regions of homozygosity may require additional testing to clarify the mechanism and inform accurate counseling."~~44~~43

In 2025 the ACMG published an addendum to their 2018 clinical practice guidelines on the use of CMA for screening neurodevelopmental disability and congenital anomalies. The update largely reaffirms the 2018 guidelines with a few with a few additions "microarray is no longer the sole first-tier go-to test per ACMG evidence-based clinical guidelines… Additional testing after chromosomal microarray remains clinically relevant for disease-specific testing (eg, testing for an autosomal recessive pathogenic variant or uniparental disomy after detection of homozygosity), as well as more general testing recommendations (eg, balanced translocations and insertions)."~~45~~44

In 2020, the ACMG published guidelines on the use of fetal exome sequencing in prenatal diagnosis. These guidelines recommend that "Exome sequencing may be considered for a fetus with ultrasound anomalies when standard CMA and karyotype analysis have failed to yield a definitive diagnosis. If a

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specific diagnosis is suspected, molecular testing for the suggested disorder (with single-gene test or gene panel) should be the initial test."[4645]

The *ACMG Technical Standards for Clinical Genetics Laboratories (2021 Revision)* state, "the contamination of both direct and cultured cells from AF and CVS with maternal cells is well documented and therefore represents a potential source of error in prenatal diagnosis. Prenatal samples should be examined in parallel with a maternal sample to rule out error due to maternal cell contamination (MCC). Laboratories should understand how their testing methods are affected by the presence and the amount of MCC. For example, prenatal detection of a deletion using PCR, as is the case in testing for DMD and SMA, is expected to be more sensitive to maternal contamination, since a normal maternal allele could mask the deletion. A prenatal test using an allele-specific PCR reaction to detect a paternal RhD gene in the fetus of a RhD-negative mother is much less sensitive to maternal contamination."[4746]

American Academy of Pediatrics (AAP)

The [20142025] AAP guidance for the ~~comprehensive evaluation of children with intellectual disability or~~Genetic Evaluation of the Child With Intellectual Disability or Global Developmental Delay noted that genome sequencing OR exome sequencing and chromosomal microarray (sequential or concurrent) are tier one tests when there is concerns for global developmental ~~delays noted that "~~delay (GDD)/intellectual disability (ID). The guidelines go on to say "Genome-wide chromosome microarray ~~is designated as~~(CMA) has been considered a first-line ~~test and replaces the standard karyotype and fluorescent in situ hybridization subtelomere tests for the child with intellectual disability of unknown etiology."[48] They further add that "CMA is now the standard for diagnosis of patients with GDD/ID, as well as other conditions, such as autism spectrum disorders or multiple congenital anomalies."[48]~~diagnostic test in the evaluation of the child with GDD/ID by the AAP, AAN, CPS, and the ACMG. The AAP continues to recommend CMA in the first-tier agnostic evaluation for GDD/ID along with exome sequencing (sequential or concurrent)."[47]

Another clinical report published by the AAP on the identification of infants and young children with developmental disorders states that "The child with suspected global developmental delay or intellectual disability should have laboratory testing done, including chromosomal microarray and fragile X testing."[4948] The authors also note that "The initial genetic workup of the child with suspected ASD is evolving; current recommendations also include chromosomal microarray and fragile X testing."[4948]

The AAP has an epilepsy webpage overview and on the genetic testing for epilepsy page states that "The genetic tests most utilized in the evaluation of children with epilepsy include chromosomal microarray (CMA), epilepsy gene panels, and whole-exome sequencing (WES). Each test has its own specific benefits and limitations, and the utility of different tests may vary for a given individual. Decisions regarding testing need to consider the clinical indication including associated symptoms, turn-around time, insurance coverage, and cost."[10] The AAP published guidelines on the evaluation of children with autism spectrum disorder. According to the guidelines, CMA is recommended if the etiology for developmental disability is not known. Since Fragile X Syndrome increases the risk for autism spectrum disorder, DNA testing for Fragile X should be recommended in all children with ASD, especially for boys and children with a family history of intellectual disability. "The cytosine-guanine-guanine trinucleotide repeat expansion that is responsible for fragile X syndrome is not detected on CMA and must be ordered as a separate test. When the history and physical examination, CMA, and fragile X analysis do not identify an

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etiology, the next step at this time in the etiologic evaluation for [autism spectrum disorder] is whole-exome sequencing (WES)." AAP does not recommend the use of commercially marketed tests as they do not provide a molecular etiologic diagnosis.[5049]

American Academy of Neurology (AAN)

The AAN published coverage policies for chromosomal microarray analysis for intellectual disabilities in 2015.[5150] The policy document notes the criteria do not represent a binding standard of care and that the criteria are proposed as clinical contexts that readily support the use of microarray testing. The authors note that chromosomal microarray analysis is reasonable and medically necessary for diagnosing a genetic abnormality when all of the following conditions are met:

- "In children with developmental delay/intellectual disability (DD/ID) or an autism spectrum disorder (ASD) according to accepted Diagnostic and Statistical Manual of Mental Disorders-IV criteria;

  AND
- If warranted by the clinical situation, biochemical testing for metabolic diseases has been performed and is negative;
- Targeted genetic testing, (for example: *FMR1* gene analysis for Fragile X), if or when indicated by the clinical and family history, is negative;
- The results for the testing have the potential to impact the clinical management of the patient;
- Face-to-face genetic counseling with an appropriately trained and experienced healthcare professional has been provided to the patient (or legal guardian(s) if a minor child). Patient or legal guardians have given their consent for testing. Cognitively competent adolescent patients have given their assent for testing as well."[5150]

The document notes the presence of major and minor congenital malformations and dysmorphic features should be considered evidence that microarray testing will be more likely to yield a diagnosis. However, dysmorphic and syndromic features are not required for testing.[5150]

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

Originally published in 2013 and reaffirmed in 20202025, the ACOG and SMFM issued joint guidelines recommending the following use of CMA for prenatal diagnosis:

- "Most genetic changes identified by chromosomal microarray analysis that typically are not identified on standard karyotype are not associated with increasing maternal age; therefore, the use of this test can be considered for all women, regardless of age, who undergo prenatal diagnostic testing.
- Prenatal chromosomal microarray analysis is recommended for a patient with a fetus with one or more major structural abnormalities identified on ultrasonographic examination and who is undergoing invasive prenatal diagnosis. This test typically can replace the need for fetal karyotype.
- In a patient with a structurally normal fetus who is undergoing invasive prenatal diagnostic testing, either fetal karyotyping or a chromosomal microarray analysis can be performed.

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- Chromosomal microarray analysis of fetal tissue (i.e., amniotic fluid, placenta, or products of conception) is recommended in the evaluation of intrauterine fetal death or stillbirth when further cytogenetic analysis is desired because of the test's increased likelihood of obtaining results and improved detection of causative abnormalities.
- Comprehensive patient pretest and posttest genetic counseling from an obstetrician–gynecologist or other health care provider with genetics expertise regarding the benefits, limitations, and results of chromosomal microarray analysis is essential. Chromosomal microarray analysis should not be ordered without informed consent, which should include discussion of the potential to identify findings of uncertain significance, nonpaternity, consanguinity, and adult-onset disease.
- The routine use of whole-genome or whole-exome sequencing for prenatal diagnosis is not recommended outside of the context of clinical trials until sufficient peer-reviewed data and validation studies are published."[6]

ACOG and SMFM do not recommend use of CMA for evaluation of first- and second-trimester pregnancy loss due to limited clinical utility information. Additionally, they recommend pre- and post-test genetic counseling "from qualified personnel such as a genetic counselor or geneticist regarding the benefits."[6]

A 2018 study of these guidelines analyzed 3223 prenatal samples undergoing CMA. Cases were categorized into two groups: those that met ACOG guidelines for CMA versus those that met ACOG guidelines for either CMA or karyotype. They found that "in patients who could have elected either CMA or karyotype, 2.5% had clinically significant chromosomal abnormalities (CSCA) that would have been missed if the patient had elected to pursue karyotype."[~~52~~51]

American Society for Reproductive Medicine (ASRM)

In 2012, ASRM published a committee opinion on evaluation and treatment of recurrent pregnancy loss with clinical practice recommendations. ASRM recommended to proceed with the evaluation of recurrent pregnancy loss after two consecutive clinical pregnancy losses. This definition of recurrent pregnancy loss was reaffirmed in 2013. The recommended assessment of recurrent pregnancy loss included screening for genetic, hormonal and metabolic factors in addition to other factors. They have stated that "karyotypic analysis of products of conception may be useful in the setting of ongoing therapy for recurrent pregnancy loss."[~~53~~52]

In 2023, the Practice Committee and Genetic Counseling Professional Group (GCPG) of the ASRM published their opinion on the clinical management of mosaic results from preimplantation genetic testing for aneuploidy (PGT-A)of blastocysts. Defining prenatal diagnostic testing as including chorionic villus sampling or amniocentesis, the group recommends the following:

- "Analyses on prenatal testing samples beyond a standard karyotype may be considered, depending on the specific PGT-A result and at the discretion of the ordering provider. These may include:
  - Chromosomal microarray, when partial chromosome aneuploidy is involved
  - Additional cell counts with a traditional karyotype or fluorescent in situ hybridization to identify lower-level mosaicism
  - Uniparental disomy studies, depending on the chromosome involved

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- Genetic counseling is strongly recommended for any patient pregnant after the transfer of a mosaic-result embryo and should include a discussion of the risks, benefits, and limitations of prenatal testing options."[5453]

Society of Obstetricians and Gynaecologists of Canada (SOGC)- Canadian College of Medical Geneticists (CCMG) Joint Technical Update

The 2018 joint guideline Armour, et al. (2018) supersedes the 2011 iteration.

- "Offer of chromosomal microarray analysis (in addition to any other relevant diagnostic testing) is recommended in cases with multiple fetal anomalies identified by a comprehensive obstetric ultrasound (II-1A). Other diagnostic testing may include specific single gene, multigene panels or other genetic tests if the pattern of anomalies suggests a specific genetic condition not identified by array."
- "Single structural defects in association with other abnormal ultrasound findings (e.g., intrauterine growth restriction (IUGR), oligohydramnios) should not be considered isolated, and thus array should be offered if RAD is normal."
- "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 where the diagnostic yield is lower may be considered, if resources are available."
- "In fetuses with a nuchal translucency ≥3.5 mm, prenatal CMA should be offered."[5554]

For "analysis of fetal loss prior to 20 weeks gestation":

- "In cases of congenital anomalies and/or IUGR, in any fetal loss prior to 20 weeks gestation, if QF-PCR 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 chromosomal microarray analysis."[5554]

For fetal deaths ≥20 weeks gestation:

- "Aneuploidy is the most common abnormal chromosomal finding in stillbirths. If RAD and/or other directed diagnostic inquiries are uninformative, it is recommended that in cases complicated by congenital anomalies and/or IUGR, karyotype be replaced with CMA when further cytogenetic analysis is desired."
- "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)."[5554]

Society of Obstetricians and Gynaecologists of Canada (SOGC)

The SOGC published a 2024 guideline on prenatal screening for fetal chromosomal anomalies where they cover the following recommendations:

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- "All pregnant persons, regardless of age, should be offered, through an informed counselling process with shared decision-making, the option of a prenatal screening test for the most common fetal aneuploidies and for major fetal anomalies
- Prenatal screening programs should be implemented with resources that support audited screening and laboratory services, ultrasound services, genetic counselling, and patient and health care provider education.
- Regardless of aneuploidy screening choice, all pregnant persons should be offered a first-trimester fetal ultrasound, (optimally between 11- and 14-weeks gestation), to assess viability, gestational age, number of fetuses, chorionicity in multiples, early fetal anatomy, and nuchal translucency. Maternal serum screening (with or without nuchal translucency measurement for aneuploidy risk estimation) should not be performed if cell-free DNA screening is performed or planned
- If a fetal structural abnormality (not a soft marker) is identified during the first- or second-trimester ultrasound, regardless of previous screening test results, genetic counselling and invasive diagnostic testing should be offered, with rapid aneuploidy detection and reflex microarray analysis or exome/genome sequencing, if rapid aneuploidy detection is normal or inconclusive. The diagnostic role of fetal exome/genome sequencing is a rapidly evolving area, and maternity care providers should be aware of this technology."[~~56~~55]

Association for Molecular Pathology (AMP)

The MCC [maternal cell contamination] Guidelines Working Group of the AMP Clinical Practice Committee issued laboratory guidelines for detecting MCC in 2011. They state, "To determine the pure fetal origin of all prenatal specimens undergoing genetic analysis, it is recommended that MCC analysis be performed in parallel with diagnostic testing, regardless of the genetic disorder or its mode of inheritance."[~~57~~56]

The Association for Molecular Pathology Training and Education Committee published a series of quick reference cards called Molecular-in-My-Pocket™ for trainees and anyone looking to quickly reference molecular diagnostics information.[~~58~~57]

In their oncology subdivision, the AMP summarize assays and techniques for molecular biomarkers for various cancers. Below are summaries of their syntheses:

- When testing for primary and recurrent tumors for the *KIT* biomarker in cutaneous melanoma, "NGS, pyrosequencing, Sanger sequencing, PCR-based assays, microarray" are applicable for therapeutic indications.
- When testing for primary and recurrent tumors for 1p/19q co-deletion in tumors of the central nervous system, "FISH, array, NGS" are approved for diagnosis~~ and prognosis~~. Moreover, when testing for EGFR amplification, gain of chromosome 7, and loss of chromosome 10, "FISH, array, NGS PCR-based assays" are applicable for diagnosis.[~~58~~57]

Similarly, in their pediatric molecular pathology section, the AMP summarizes assays and techniques for pediatric brain tumors. The following table, adapted from the oncology Molecular-in-my-Pocket™ card, lists the assays and techniques mentioning CMA and their corresponding tumor types:[~~58~~57]

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Tumor type	Gene/Biomarker	~~Gene/Biomarker~~Alteration	Significance	Primary assays
Low grade gliomas	*FGFR*	~~*FGFR*~~ mutation, fusion	Diagnosis	NGS (DNA), CMA
	NF1	~~*NF1*~~ loss or inactivating mutation, loss of heterozygosity	Diagnosis, familial cancer if germline	NGS (DNA), CMA
	MYB	~~*MYB*~~ fusion, amplification	Diagnosis, prognosis	NGS (DNA), CMA
	MYBL1	~~*MYBL1*~~ fusion, amplification	Diagnosis, prognosis	NGS (DNA), CMA
High grade gliomas, IDH wildtype	*EGFR*	~~*EGFR*~~ amplification	Prognosis	NGS (DNA), CMA, FISH
	CDKN2A/B	~~*CDKN2A/B*~~ homozygous deletion	Prognosis	CMA, NGS (DNA)
	TP53	~~*TP53*~~ loss-of-function (LOF) and gain-of-function mutations, loss, LOH	Prognosis	NGS (DNA), CMA
	NF1	~~*NF1*~~ loss or inactivating mutation, loss of heterozygosity	Prognosis	NGS(DNA), CMA
	PDGFRA	~~*PDGFRA*~~ amplification	Prognosis	CMA, NGS (DNA)
	RB1	~~*RB1*~~ loss or inactivating mutation, loss of heterozygosity	Prognosis	NGS (DNA), CMA
	MDM4	~~*MDM4*~~ amplification	Prognosis	NGS (DNA), CMA, FISH
	MET	~~*MET*~~ amplification, fusion, mutation	Prognosis	NGS (DNA), CMA, FISH
	Gain of chromosome 7	~~Gain of chromosome~~Chromosomal abnormality (gain of 7)	Prognosis	CMA
	10q loss	~~10q~~ Chromosomal abnormality (loss of 10)	Prognosis	CMA
Oligodendroglioma	*1p/10q codeletion*	Chromosomal abnormality (loss of 1p~~/10q codeletion~~ and 19q)	Diagnosis	CMA, FISH
Ependymoma	*1q gain*	~~1q~~ Chromosomal abnormality (gain of 1p)	Prognosis	CMA, FISH
Medulloblastom	*Monosom*	chromosomal	diagnosis	CMA, FISH

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a, WNT-activated	*y 6*	abnormality (loss) Subtype-		
Medulloblastoma, SHH-activated	*PTCH1*	~~*PTCH1*~~ inactivating mutation, loss of heterozygosity	Subtype-diagnosis, familial cancer risk if germline ~~N~~	NGS (DNA), CMA
	SUFU	~~*SUFU*~~ inactivating mutation, loss of heterozygosity	Subtype-diagnosis, familial cancer risk if germline ~~N~~	NGS (DNA), CMA
	TP53	~~*TP53*~~ loss-of-function (LOF) and gain-of-function mutations, loss, loss of heterozygosity, structural alterations (rare)	Prognosis	NGS (DNA), CMA
	10q loss or loss of heterozygosity	chromosomal abnormality (loss or ~~10q loss or loss of heterozygosity~~LOH)	Diagnosis	CMA, FISH
	TERT promoter	Mutation	Diagnosis	CMA, FISH
	MYCN	~~*MYCN*~~ amplification	Diagnosis, prognosis	FISH, CMA, NGS (DNA)
Medulloblastoma, Group 3	Isochromosome 17q	~~Isochromosome~~chromosomal abnormality (loss of 17p and gain of 17q)	Subtype-diagnosis	CMA, FISH
	MYC	~~*MYC*~~ amplification, fusion (PVT1)	Prognosis	CMA, FISH
Medulloblastoma, Group 4	Isochromosome 17q	~~Isochromosome~~chromosomal abnormality (loss of 17p and gain of 17q)	Subtype-diagnosis	CMA, FISH
	MYCN	~~*MYCN*~~ amplification	Diagnosis, prognosis	FISH, CMA, NGS
Meningioma	*NF2*	~~*NF2*~~ loss-of-function (LOF) and gain-of-function mutations, loss, loss of heterozygosity	Diagnosis, familial cancer risk if germline	NGS, CMA, MLPA
Choroid plexus tumors	*TP53*	~~*TP53*~~ loss-of-function (LOF) and gain-of-function mutations, loss, loss of heterozygosity, structural alterations (rare)	Diagnosis, familial cancer risk if germline	NGS, CMA, MLPA
ETMR	*C19MC*	~~*C19MC*~~ amplification and gain	Diagnosis, prognosis	CMA, FISH

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Regarding pediatric solid tumors, the following table, adapted from the oncology Molecular-in-my-Pocket™ card, lists the assays and techniques mentioning CMA and their corresponding tumor types:[58][57]

Tissue type	Tumor type	Gene/Biomarker	Alteration	Significance	Primary assays
Kidney	Wilms Tumor	1q ~~1q gain,~~ 1p/16q ~~loss of heterozygosity~~	Copy gain LOH	Prognosis	CMA, NGS (DNA)
	Rhabdoid Tumor	*SMARCB1 (INI1; >90%), SMARCA4 (BRG1)* ~~loss~~	Loss (sequence variant, deletion)	Diagnosis, familial cancer risk	IHC (INI1, BRG1), CMA, NGS~~,~~ (DNA), MLPA
Eye	Retinoblastoma	*RB1* ~~inactivating mutation, loss, or loss of heterozygosity~~	inactivating mutation, loss, or loss of heterozygosity	Diagnosis, familial cancer risk ~~if germline~~	~~Sanger sequencing,~~ MLPA, CMA, NGS (DNA)
~~Adrenal~~**Neural Crest**	Neuroblastoma	1p/11q LOH~~loss~~	LOH	Prognosis	CMA, NGS (DNA)
		MYCN	amplification	prognosis	FISH, CMA, NGS (DNA)
		DNA ploidy	Hyperdiploidy	prognosis	CMA, flow cytometry
Multi-system	Gorlin Sydrome	*SUFU*, *PTCH1* ~~loss-of-function sequence variants, deletion/duplication~~	loss-of-function sequence variants, deletion/duplication (germline)	Diagnosis, familial cancer risk	~~Sequencing~~NGS (DNA), CMA, MLPA

Regarding pediatric soft tissue tumors, the following table, adapted from the oncology Molecular-in-my-Pocket™ card, lists the assays and techniques mentioning CMA and their corresponding tumor types:[58][57]

Tissue type	Tumor type	Gene/Biomarker	Alteration	Significance	Primary assays
Miscellaneous	Chordoma (Poorly differentiated)	*SMARCB1 (INI1)* ~~loss (sequence variant, partial deletion)~~	loss (usually partial deletion)	Diagnosis, prognosis	IHC (INI1), CMA, NGS~~,~~ (DNA), MLPA
	Rhabdoid tumor (Extra-renal)	*SMARCB1 (INI1~~-~~ ~~and~~; >95%), SMARCA4 (BRG1)*	Loss (usually deletion)	diagnosis, familial ~~Diagnosis~~cancer risk	IHC (INI1, BRG1), CMA, NGS~~, MLPA~~ (DNA), MLPA
	Epithelioid sarcoma	*SMARCB1 (INI1~~-~~ ~~and~~; >95%), SMARCA4 (BRG1)*	Loss (usually deletion)	Diagnosis~~,~~ ~~treatment~~	IHC (INI1, BRG1), CMA, NGS~~, MLPA~~ (DNA), MLPA
Multi-system	Gorlin Syndrome	*SUFU*, *PTCH1* ~~loss-of-function~~	loss-of-function sequence	Diagnosis, familial	~~Sequencing~~NGS (DNA), CMA,

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		~~sequence variants, deletion/duplication~~	variant, deletion/duplication (germline)	cancer risk	MLPA

Society for Maternal-Fetal Medicine (SMFM)

The SMFM recommends chromosomal microarray for evaluation of mild fetal ventriculomegaly ~~and~~(reaffirmed in 2024) and nonimmune hydrops fetalis~~.~~[59,60] (published in 2026).[58,59]

The SMFM released guidelines on the diagnosis and management of fetal growth restriction. The following recommendations were made:

- SMFM recommends that pregnant individuals "be offered fetal diagnostic testing, including chromosomal microarray analysis, when fetal growth restriction is detected and a fetal malformation, polyhydramnios, or both are also present regardless of gestational age."
- They also recommend that pregnant individuals "be offered prenatal diagnostic testing with chromosomal microarray analysis when unexplained isolated fetal growth restriction is diagnosed at <32 weeks of gestation."[~~61~~60]

International Standard Cytogenomic Array (ISCA) Consortium

The ISCA (an international group of experts in the field) assembled to "address mutual concerns about standardization and collaboration for clinical CMA testing."[22] After much research, the ISCA has stated that "Our recommendation based on current evidence is to offer CMA as the first-tier genetic test, in place of G-banded karyotype, for patients with unexplained DD/ID, ASD, or MCA [multiple congenital anomalies]."[22]

International Society for Prenatal Diagnosis (ISPD), the Society for Maternal Fetal Medicine (SMFM), and the Perinatal Quality Foundation (PQF)

Joint guidelines on the use of genome-wide sequencing for fetal diagnosis were published by the ISPD, SMFM and PQF. However, these guidelines also mention CMA quite frequently because "The use of diagnostic sequencing is currently being introduced for evaluation of fetuses for whom standard diagnostic genetic testing, such as chromosomal microarray analysis (CMA), has already been performed and is uninformative or is offered concurrently according to accepted practice guidelines, or for whom expert genetic opinion determines that standard genetic testing is less optimal than sequencing for the presenting fetal phenotype."[~~62~~61]

Fetal sequencing is recommended in several scenarios, including the following which also mention CMA:

- "A current pregnancy with a fetus with a single major anomaly or with multiple organ system anomalies that are suggestive of a possible genetic etiology, but no genetic diagnosis was found after CMA; or in select situations with no CMA result, following a multidisciplinary review and consensus, in which there is a fetus with a multiple anomaly 'pattern' that strongly suggests a single gene disorder.

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- A personal (maternal or paternal) history of a prior undiagnosed fetus (or child) affected with a major single anomaly or multiple anomalies suggestive of a genetic etiology, and a recurrence of similar anomalies in the current pregnancy without a genetic diagnosis after karyotype or CMA
- In families with a history of recurrent stillbirths of unknown etiology after karyotype and/or CMA, where the fetus in the current pregnancy has a recurrent pattern of anomalies."~~62~~61

These recommendations show that CMA should be used as an initial strategy (before fetal sequencing) to determine the genetic causation during pregnancy of the aforementioned cases.

In a 2022 update from ISPD, the society points out that although much remains to be learned about its science and clinical application, fetal diagnostic sequencing has increased over the last five years, providing sufficient experience to permit the development of suggestions for clinical use. These guidelines also mention CMA as a tool to support prenatal exome sequencing (pES).[62]

"The current existing data support that prenatal sequencing is beneficial for the following indications:

1. A current pregnancy with a fetus having a major single anomaly or multiple organ system anomalies:
   A. For which no genetic diagnosis was found after CMA and a clinical genetic expert review considers the phenotype suggestive of a possible genetic etiology.
   B. For which the multiple anomaly "pattern" strongly suggests a single gene disorder with no prior genetic testing. As pES is not currently validated to detected all CNVs, CMA should be run before or in parallel with pES in this scenario."[62]

Autism Consortium Clinical Genetics/DNA Diagnostics Collaboration

These guidelines focus on clinical genetic testing for patients with autism spectrum disorders (ASDs). The authors note that "CMA had the highest detection rate among clinically available genetic tests for patients with ASD. Interpretation of microarray data is complicated by the presence of both novel and recurrent copy-number variants of unknown significance. Despite these limitations, CMA should be considered as part of the initial diagnostic evaluation of patients with ASD."[63] Further, the guidelines later state that "our results suggest that CMA with whole genome coverage should be adopted as a national standard of care for genetic testing among patients with ASDs."[63]

Endocrine Society (ES)

The Endocrine Society published guidelines on the diagnosis and treatment of children with idiopathic short stature (ISS) in 2008. These guidelines state that "In situations where a specific genetic diagnosis associated with short stature is expected (such as Noonan syndrome or GH insensitivity syndrome), the genes of interest should be examined."[64] These guidelines do not mention CMA.

The National Fragile X Foundation

The National Fragile X Foundation's statement on genetic testing for Fragile X Syndrome and associated disorders includes within its recommendations the ~~use of chromosomal microarray analysis and exome sequencing for the diagnosis of "the underlying cause of a child's developmental delays, autism, or intellectual disability.." However, though the above are viable options for genetic testing in general,~~

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~~"Currently, Fragile X testing must be ordered as a separate test since~~highly accurate FMR1 DNA Test for Fragile X to identify individuals with all types of repeat expansions ~~of~~within the FMR1 gene~~ cannot be detected through microarray or exome sequencing", and as such a specific DNA test for Fragile X Syndrome via PCR and Southern Blot analysis will need to be used.~~[65]. PCR and southern blot analysis are the two main testing techniques recommended.

- "Polymerase Chain Reaction (PCR): This technique is able to identify the size of the repetitive section of the FMR1 gene, including CGG repeat numbers in the normal, intermediate, premutation, and full mutation ranges.
- Southern Blot Analysis: For full mutations, labs generally follow up with a Southern blot analysis to confirm whether the gene is methylated, a chemical change that prevents it from producing its normal protein, known as FMRP.
    - Testing for AGG interruptions can be done as a separate test and is most relevant as part of carrier (premutation) testing. AGG analysis is often ordered as a follow-up test when a premutation or intermediate result is reported in women who plan to have children."[65]

VII. Applicable State and Federal Regulations

DISCLAIMER: If there is a conflict between this Policy and any relevant, applicable government policy for a particular member [e.g., Local Coverage Determinations (LCDs) or National Coverage Determinations (NCDs) for Medicare and/or state coverage for Medicaid], then the government policy will be used to make the determination. For the most up-to-date Medicare policies and coverage, please visit the Medicare search website: https://www.cms.gov/medicare-coverage-database/search.aspx. For the most up-to-date Medicaid policies and coverage, visit the applicable state Medicaid website.

Food and Drug Administration (FDA)

Many labs have developed specific tests that they must validate and perform in house. These laboratory-developed tests (LDTs) are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA '88). LDTs are not approved or cleared by the U. S. Food and Drug Administration; however, FDA clearance or approval is not currently required for clinical use.

In 2014 the FDA approved CytoScan® Dx Assay as a "qualitative assay intended for the postnatal detection of copy number variations (CNV) in genomic DNA obtained from peripheral whole blood in patients referred for chromosomal testing based on clinical presentation. CytoScan® Dx Assay is intended for the detection of CNVs associated with developmental delay, intellectual disability, congenital anomalies, or dysmorphic features."[66]

In 2017 the FDA approved GenetiSure Dx Postnatal Assay as a "qualitative assay intended for the postnatal detection of copy number variations (CNV) and copy-neutral loss of heterozygosity (cnLOH) in genomic DNA obtained from peripheral whole blood in patients referred for chromosomal testing based on clinical presentation. GenetiSure Dx Postnatal Assay is intended for the detection of CNVs and cnLOH associated with developmental delay, intellectual disability, congenital anomalies, or dysmorphic features."[67]

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VIII. Applicable CPT/HCPCS Procedure Codes

CPT	Code Description
81228	Cytogenomic (genome-wide) analysis for constitutional chromosomal abnormalities; interrogation of genomic regions for copy number variants, comparative genomic hybridization [CGH] microarray analysis
81229	Cytogenomic (genome-wide) analysis for constitutional chromosomal abnormalities; interrogation of genomic regions for copy number and single nucleotide polymorphism (SNP) variants, comparative genomic hybridization (CGH) microarray analysis
81265	Comparative analysis using Short Tandem Repeat (STR) markers; patient and comparative specimen (eg, pre-transplant recipient and donor germline testing, post-transplant non-hematopoietic recipient germline [eg, buccal swab or other germline tissue sample] and donor testing, twin zygosity testing, or maternal cell contamination of fetal cells)
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
0209U	Cytogenomic constitutional (genome-wide) analysis, interrogation of genomic regions for copy number, structural changes, and areas of homozygosity for chromosomal abnormalities Proprietary test: CNGNome™ Lab/Manufacturer: PerkinElmer Genomics
0252U	Fetal aneuploidy short tandem–repeat comparative analysis, fetal DNA from products of conception, reported as normal (euploidy), monosomy, trisomy, or partial deletion/duplications, mosaicism, and segmental aneuploidy Proprietary test: POC (Products of Conception) Lab/Manufacturer: Igenomix®
0469U	Rare diseases (constitutional/heritable disorders), whole genome sequence analysis for chromosomal abnormalities, copy number variants, duplications/deletions, inversions, unbalanced translocations, regions of homozygosity (ROH), inheritance pattern that indicate uniparental disomy (UPD), and aneuploidy, fetal sample (amniotic fluid, chorionic villus sample, or products of conception), identification and categorization of genetic variants, diagnostic report of fetal results based on phenotype with maternal sample and paternal sample, if performed, as comparators and/or maternal cell contamination Proprietary test: IriSightTM CNV Analysis Lab/Manufacturer: Variantyx Inc
S3870	Comparative genomic hybridization (CGH) microarray testing for developmental delay, autism spectrum disorder and/or intellectual disability

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Procedure codes appearing in Medical Policy documents are included only as a general reference tool for each policy. They may not be all-inclusive.

IX. Important Reminder

The purpose of this Medical Policy is to provide a guide to coverage. This Medical Policy is not intended to dictate to providers how to practice medicine. Nothing in this Medical Policy is intended to

discourage or prohibit providing other medical advice or treatment deemed appropriate by the treating physician.

Benefit determinations are subject to applicable member contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

This Medical Policy has been developed through consideration of the medical necessity criteria under Hawaii's Patients' Bill of Rights and Responsibilities Act (Hawaii Revised Statutes §432E-1.4) or for QUEST members, under Hawaii Administrative Rules (HAR 1700.1-42), generally accepted standards of medical practice and review of medical literature and government approval status.

HMSA has determined that services not covered under this Medical Policy will not be medically necessary under Hawaii law in most cases. If a treating physician disagrees with HMSA's determination as to medical necessity in a given case, the physician may request that HMSA reconsider the application of the medical necessity criteria to the case at issue in light of any supporting documentation.

Genetic testing is covered for level 1 or 2A recommendations of the National Comprehensive Cancer Network (NCCN and in accordance with Hawaii's Patients' Bill of Rights and Responsibilities Act (Hawaii Revised Statutes §432E-1.4) or for QUEST members, the Hawaii Administrative Rules (HAR 1700.1-42).

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XI. Revision History

Revision Date	Summary of Changes
06/03/2026	Reviewed and Updated: Updated the background, guidelines and recommendations, and evidence-based scientific references. Literature review did not necessitate any modifications to coverage criteria. The following edits were made for clarity: Removed CC2.g., as a third trimester loss would be covered by the "second-trimester or later pregnancy loss" found in CC1.

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