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The use of chromosomal microarray for prenatal diagnosis

Society for Maternal-Fetal Medicine (SMFM); Lorraine Dugoff, MD; Mary E. Norton, MD; Jeffrey A. Kuller, MD

Chromosomal microarray analysis is a high-resolution, whole-genome technique used to identify chromosomal abnormalities, including those detected by conventional cytogenetic techniques, as well as small submicroscopic deletions and duplications referred to as copy number variants. Because chromosomal microarray analysis has a greater resolution than conventional karyotyping, it can detect deletions and duplications down to a 50- to 100-kb level. The purpose of this document is to discuss the technique, advantages, and disadvantages of chromosomal microarray analysis and its indications and limitations. We recommend the following: (1) that chromosomal microarray analysis be offered when genetic analysis is performed in cases with fetal structural anomalies and/or stillbirth and replaces the need for fetal karyotype in these cases (GRADE 1A); (2) that providers discuss the benefits and limitations of chromosomal microarray analysis and conventional karyotype with patients who are considering amniocentesis and chorionic villus sampling (CVS), and that both options should be available to women who choose to undergo diagnostic testing (GRADE 1B); (3) that pre- and posttest counseling should be performed by trained genetic counselors, geneticists, or other providers with expertise in the complexities of interpreting chromosomal microarray analysis results (Best Practice); (4) that patients be informed that chromosomal microarray analysis does not detect every genetic disease or syndrome and specifically does not detect autosomal-recessive disorders associated with single gene point mutations, as well as that chromosomal microarray analysis can detect consanguinity and nonpaternity in some cases (Best Practice); (5) that patients in whom a fetal variant of uncertain significance is detected by prenatal diagnosis receive counseling from experts who have access to databases that provide updated information concerning genotype-phenotype correlations (Best Practice).

Key words: chromosomal abnormalities, chromosomal microarray analysis, microarray, prenatal diagnosis

Chromosomal microarray analysis (CMA) is a high-resolution, whole-genome screening technique that can identify most of the chromosomal imbalances detected by conventional cytogenetic analysis, as well as smaller submicroscopic deletions and duplications that are referred to as copy-number variants (CNVs). CNVs may cause a wide range of human disorders, including neurodevelopmental disorders and congenital anomalies such as cardiac defects. CMA is recommended as the first-tier test in the postnatal evaluation of congenital abnormalities and neurodevelopmental disorders. With accumulating experience during the last decade and data demonstrating improved detection of chromosomal abnormalities compared to conventional karyotyping, CMA is proving to be a valuable diagnostic tool in the prenatal setting. CMA can be performed on uncultured DNA samples, including those obtained from CVS and amniocentesis, which may lead to a quicker turnaround time than a karyotype.

What are the different types of microarray?

There are 2 major microarray platforms used in prenatal diagnosis: single-nucleotide polymorphism (SNP) arrays and comparative genomic hybridization (CGH) arrays. With SNP and CGH arrays, DNA from a fetal sample, such as CVS

Corresponding author: The Society for Maternal-Fetal Medicine: Publications Committee. pubs@smfm.org

or amniocentesis, is hybridized to an array platform consisting of DNA probes on a solid surface, such as a microscope slide or a silicon chip.

CGH compares the fetal DNA sample with a normal reference DNA sample (Figure 1). The test DNA and the reference DNA samples are labeled with 2 different-colored fluorescent dyes, then combined and hybridized to an array platform. The relative intensities of the different colors are compared with bioinformatics tools. Cases with duplications will have a greater hybridization signal, whereas cases with deletions will have a lower hybridization signal compared to the reference sample.

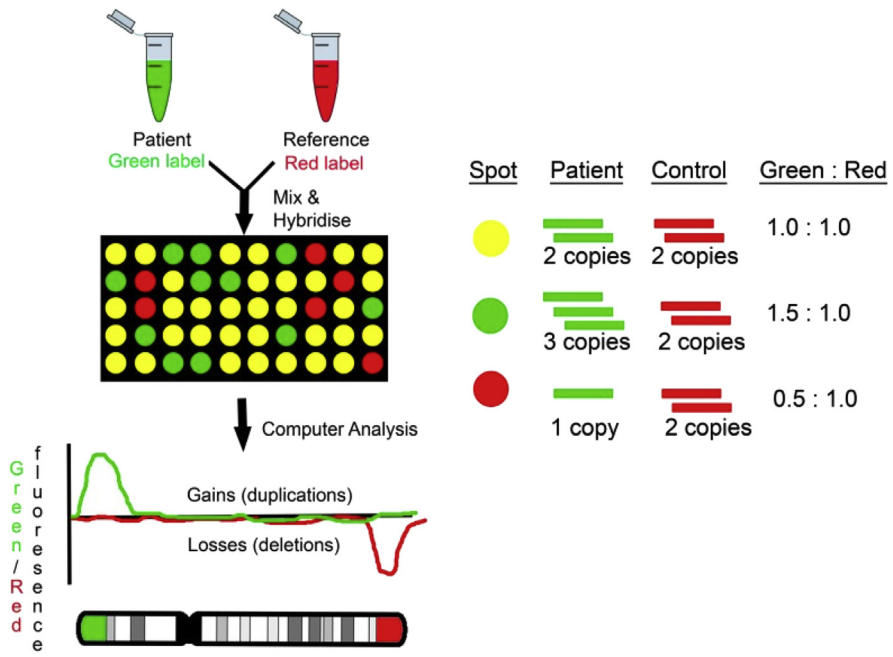
A SNP is a variation at a single position in a DNA sequence among individuals. With SNP arrays, only the DNA test sample is hybridized to the array platform (Figure 2). SNP arrays detect CNVs by measuring probe signal intensities as used in the CGH approach. Although CGH arrays are only able to detect CNVs, SNP arrays also can detect triploidy and regions on the 2 homologous chromosomes that are identical to each other, as occurs with uniparental disomy (UPD) and consanguinity. With UPD, both copies of a chromosome are inherited from the same parent instead of 1 from each parent. UPD has been associated with genetic disorders such as Prader-Willi syndrome, which can occur when both copies of chromosomes 15 are inherited maternally.[1] SNP arrays also can detect some cases of maternal cell contamination and mosaicism.

Arrays may include probes that cover the whole genome, or may be targeted with concentrated coverage in known disease-causing regions of the genome and more limited coverage of the rest of the genome. An advantage of targeted arrays is that they decrease the chance of identifying a variant of uncertain significance (see section "What are the risks of using CMA? What are variants of uncertain significance and how should they be managed?"). In general, arrays used for prenatal diagnosis have lower resolution than those used for postnatal testing for this reason.

What can CMA detect? How does it differ from a karyotype?

A standard karyotype can detect aneuploidies (abnormalities in chromosome number), relatively large structural abnormalities such as deletions or duplications that are microscopically visible down to a resolution of approximately 5–10 Mb, and balanced or unbalanced translocations and inversions. CMA has a greater resolution than conventional karyotyping, allowing for the detection of much smaller, submicroscopic deletions, and duplications typically down to a 50- to 100-kb level.[2] CMA also can detect some copy number changes near the chromosomal breakpoint sites in rearrangements that appear to be balanced on a conventional karyotype. The types of abnormalities that can be detected with CGH and SNP arrays and conventional karyotype are summarized in Table 1.

FIGURE 1
Comparative genomic hybridization array



Source: Karampetsou E, Morrogh D, Chitty L. Microarray technology for the diagnosis of fetal chromosomal aberrations: which platform should we use? J Clin Med 2014;3:663–78.

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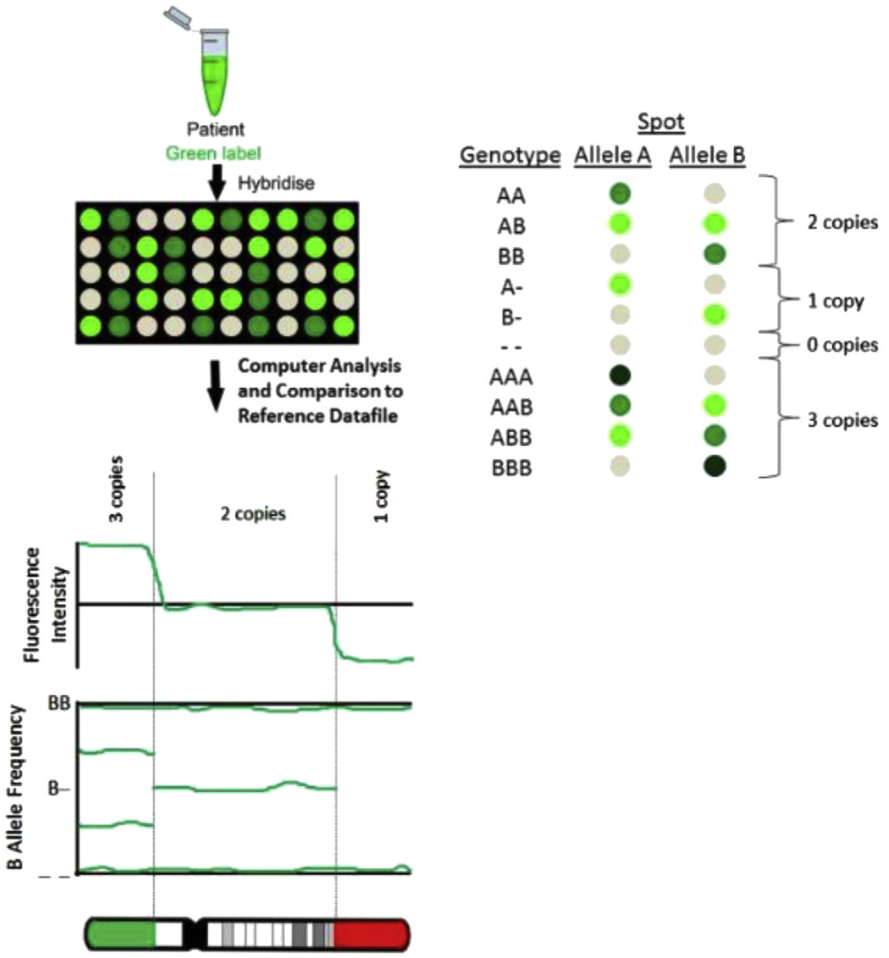
FIGURE 2
Single-nucleotide polymorphism (SNP) array



Source: Karampetsou E, Morrogh D, Chitty L. Microarray technology for the diagnosis of fetal chromosomal aberrations: which platform should we use? J Clin Med 2014;3:663–78.

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Several large-scale studies have compared the prenatal use of chromosomal microarray to conventional karyotyping. A 2012 multicenter trial sponsored by the National Institute of Child Health and Human Development (NICHD) demonstrated that CMA is most beneficial in fetuses with abnormal ultrasound findings. In pregnancies with a fetal structural abnormality identified by ultrasound and a normal karyotype, CMA revealed clinically relevant

TABLE 1
Abnormalities detected with conventional karyotype, CGH, and SNP arrays

Technique	Aneuploidy	Balanced translocations and inversions	Unbalanced translocations	Triploidy	AOH/consanguinity	CNVs
Conventional karyotype	+	+	+	+	–	–
CGH array	+	–	+	–	–	+
SNP array	+	–	+	+	+	+

AOH, absence of heterozygosity; *CGH*, comparative genomic hybridization; *CNV*, copy-number variants; *SNP*, single-nucleotide polymorphism.

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deletions or duplications in 6.0% of cases. In pregnancies with a structurally normal fetus by ultrasound and a normal karyotype in which CVS or amniocentesis was performed secondary to advanced maternal age or a positive aneuploidy screen, CMA revealed clinically relevant findings in 1.7% of cases.[3] A systematic review of 4 large-scale studies, including the NICHD trial, reported clinically significant deletions or duplications in 6.5% (201/3090) of cases with abnormal ultrasound findings, 1.0% (50/5108) of cases with advanced maternal age, and 1.1% (44/4164) of cases in which CVS or amniocentesis was performed as the result of another reason, including parental anxiety, an abnormal serum screening result, or history of a chromosome abnormality. All of these cases had normal karyotypes.[4]

Another advantage of CMA is that this technique does not require dividing cells, in contrast to conventional karyotyping, which requires cell culture. This difference can allow a quicker turnaround time. In addition, CMA can be performed on macerated tissue obtained from stillbirth specimens that may not grow in tissue culture; therefore, CMA may be more likely to provide a result as long as sufficient good-quality DNA can be obtained. A population-based study of 532 stillbirth cases by the Stillbirth Collaborative Research Network reported that microarray analysis yielded results more often than standard karyotype analysis (87.4% vs 70.5%, $P < .0001$) and provided increased detection of genetic abnormalities (8.3% vs 5.8%, $P = .0067$).[5] **We recommend that CMA be offered when genetic analysis is performed in cases with fetal structural anomalies and/or stillbirth and replaces the need for fetal karyotype in these cases (GRADE 1A)**.

What are the limitations of CMA?

Because CMA looks for genomic imbalance, this technique is not able to detect totally balanced chromosomal rearrangements, such as translocations or inversions. The large majority of balanced rearrangements, however, result in a normal outcome. In addition, CMA does not provide information about the chromosomal mechanism of a genetic imbalance.[6] For example, if there is a gain of an entire chromosome 13, CMA cannot distinguish between trisomy 13 and an unbalanced Robertsonian translocation, which has relevance for recurrence risk counseling.[2] Therefore, a karyotype should be performed in such cases to rule out a translocation that may have been inherited. Low-level mosaicism may not be detected by CMA, and some arrays do not detect triploidy. SNP arrays, however, generally are able to detect lower levels of mosaicism, as well as triploidy.[7] CMA will not detect all CNVs, such as those that are in regions not represented on the array platform and very small CNVs that are below the level of detection. In some cases, a postnatal CMA may identify a CNV that was not identified prenatally because of the greater resolution of postnatal arrays. In addition, CMA will not detect point mutations within single genes, including those that cause disorders such as sickle-cell anemia, cystic fibrosis, and many of the skeletal dysplasias.[6]

What are the risks of using CMA? What are variants of uncertain significance and how should they be managed?

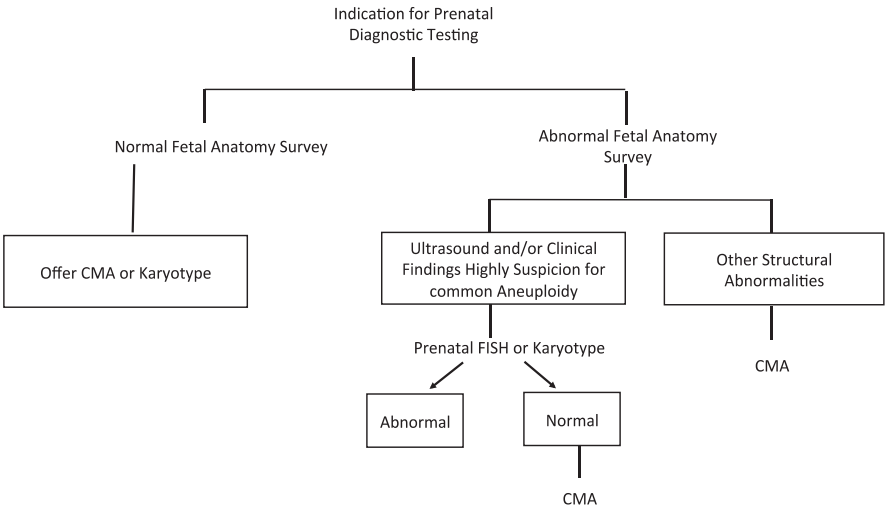
A disadvantage of CMA is the inability to precisely interpret the clinical significance of a previously unreported CNV or to accurately predict the phenotype of some CNVs that are associated with variable outcomes. CNVs are characterized as benign, clinically significant (ie, pathogenic), and as a variant of uncertain significance (VUS). The overall prevalence of VUS is approximately 1–2%.[3,8,9] The NICHD-sponsored multicenter trial reported a 0.9% prevalence of pathogenic CNVs and a 1.5% prevalence of VUS in cases with normal karyotypes.[3] A qualitative study of 12 couples who received a pathogenic ($n = 6$) or uncertain microarray result ($n = 6$) reported that participants whose fetuses carried a VUS experienced heightened anxiety and frustration at the limited scope of information available to them to understand and plan for the future health and development of their child and make decisions about continuing the pregnancy. Some of these couples felt "even more uninformed after microarray."[10] Fortunately, additional information on the classification of CNVs is accumulating rapidly, which should lead to a decrease in the incidence of reported VUS over time.

We recommend that patients in whom a fetal VUS is detected receive counseling from experts who have access to databases that provide updated information concerning genotype-phenotype correlations (Best Practice). Patients should be educated regarding the significance of the finding, including the potential range of outcomes, and should be provided with resources and support. Further testing should be offered if indicated. One of the initial steps in the evaluation is to determine whether either parent has the same CNV as was detected in the fetus. Although de novo CNVs are more likely to be pathogenic, an abnormal fetal outcome cannot always be excluded even if a parent with the same CNV as a fetus is normal, as some have a variable outcome.[11] When interpreting VUS, it may be helpful to evaluate the specific genes that are contained in the deleted or duplicated regions. In general, small duplications are less likely to be clinically significant than small deletions.

When should array be offered, and what are the indications?

The American College of Obstetricians and Gynecologists (ACOG) and the Society for Maternal-Fetal Medicine (SMFM) recommend that "[A]ll pregnant women should be offered prenatal assessment for aneuploidy by screening or diagnostic testing regardless of maternal age or other risk factors…The differences between screening and diagnostic testing also should be discussed."[12] CMA in particular is recommended when genetic analysis is performed in cases with fetal structural anomalies and/or fetal demise. CMA

FIGURE 3
Algorithm for use of chromosomal microarray analysis (CMA) with prenatal diagnostic testing



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replaces the need for fetal karyotype in these cases. The ACOG and SMFM recommend that either fetal karyotype or CMA can be performed when invasive prenatal diagnosis is performed in cases with structurally normal fetuses regardless of maternal age[13] (Figure 3).

Currently, some clinical providers recommend CMA as a first-line test whenever fetal chromosomal analysis is planned,[4,14] whereas other clinical providers reserve CMA for cases in which there are fetal structural abnormalities to avoid the possibility of discovering a VUS. The prevalence of significant abnormalities identified by CMA in cases with a normal karyotype and normal ultrasound was 1/60 (1.7%) in the NICHD study.[3] Data combined from 5 studies on prenatal CMA revealed a 0.5% prevalence of abnormalities detected by array that would not be detectable by conventional karyotype in 3151 women who had invasive testing due to advanced maternal age.[9] This prevalence is high enough that providers should discuss the benefits and limitations associated with CMA and conventional karyotype with their patients who are considering amniocentesis and CVS. **We recommend that providers discuss the benefits and limitations of CMA and conventional karyotype with patients who are considering amniocentesis and CVS and that both options be available to women who choose to undergo diagnostic testing (GRADE 1B)**.

CMA should be considered as further evaluation when an apparently balanced de novo rearrangement is detected by karyotyping to exclude an imbalance at one or both of the translocation breakpoints. A study in which CMA was performed in 239 prenatal cases of apparently balanced rearrangements detected by karyotyping reported a 7.9% incidence of a gain or loss at one or both of the translocation breakpoints. An additional 1.7% had a clinically significant gain or loss at another location in the genome that explained the prenatal phenotype. CMAs may also prove helpful in identifying the chromosomal origin and gene content of marker or ring chromosomes identified with conventional karyotype.[9]

When is it appropriate to perform just a karyotype? Is it necessary to do a karyotype if a microarray is being done?

Conventional karyotype and/or rapid FISH testing may be more appropriate when a common aneuploidy such as trisomy 21, 18, 13 or monosomy X is strongly suspected based on prenatal ultrasound findings. In these circumstances, conventional karyotype and fluorescence in situ hybridization (FISH) analysis might provide a more rapid turn-around, allow for more sensitive detection of low-level mosaicism and rule out a translocation-associated trisomy. A CMA can be performed in the event that the FISH or karyotype is normal. Conventional karyotype to identify potential balanced translocations is the most appropriate first-line test for couples with a history of recurrent miscarriage.[15] **We recommend against the use of CMA as a first-line test to evaluate first trimester pregnancy losses due to limited data (GRADE 1C)**.

There are some situations in which a karyotype should be performed after an abnormal microarray result. When trisomy of an acrocentric chromosome (13, 14, 15, 21, or 22) is identified by CMA, a karyotype should be performed in order to rule out an unbalanced Robertsonian translocation that might have been inherited. Depending on the size, either FISH or a karyotype is sometimes recommended to rule out inherited rearrangements in some cases involving smaller copy number gains. This information is needed in

order to provide accurate information regarding future recurrence risks.

How should patients be counseled before CMA?

Pre- and posttest counseling should be performed by trained genetic counselors, geneticists, or other providers with expertise in the complexities of interpreting CMA results (Box 1). **We recommend that pre- and posttest counseling be performed by trained genetic counselors, geneticists or other providers with expertise in the complexities of interpreting CMA results (Best practice)**. Providers should be familiar with the microarray platform used by their laboratory, including the rate of VUS. Patients should be informed that compared with conventional karyotype, CMA will detect a potentially pathogenic CNV in an additional 6–7% of cases with fetal structural abnormalities on ultrasound[3,4,8] and in 1–1.7% of cases with a structurally normal fetus.[3,4] Patients also should be informed of the 1.4-2.1% chance that a VUS will be detected.[3,8] Pretest counseling should include a discussion of the spectrum of disorders that can be detected with CMA, including disorders with severe neurologic phenotypes as well as those with more mild or adult onset phenotypes.[16] Patients also should be informed that CMA does not detect every genetic disease or syndrome, including autosomal-recessive disorders associated with single gene point mutations. Patients should also be informed that CMA can detect consanguinity and non-paternity in some cases. **We recommend that patients be informed that CMA does not detect every genetic disease or syndrome, and specifically does not detect single gene point mutations, as well as that CMA can detect consanguinity and non-paternity in some cases (Best Practice)**.

BOX 1
Sample script for counseling patients before CMA

Patients considering prenatal diagnosis and chromosomal microarray should be told that:
"Chromosomal microarray is a genetic test that exams the chromosomes in finer detail than what is done by routine karyotype or chromosome analysis. This means that a microarray can find abnormalities that would be missed by routine karyotype testing. However, it also means that sometimes small abnormalities are identified that are of uncertain significance and may or may not indicate a problem with the fetus."
In addition, pretest counseling should include:

- Chromosomal microarray analysis can identify the large majority of significant abnormalities identified by karyotype as well as many additional genetic diseases. It will not identify all genetic disorders.
- Diseases may be identified for which the clinical presentation may vary greatly and range from mild to severe. It may not be possible to predict what the outcome will be in a given patient.
- The test may identify consanguinity or nonpaternity.
- Genetic changes may be identified that may or may not cause disease. Samples from both parents may be required to help understand the significance of the results.
- Test results may identify adult-onset diseases that will not affect health during the newborn period or childhood but may have unknown severity later in life. Identification of such findings may also indicate that one of the parents has the same adult-onset disease but has not yet developed symptoms.

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What samples can be used?

CMA may be performed on DNA obtained from amniocentesis, CVS, fetal cord blood, and stillbirth specimens. DNA obtained from the mesenchymal core cells of the chorionic villi and uncultured amniocytes is preferable to DNA from cultured cells to allow for quicker turnaround and to avoid the possibility of culture artifacts.[11] Some labs require that a maternal blood specimen be sent with the original CMA specimen while other labs only request parental samples when a CNV is detected, to distinguish between an inherited and a de novo CNV.

Are there differences between prenatal and postnatal microarray?

In the postnatal setting, CMAs are used to explain existing abnormalities, whereas in the prenatal setting CMAs are obtained to predict fetal outcomes. In many prenatal cases, patients opt to have CMA for reassurance that a significant finding is absent.[17,18] CMAs are recommended as the first-tier diagnostic test for the postnatal evaluation of individuals with multiple congenital anomalies, developmental delay/intellectual disability, and/or autism spectrum disorders, with clinically significant findings reported in approximately 15% of cases with normal conventional karyotypes.[15] In postnatal cases, identification of a diagnosis is important to parents for many reasons, including ending the search for a diagnosis, obtaining resources, and planning future care for the child as well as future reproduction. The benefit of finding a clinically significant abnormality with CMA may offset the downside of finding a VUS.[19] In the prenatal setting, particularly in cases with a structurally normal fetus on ultrasound, a VUS may cause considerable stress and anxiety as the parents may consider the option of pregnancy termination. It may be difficult to interpret the significance of a CNV prenatally due to the limitations of fetal imaging and the limited information currently available correlating prenatal CNV findings with postnatal phenotypes.[17]

To decrease the likelihood of identifying a VUS, many specialists advocate using a targeted rather than a whole-genome approach in prenatal cases.[20] Targeted arrays use platforms that primarily identify CNVs in which clinical interpretation is nonequivocal, including trisomies, or well-documented microdeletion/duplication syndromes.[21] Targeted arrays, however, also may result in a lower diagnostic yield. The probe density of targeted arrays has increased over the last several years, and as the knowledge regarding classification of CNVs continues to expand, the difference

Summary of Recommendations

Number	Recommendations	GRADE
1	We recommend that CMA be offered when genetic analysis is performed in cases with fetal structural anomalies and/or stillbirth and replaces the need for fetal karyotype in these cases.	1A Strong recommendation, high-quality evidence
2	We recommend that providers discuss the benefits and limitations of CMA and conventional karyotype with patients who are considering amniocentesis and CVS, and that both options be available to women who choose to undergo diagnostic testing.	1B Strong recommendation, moderate-quality evidence
3	We recommend that pre- and posttest counseling be performed by trained genetic counselors, geneticists, or other providers with expertise in the complexities of interpreting CMA results.	Best Practice
4	We recommend that patients be informed that CMA does not detect every genetic disease or syndrome and specifically does not detect single gene point mutations, as well as that CMA can detect consanguinity and nonpaternity in some cases.	Best Practice
5	We recommend that patients in whom a fetal VUS is detected receive counseling from experts who have access to databases that provide updated information concerning genotype–phenotype correlations.	Best practice

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between whole genome arrays and targeted arrays is narrowing.[22] As mentioned previously, postnatal CMA does generally have a greater resolution than those used in a prenatal setting, and therefore may identify a CNV that was not identified prenatally in some cases.

What guidelines exist from other societies regarding the use of CMA?

Recent guidelines from several international and national societies have advocated the selective use of CMAs for pregnancies undergoing prenatal testing. ACOG and SMFM published joint recommendations on the use of microarray in prenatal diagnosis in 2013.[13] CMA is recommended when genetic analysis is performed in cases with fetal structural abnormalities and/or stillbirth. In these circumstances, CMA replaces the need for karyotype. In cases with a structurally normal fetus, either CMA or conventional karyotyping can be performed. Comprehensive patient pretest and posttest genetic counseling and informed consent are noted to be essential. Although the American College of Medical Genetics has published guidelines for clinical laboratories,[6] the organization has not published guidelines for clinical providers regarding use of prenatal microarray.

The Society of Obstetricians and Gynecologists of Canada and the Canadian College of Medical Geneticists state that CMA is not recommended in pregnancies at low risk for a structural chromosomal abnormality but it may be an appropriate diagnostic test in cases with fetal structural abnormalities detected on ultrasound or fetal magnetic resonance imaging.[23]

A working group on behalf of the UK Joint Committee on Genomics in Medicine recommended in June, 2015, that prenatal CMA testing is indicated in cases with one or more structural anomalies identified on ultrasound, an isolated nuchal translucency $\geq$3.5 mm and in fetuses with a sex chromosome aneuploidy by karyotype that is unlikely to explain the ultrasound anomaly (eg, XXX, XXY, and XYY).[24] A 2012 position statement of the Italian Society of Human Genetics recommended that CMAs only be used as a second tier test to complement, but not replace, standard karyotype in prenatal cases with fetal structural abnormalities, as well as with de novo chromosomal rearrangements and supernumerary marker chromosomes in order to characterize their origin and genomic content.[25]

Guidelines

Organization	Title	Year of publication
ACOG and SMFM	Committee Opinion #581, The use of chromosomal microarray analysis in prenatal diagnosis[13]	2013
ACOG and SMFM	Practice bulletin no. 162: prenatal diagnostic testing for genetic disorders[12]	2016
SOGC and CCMG	Use of array genomic hybridization technology in prenatal diagnosis in Canada[23]	2011
UK Joint Committee on Genomics in Medicine, Royal College of Pathologists	Recommendations for the use of chromosome microarray in pregnancy[24]	2015
Italian Society of Human Genetics	Microarray application in prenatal diagnosis: a position statement for the cytogenetics working group[25]	2011

The content of this document reflect the national and international guidelines related to the use of chromosomal microarray for prenatal diagnosis.

ACOG, American College of Obstetricians and Gynecologists; *CCMG*, Canadian College of Medical Geneticists; *SMFM*, Society for Maternal-Fetal Medicine; *SOGC*, Society of Obstetricians and Gynecologists of Canada.

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What are the issues of cost and insurance coverage of CMA?

The cost of chromosomal microarray is currently greater than conventional karyotyping but is expected to decrease with increasing volumes and technical advances. Insurance coverage in the United States largely conforms to the recommendations of the joint ACOG and SMFM Committee Opinion. Two major carriers currently consider CMA medically necessary for all patients undergoing invasive prenatal diagnostic testing as well as the evaluation of a fetal demise in cases with structural abnormalities.[26,27] The second carrier also considers CMA medically necessary for cases of stillbirth in which karyotype results cannot be obtained.[27] A third major carrier considers CMA medically necessary for all women undergoing invasive prenatal testing and cases of fetal demise and stillbirth.[28]

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