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# Chromosomal Microarray and Low-pass Whole Genome Sequencing

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| **Policy Number:**<br>AHS – M2033 | **Prior Policy Name and Number:**<br>Not applicable |
| **Initial Effective Date:**<br>June 01, 2023 | **Current Effective Date:**<br>February 01, 2025 |
| **Line(s) of Business:**<br>HMO; PPO; QUEST Integration; Medicare; FEP | **Precertification:**<br>Refer to the GTM Utilization Review Matrix |

## 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 (Schrijver & Zehnder, 2024). 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 (Gencove, 2023).

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

## II. 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 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) 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.
   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.**

*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**.

## III. 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 |

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|---|---|
| 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 |
| 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 |

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|---|---|
| VPS | Variant of possible significance |
| WES | Whole exome sequencing |
| WGS | Whole genome sequencing |

## IV. Scientific Background

Chromosomal abnormalities are associated with a variety of disorders including developmental delay (DD), intellectual disability (ID), and congenital anomalies (Miller et al., 2010), as well as pregnancy loss (Reddy, Page, Saade, et al., 2012).

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 (Miller et al., 2010; Pivalizza & Lalani, 2024; Schrijver & Zehnder, 2024). 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 (Miller, 2022), 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 (ACOG, 2016; Reddy, Page, & Saade, 2012). **"**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" (Wang et al., 2020).

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 (Aradhya & Cherry, 2007). 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 (Schrijver & Zehnder, 2024). 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 (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 (Miller, 2022).

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 (Miller, 2022).

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 (Illumina, 2024). 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 (Gencove, 2023).

**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 (Poduri et al., 2014) and has a diagnostic yield of approximately 8% with several studies reporting higher values (Dubbs, 2022). 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 (Dubbs, 2022). However, if results are negative, CMA or gene testing should commence as this is likely more appropriate than testing several more genes individually (Mefford, 2015). 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" (Olson et al., 2014).

**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 (Richmond & Rogol, 2024). The most common causes of short stature are genetic and delayed growth; these are considered normal or nonpathologic variants of growth (Richmond & Rogol, 2024).

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 cause significant morbidity and mortality in infants (Mandy, 2024). CMA has been used for diagnostic purposes in fetuses due to IUGR (Daum et al., 2019).

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 (Richmond & Rogol, 2024). 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" (Dauber et al., 2014). A significant association has been identified between CNVs and short stature (Yu et al., 2015), and many report that CMA is a promising tool to identify pathogenic CNVs in patients with ISS (Richmond & Rogol, 2024).

**Proprietary Testing**

The only FDA-approved commercial CMA test is CytoScan® by Affymetrix. This test helps identify the underlying genetic causes of developmental delay, intellectual disability, congenital anomalies, or dysmorphic features in children. CytoScan® detects chromosomal copy number variants (CNV) in genomic DNA from peripheral whole blood (Affymetrix, 2013).

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 (GeneDx, 2024). 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 (GeneDx, 2024).

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 (Quest, 2024). 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.

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 (LabCorp, 2023). Results are provided in 14-17 days.

The FirstStep$^{DX}$ PLUS®, developed by Lineagen (2024), is a CMA test that uses a buccal sample to identify developmental disabilities. Lineagen claims that cheek swabs are a more effective way to ensure accurate CMA results than blood-based samples, and that "mosaicism is better diagnosed through DNA collected by cheek swab than by blood draw" (Lineagen, 2024).

Invitae released a Pregnancy Loss Chromosomal Microarray Analysis test which analyzes products of conception tissue to determine whether a chromosomal abnormality caused a miscarriage, intrauterine fetal demise, or a stillbirth. The average turnaround time is 10-12 days. This test can detect whole and segmental aneuploidies, submicroscopic gains and losses that cannot be detected using karyotype, size and gene content of copy number variations, regions of homozygosity, uniparental isodisomy, and triploidy and complete molar pregnancies (Invitae, 2024).

CentoArrayCyto® is a CMA test released by Centogene which detects known structural aberrations such as CNVs, chromosomal imbalances, regions exhibiting loss/absence of heterozygosity (LOH), uniparental isodisomy (UPD), and mosaicism. The test has a turnaround time of 15 days. CentoArrayCyto® can be used as a first-step analysis for detection of intellectual disability and multiple malformation, in conjunction with whole exome sequencing to complement large CNVs, for deletion/duplication analysis of extremely large genes, and for prenatal testing to help determine a cause of ultrasound-detected abnormalities (CentoGene, 2024).

**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 (Miller et al., 2010; Schrijver & Zehnder, 2024). Miller et al. (2010) noted that 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.

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” (Zhu et al., 2021).

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” (Chaubey et al., 2020). The authors suggest that this study could be used by professional societies to recommend replacing CMAs with LP-GS.

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" (Mazzonetto et al., 2024).

**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 imbalances with an average diagnostic yield of 12.2% across all studies in this patient population, which is about 10% more than karyotyping alone (Miller et al., 2010).

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 (Hillman et al., 2013).

Reddy, Page, Saade, 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 (Reddy, Page, Saade, et al., 2012).

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 (Coulter et al., 2011).

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 10 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 (Brady et al., 2013).

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 10 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 (Borrell et al., 2017).

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" (Robson et al., 2017).

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" (Li et al., 2018). The authors also found that performing both tests sequentially result in the same number of diagnoses but costs less 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" (Li et al., 2018).

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 of all 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" (Mardy et al., 2020). This shows that CMA is not an effective diagnostic tool for NIHF.

Another study 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" (Pasternak et al., 2020). CMA identified more chromosomal abnormalities than karyotype and did not require dividing cells, making it a more practical option after termination.

Rodriguez-Revenga et al. (2020) studied the diagnostic yield of CMA in prenatal diagnosis. 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" (Rodriguez-Revenga et al., 2020).

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" (Bajaj Lall et al., 2021).

In cases of isolated fetal growth restriction, the clinical utility of chromosomal microarray analysis has yet to be evaluated fully, leading Monier et al. (2021) to evaluate the use of chromosomal microarray analysis as compared to karyotyping in these situations. Both karyotyping and chromosomal microarray 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" (Monier et al., 2021).

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 (Zhang et al., 2021).

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" (Chau et al., 2020).

## V. 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 (Manning & Hudgins, 2010):

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

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"(Manning & Hudgins, 2010). 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 2016 the ACMG published guidelines on the use of noninvasive prenatal screening for the diagnosis of fetal aneuploidy which recommends (Gregg et al., 2016):

- "Informing all pregnant [individuals] that NIPS is the most sensitive screening option for traditionally screened aneuploidies (i.e., Patau, Edwards, and Down syndromes)."
- "Allowing patients to select diagnostic or screening approaches for the detection of fetal aneuploidy and/or genomic changes that are consistent with their personal goals and preferences."
- "Offering diagnostic testing (CVS or amniocentesis) with CMA when NIPS identifies a CNV"
- "Offering diagnostic testing with CMA when a no-call result is obtained after NIPS due to possible UPD or parental consanguinity" (Gregg et al., 2016).

In 2017 the ACMG published a laboratory practice resource outlining an algorithm for diagnostic cytogenetic testing following positive noninvasive prenatal screening results which recommends (Cherry et al., 2017):

- "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."
- 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."

- 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.

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 (Seaver & Irons, 2009).

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 "Chromosomal microarray (CMA) is recommended as the first tier test in evaluation of individuals with neurodevelopmental disability and congenital anomalies. CMA may not detect balanced cytogenomic abnormalities or uniparental disomy (UPD), and deletion/duplications and regions of homozygosity may require additional testing to clarify the mechanism and inform accurate counseling" (Waggoner et al., 2018).

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 specific diagnosis is suspected, molecular testing for the suggested disorder (with single-gene test or gene panel) should be the initial test" (Monaghan et al., 2020).

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" (ACMG, 2021).

**American Academy of Pediatrics (AAP)**

The 2014 AAP guidance for the comprehensive evaluation of children with intellectual disability or global developmental delays noted that "chromosome microarray is designated as a first-line test and replaces the standard karyotype and fluorescent in situ hybridization subtelomere tests for the child with intellectual disability of unknown etiology" (Moeschler & Shevell, 2014). It further added 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."

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" (Lipkin & Macias, 2020). Further, 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" (Lipkin & Macias, 2020).

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" (Dubbs, 2022).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 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 (Hyman et al., 2020).

**American Academy of Neurology (AAN)**

The AAN published coverage policies for chromosomal microarray analysis for intellectual disabilities in 2015 (Satya-Murti, 2015). 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 (Satya-Murti, 2015):

- "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."

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 (Satya-Murti, 2015).

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

Originally published 2013 reaffirmed in 2020, 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.
- 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."

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" (ACOG, 2016). This position was reaffirmed in 2023.

A 2018 study of these guidelines analyzed 3223 prenatal samples undergoing CMA. Cases were categorized into 2 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" (Hay et al., 2018).

**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" (ASRM, 2012).

In 2020, 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:

- "Prenatal genetic counseling is strongly recommended for any pregnancy resulting from the transfer of embryos with mosaic results and should include a discussion of the risks, benefits, and limitations of CVS and amniocentesis. If prenatal diagnostic testing is performed, additional analyses beyond routine karyotyping should be considered depending on the specific PGT-A result. At the discretion of the ordering provider, these may include:
    - Chromosomal microarray, if a partial chromosome aneuploidy is involved.
    - Uniparental disomy studies (UPD), depending on the chromosome involved.
    - Additional cell counts, in an effort to identify lower-level mosaicism.
- Postnatal evaluation by peripheral blood karyotype and/or microarray should be considered, particularly if prenatal diagnostic testing is declined. Referral to a pediatric specialist in genetics is recommended in the event of an abnormal physical or developmental phenotype" (ASRM, 2020).

**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."

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."

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)" (Armour et al., 2018).

**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" (Nagan et al., 2011).

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.

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" are applicable for diagnosis.

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 (AMP, 2023):

| Tumor type | Gene/Biomarker | Significance | Primary assays |
|---|---|---|---|
| **Low grade gliomas** | *FGFR* mutation, fusion | Diagnosis | NGS (DNA), CMA |
| | *NF1* loss or inactivating mutation, loss of heterozygosity | Diagnosis, familial cancer if germline | NGS (DNA), CMA |
| | *MYB* fusion, amplification | Diagnosis, prognosis | NGS (DNA), CMA |
| | *MYBL1* fusion, amplification | Diagnosis, prognosis | NGS (DNA), CMA |

| | | | |
|---|---|---|---|
| **High grade gliomas, IDH wildtype** | *EGFR* amplification | Prognosis | NGS (DNA), CMA, FISH |
| | *CDKN2A/B* homozygous deletion | Prognosis | CMA, NGS (DNA) |
| | *TP53* loss-of-function (LOF) and gain-of-function mutations, loss, LOH | Prognosis | NGS (DNA), CMA |
| | *NF1* loss or inactivating mutation, loss of heterozygosity | Prognosis | NGS(DNA), CMA |
| | *PDGFRA* amplification | Prognosis | CMA, NGS (DNA) |
| | *RB1* loss or inactivating mutation, loss of heterozygosity | Prognosis | NGS (DNA), CMA |
| | *MDM4* amplification | Prognosis | NGS (DNA), CMA, FISH |
| | *MET* amplification, fusion, mutation | Prognosis | NGS (DNA), CMA, FISH |
| | Gain of chromosome 7 | Prognosis | CMA |
| | 10q loss | Prognosis | CMA |
| **Oligodendroglioma** | 1p/10q codeletion | Diagnosis | CMA, FISH |
| | 1q gain | Prognosis | CMA, FISH |
| **Medulloblastoma, SHH-activated** | *PTCH1* inactivating mutation, loss of heterozygosity | Subtype-diagnosis, familial cancer risk if germline N | NGS (DNA), CMA |
| | *SUFU* inactivating mutation, loss of heterozygosity | Subtype-diagnosis, familial cancer risk if germline N | NGS (DNA), CMA |
| | *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 | Diagnosis | CMA, FISH |
| | *MYCN* amplification | Diagnosis, prognosis | FISH, CMA, NGS (DNA) |
| **Medulloblastoma, Group 3** | Isochromosome 17q | Subtype-diagnosis | CMA, FISH |
| | *MYC* amplification, fusion (PVT1) | Prognosis | CMA, FISH |
| **Medulloblastoma, Group 4** | Isochromosome 17q | Subtype-diagnosis | CMA, FISH |
| | *MYCN* amplification | Diagnosis, prognosis | FISH, CMA, NGS |
| **Meningioma** | *NF2* loss-of-function (LOF) and gain-of-function mutations, loss, | Diagnosis, familial cancer risk if | NGS, CMA, MLPA |

| | | | |
|---|---|---|---|
| | loss of heterozygosity | germline | |
| **Choroid plexus tumors** | *TP53 l*oss-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* amplification and gain | Diagnosis, prognosis | CMA, FISH |

Regarding pediatric solid tumors, the following table, adapted from the oncology Molecular-in-my-Pocket™ card (AMP, 2023), lists the assays and techniques mentioning CMA and their corresponding tumor types:

| Tissue type | Tumor type | Gene/Biomarker | Significance | Primary assays |
|---|---|---|---|---|
| **Kidney** | Wilms Tumor | 1q gain, 1p/16q loss of heterozygosity | Prognosis | CMA, NGS (DNA) |
| | Rhabdoid Tumor | *SMARCB1 (INI1), SMARCA4 (BRG1)* loss | Diagnosis | IHC, CMA, NGS, MLPA |
| **Eye** | Retinoblastoma | *RB1* inactivating mutation, loss, or loss of heterozygosity | Diagnosis, familial cancer risk if germline | Sanger sequencing, MLPA, CMA, NGS (DNA) |
| **Adrenal** | Neuroblastoma | 1p/11q LOH loss | Prognosis | CMA, NGS |
| **Multi-system** | Gorlin | *SUFU*, *PTCH1* loss-of-function sequence variants, deletion/duplication | Diagnosis, familial cancer risk | Sequencing, CMA, MLPA |

Regarding pediatric soft tissue tumors, the following table, adapted from the oncology Molecular-in-my-Pocket™ card (AMP, 2023), lists the assays and techniques mentioning CMA and their corresponding tumor types:

| Tissue type | Tumor type | Gene/Biomarker | Significance | Primary assays |
|---|---|---|---|---|
| **Miscellaneous** | Chordoma (Poorly differentiated) | *SMARCB1 (INI1)* loss (sequence variant, partial deletion) | Diagnosis, prognosis | IHC, CMA, NGS, MLPA |
| | Rhabdoid (Extra-renal) | *SMARCB1 (INI1)* and *SMARCA4 (BRG1)* | Diagnosis | IHC, CMA, NGS, MLPA |
| | Epithelioid sarcoma | *SMARCB1 (INI1)* and *SMARCA4 (BRG1)* | Diagnosis, treatment | IHC, CMA, NGS, MLPA |
| **Multi-system** | Gorlin | *SUFU*, *PTCH1* loss-of-function sequence variants, deletion/duplication | Diagnosis, familial cancer risk | Sequencing, CMA, MLPA |

**Society for Maternal-Fetal Medicine (SMFM)**

The SMFM recommends chromosomal microarray for evaluation of mild fetal ventriculomegaly and nonimmune hydrops fetalis (Fox et al., 2018; Norton et al., 2015).
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" (Martins et al., 2020).

**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" (Miller et al., 2010). 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]" (Miller et al., 2010).

**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" (ISPD, 2018).

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.
- 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" (ISPD, 2018).

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.

**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" (Shen et al., 2010). 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" (Shen et al., 2010).

**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" (Cohen et al., 2008). 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, "Currently, Fragile X testing must be ordered as a separate test since expansions of 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 (National FragileX Foundation, 2024).

## VI. 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. For the most up-to-date Medicaid policies and coverage, visit the applicable state Medicaid website.

**Food and Drug Administration (FDA)**

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" (FDA, 2014).

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" (FDA, 2017).

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.

## VII. 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).

## VIII. Evidence-based Scientific References


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## IX. Policy History

| Action Date | Action |
|---|---|
| June 01, 2023 | Policy created |
| December 03, 2024 | Policy approved by Medical Directors |
| December 20, 2024 | Policy approved at UMC |
| February 01, 2025 | Policy effective date following notification period |