

ACOG and SMFM guidelines for prenatal diagnosis: Is karyotyping really sufficient?

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Abstract

Objective: The American College of Obstetricians and Gynecologists (ACOG) and Society for Maternal-Fetal Medicine (SMFM) recommend chromosomal microarray analysis (CMA) for prenatal diagnosis in cases with 1 or more fetal structural abnormalities. For patients who elect prenatal diagnosis and have a structurally normal fetus, either microarray or karyotype is recommended. This study evaluates the frequency of clinically significant chromosomal abnormalities (CSCA) that would have been missed if all patients offered the choice between CMA and karyotyping chose karyotyping.

Methods: A total of 3223 prenatal samples undergoing CMA were evaluated. Cases were categorized into 2 groups: those that met ACOG guidelines for CMA versus those that met ACOG guidelines for either CMA or karyotype.

Results: Of the 3223 cases, 1475 (45.8%) met ACOG recommendations for CMA, and 1748 (54.2%) met recommendations for either CMA or karyotype. In patients who could have elected either CMA or karyotype, 2.5% had CSCA that would have been missed if the patient had elected to pursue karyotype.

Conclusion: This study suggests that 2.5% of patients will have a CSCA that may be missed if the guidelines continue to suggest that CMA and karyotyping have equivalent diagnostic value for patients without a fetal structural abnormality.

1 | INTRODUCTION

Chromosomal microarray analysis (CMA) is increasingly being utilized in prenatal diagnosis due to its improved detection rate of clinically significant chromosomal abnormalities (CSCA) compared with karyotyping. High-resolution single nucleotide polymorphism (SNP)-based microarrays can detect a variety of abnormalities, including whole chromosome aneuploidies, unbalanced rearrangements, microdeletions and microduplications, triploidy, uniparental isodisomy, and low-level mosaicism; whereas karyotyping is limited to detecting whole chromosome aneuploidies, large deletions and duplications (≥ 5 –10 Mb), polyploidy, and some balanced chromosomal rearrangements. Due to the significant differences in resolution and the increased detection rate of chromosomal abnormalities, CMA has been recommended

as a first tier test in the pediatric setting for the evaluation of children with developmental delays, intellectual disabilities, multiple congenital abnormalities, or autism spectrum disorders for over a decade.^{1,2}

In prenatal diagnosis, CMA has begun to emerge as a favorable alternative to karyotype analysis. Wapner et al reported that following a normal karyotype, CMA identified an additional 6.0% of pregnancies with a CSCA when there was at least 1 major structural ultrasound abnormality, and in an additional 1.7% of pregnancies with standard indications for testing, such as an increased risk due to an abnormal maternal serum screening or advanced maternal age.³ Following the publication of this data, the American College of Obstetricians and Gynecologists (ACOG) and the Society for Maternal-Fetal Medicine (SMFM) published joint recommendations regarding the use of microarray analysis in prenatal diagnosis. The

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societies recommended CMA in lieu of karyotyping for patients who wished to proceed with prenatal diagnosis by chorionic villus sampling (CVS) or amniocentesis in the setting of 1 or more structural fetal anomalies identified by ultrasound. For patients who wished to pursue prenatal diagnosis in the setting of a normal fetal ultrasound, the societies recommend offering either CMA or karyotyping.⁴ In the years following these recommendations, microarray technology has transitioned to more sensitive SNP-based methods allowing for the detection of triploidy, uniparental isodisomy, and regions of homozygosity, in addition to copy number variations. Significant advances were also made in prenatal screening technologies, specifically, the ability to analyze cell free placental DNA from maternal blood. Therefore, it is important to reassess current trends as well as the utility of these published recommendations.

In this study, we identified and characterized the reason for referral and any additional clinical data provided for all patients undergoing prenatal CMA, and then classified the patients into 2 groups based upon ACOG/SMFM recommendations. The types of results for both groups were characterized as abnormal (a clinically significant chromosomal alteration was identified), normal (no clinically significant chromosomal alterations were identified), or a variant of uncertain significance (VOUS; a chromosomal alteration was identified that is not clearly associated with a known syndrome, but may act as a risk factor). The purpose of this study was to determine the frequency of CSCA in structurally normal fetuses that would not have been detected if they had been evaluated only by karyotyping rather than CMA.

2 | MATERIALS AND METHODS

We analyzed 3234 consecutive prenatal samples referred for evaluation by CMA over a 3-year period. All samples included in this study were from ongoing pregnancies. Miscarriage tissue and intrauterine fetal demise cases were excluded from analysis. Of the 3234 samples, 3223 were successfully resulted using CMA testing. All CMA testing was performed by CombiMatrix Diagnostics (310 Goddard, St. 150, Irvine, CA 92618). We analyzed 3226 prenatal samples using the CombiSNP Prenatal microarray, manufactured by Illumina (Illumina Inc., San Diego, CA). The CombiSNP Prenatal microarray is composed of 851,622 SNP probes with a median spatial resolution of 1 Kb within gene-rich regions and 5 Kb outside of gene-rich regions. Of the 3226 samples analyzed, 2472 were amniotic fluid/amniocytes, 739 were chorionic villi/CVS cultures, and the remaining 15 cases were other various sample types, such as fetal blood, fetal urine, and extracted DNA. The extracted DNA from these samples was evaluated for copy number changes involving ≥ 16 contiguous probes (~ 20 kb) and for regions of homozygosity ≥ 5 Mb. Mosaicism for partial or whole chromosome aneuploidy was reported when present at or above the detection threshold of 15%. Genomic imbalances were reported using UCSC's Human Genome Build 19 (NCBI build 37, Feb 2009).

The clinical data provided for each case were used to stratify patients into 1 of 2 previously described groups: those that met ACOG guidelines for CMA in lieu of karyotyping versus those that met ACOG guidelines for CMA or karyotyping (see Table 1). Each group was further subdivided by CMA results: normal, abnormal, and variant

What's already known about this topic?

- Current professional guidelines regarding the use of chromosomal microarray analysis (CMA) versus karyotyping in prenatal diagnosis support CMA over karyotype only when fetal structural abnormalities are present.
- Examination of the clinical utility of these guidelines, given advances in microarray technology and prenatal screening, is largely unaddressed.

What does this study add?

- This study demonstrates the diagnostic superiority of CMA by SNP microarray compared with karyotyping for prenatal diagnosis, regardless of the clinical indication for testing.

of uncertain significance (VOUS). For the purpose of this study, VOUS likely benign results were included in the normal group and VOUS likely pathogenic results were included in the VOUS group. Abnormal array results were then evaluated to determine detectability by karyotyping, and were classified as "detectable," "possibly/partially detectable," or "not detectable." For cases in which a karyotype was not performed, classification was determined by copy number size, using the standard detection limit of >10 Mb for a standard resolution karyotype analysis. Abnormalities that were mosaic but >10 Mb were classified as "possibly/partially detectable," because detection by karyotype is dependent upon the level of mosaicism and the possibility of preferential overgrowth of the normal cell line in culture. If there were multiple copy number variants (CNVs) present and not all would be detected by karyotype, the case was classified as "possibly/partially detected." Mosaic aneuploidies were included in the "detectable" group.

3 | RESULTS

Of the 3234 prenatal samples received for CMA, 3223 (99.7%) were successfully analyzed and resulted, 8 (0.2%) cases were not tested due to suboptimal DNA quantity or quality (QNS; quality/quantity not sufficient), and 3 (0.1%) cases were tested but not resulted due to significant maternal cell contamination (MCC). The majority of samples were direct amniotic fluid (1744/3223, 54.1%) and cultured amniocytes (727/3223, 22.5%), and a smaller number of samples were direct chorionic villi (360/3223, 11.2%) or cultured chorionic villi (377/3223, 11.7%). The remaining 15 (0.5%) cases included the following sample types: fetal urine, extracted DNA, fetal blood, amniocyte cell pellet, fetal cyst fluid, and peritoneal fluid. All 8 QNS cases were CVS samples that were inadequate for CMA. Of the 3 cases with significant MCC, 2 were CVS culture, and one was amniotic fluid.

TABLE 1 Categorization of testing indications into CMA group vs CMA/karyotype group

CMA Group	CMA/Karyotype Group
One or more fetal structural abnormality identified by ultrasound (N = 1475)	Structurally normal fetus by ultrasound (N = 1748)
<p>Anomaly categories included:</p> <ul style="list-style-type: none"> - Cardiac abnormalities - Central nervous system abnormalities - Cystic hygroma/ascites/hydrops - Facial dysmorphisms - Gastrointestinal abnormalities - Genitourinary abnormalities - Limb/digit abnormalities - Oligo- or polyhydramnios - Pulmonary/chest/thorax abnormalities - Situs inversus 	<p>Test indications included:</p> <ul style="list-style-type: none"> - Advanced maternal age - Abnormal maternal serum screen - Family history - Soft ultrasound markers, including: <ul style="list-style-type: none"> • absent/hypoplastic nasal bone • choroid plexus cysts • echogenic bowel • echogenic intracardiac focus • intrauterine growth restriction • pyelectasis • single umbilical artery

3.1 | Distribution of cases between the two recommendation groups

Of the 3223 resulted cases, 1475 (45.8%) met ACOG recommendations for CMA based upon reported clinical data of 1 or more structural fetal anomalies on ultrasound ("CMA group"). The remaining 1748 (54.2%) cases had no obvious fetal structural anomalies and were thus offered either CMA or karyotype ("CMA/Karyotype group") (Table 1). For the CMA group, the mean maternal age was 30.1 ± 5.0 years, and the mean gestational age was 21 weeks ± 4 weeks. For the CMA/Karyotype group, the mean maternal age was 34.6 ± 5.0 years, and the mean gestational age was 17.1 weeks ± 4 weeks. For the CMA group, 7.8% (116/1475) had CVS, and 91.2% (1345/1475) had amniocentesis (the remaining 1% were other samples types), while for the CMA/Karyotype group, 35.5% (621/1748) had CVS and 64.4% (1126/1748) had amniocentesis.

3.2 | CMA results for the two groups

For the CMA group, 1149 patients (77.9%) had normal results, 257 (17.4%) had clinically significant abnormal results, and 69 (4.7%) had a VOUS result. In the CMA/Karyotype group, 1497 patients (85.7%) had normal results, 156 (8.9%) had abnormal results, and 95 (5.4%) had a VOUS result (Table 2). Of all 3223 samples in both groups, 1 (0.03%) aneuploid sample was found to also have a balanced translocation by karyotype.

TABLE 2 Overall prenatal CombiSNP array data sorted by ACOG recommendations

CMA Result	CMA Group (N = 1475)		CMA/Karyotype Group (N = 1748)	
NORMAL	1149	77.9%	1497	85.7%
ABNORMAL	257	17.4%	156	8.9%
VOUS	69	4.7%	95	5.4%

3.3 | Additional classification of abnormal results by karyotype result

All abnormal results for each group were further classified based upon actual or predicted karyotype results (Table 3). In the CMA group, 105 (40.8%) of the cases with abnormal CMA results had a karyotype performed at CombiMatrix or an outside laboratory. The remaining 152 (59.1%) did not have a karyotype. In the CMA/Karyotype group, 56 (35.9%) of the cases with abnormal CMA results had a karyotype performed at CombiMatrix or at an outside laboratory; the remaining 100 (64.1%) did not have a karyotype performed.

In the CMA group, of the 257 patients that had a clinically significant abnormality identified by CMA, 177 patients (12% of the CMA group) had abnormalities that were classified as "detectable" by karyotype analysis; 10 (0.7% of the CMA group) had abnormalities that were "possibly/ partially detectable" by karyotype, and 70 (4.7% of the CMA group) had abnormalities that were classified as "not detectable" by karyotype (Table 3).

In the CMA/Karyotype group, of the 156 patients that had a clinically significant abnormality identified by CMA, 112 patients (6.4% of the CMA/Karyotype group) had abnormalities that were classified as "detectable" by karyotype analysis; 1 patient (0.06% of the CMA/Karyotype group) had abnormalities that were "possibly/partially detectable" by karyotype, and 43 (2.5% of the CMA/Karyotype group) had abnormalities that were classified as "not detectable" by karyotype (Table 3).

3.4 | Abnormality types for each group sorted by karyotype detection/detectability

For both the CMA group and the CMA/Karyotype group, the majority of abnormalities that would be detected both by array and karyotyping were aneuploidies (124/177 or 70.0% and 89/112 or 79.5%, respectively). For both groups, microdeletions and microduplications were the most common type of abnormality detectable by CMA but "not detectable" by karyotype (58/70 or 82.9% in the CMA group, 33/43 or 76.7% in the CMA/Karyotype group). Additional CMA findings that were classified as "not detectable" by karyotype included cases with uniparental isodisomy and a single region of homozygosity (Table 4).

4 | DISCUSSION

Chromosomal microarray analysis is becoming widely implemented as a first tier diagnostic test for prenatal diagnosis due to its significantly improved detection rates for chromosomal abnormalities compared with karyotyping. While many providers are currently recommending CMA for pregnancies with 1 or more fetal structural anomalies, CMA is less frequently utilized in the setting of a structurally normal fetal ultrasound—likely due to the current recommendations, which include the option of either CMA or karyotyping.

Our data show that at least 4.7% of patients with 1 or more fetal structural abnormalities have a clinically significant microarray abnormality that would have been missed by karyotype analysis, similar to previous reports.^{3,5-7} Additionally, at least 2.5% of patients whose indication did not include a structural fetal abnormality had a CSCA

TABLE 3 Abnormality classification based on detectability by karyotype

	CMA Group (N = 1475)	CMA/Karyotype Group (N = 1748)
Cases with abnormal CMA results	257	156
Karyotype performed (at CombiMatrix/outside lab)	105	56
Detectable by karyotype	77	33
Possibly/partially detectable by karyotype	7	0
Not detectable by karyotype	21	23
Karyotype not performed	152	100
Detectable by karyotype	100	79
Possibly /partially detectable by karyotype	3	1
Not detectable by karyotype	49	20
Overall detection by karyotype?		
Detectable	177 (12.0%)	112 (6.4%)
Possibly/partially detectable	10 (0.7%)	1 (0.06%)
Not detectable	70 (4.7%)	43 (2.5%)

detected by CMA that would have been missed by karyotyping alone. It may be worth noting that the above data do reflect an increase in detection over previously reported and comparable data (a 47.1% increase compared with previous estimates of 1.7%).³ Bornstein et al recently reported the prevalence of pathogenic CNVs in 1980 high-risk versus low-risk patients who had undergone prenatal diagnosis by CMA. As expected, pathogenic CNVs were much more common in the high-risk group than the low-risk group, but upon stratification of the high-risk group into subgroups based on the presence or absence of a structural fetal abnormality, the authors reported a pathogenic CNV rate of 2.8% for high-risk patients without structural fetal anomalies and 5.9% for high-risk patients with fetal anomalies, which further supports our findings.⁸

Another factor to consider is the average gestational age of each group and how that impacts the testing the patient is offered. In our study, the CMA group had a higher average gestational age (21 weeks \pm 4 days) compared with the CMA/Karyotype group (17 weeks \pm 4 days), likely because many fetal anomalies are not detectable until later in pregnancy. Accordingly, the CMA group included only 8% CVS procedures, while the CMA/Karyotype group included 36% CVS procedures. This marked difference in gestational age/procedure type between the 2 groups raises an interesting point about the current recommendation that CMA be offered in lieu of karyotyping only when a fetal structural abnormality is present. Under the current guidelines, patients who undergo CVS are more likely to fall into the CMA/Karyotype group due to the limited ability to assess fetal anatomy by ultrasound during the first trimester. By the time amniocentesis is performed, a majority of fetal structural abnormalities diagnosable by ultrasound will be apparent, and patients will be more readily triaged to the appropriate group. Thus, patients who are undergoing CVS are more likely to have CMA-detectable chromosomal abnormalities missed than patients undergoing amniocentesis.

4.1 | Clinical considerations of microarray analysis

Since its introduction to prenatal diagnosis, the benefits and limitations of CMA have been widely debated. Both health care providers and patients have expressed hesitation about replacing karyotyping with CMA due to concerns about the possibility of a VOUS result and the cost of CMA compared with karyotyping.

The frequency of encountering a VOUS by CMA has become a primary concern for patients and their providers. Wapner et al³ reported a VOUS rate of 3.4% in their landmark study comparing CMA by aCGH to karyotyping. As we have learned more about incompletely penetrant CNVs, the VOUS category has broadened. Previously, if a variant were identified in a parent, it may have been considered a "likely benign" or "familial" variant, which removed it from the VOUS designation. However, it is now recognized that there are a number of recurrent variants that are incompletely penetrant or act as risk factors for specific phenotypes and thus are not appropriately designated as "likely benign." In addition, with the replacement of aCGH with SNP-based microarray, CMA's diagnostic capabilities increased by allowing for the detection of triploidy, molar pregnancies, uniparental isodisomy, copy neutral regions of homozygosity, low level mosaicism, and MCC. In this study, we had an average VOUS rate of ~5%, which is consistent with our overall prenatal VOUS rate. Findings associated with uncertainty and/or clinical variability are not new to the practice of prenatal diagnosis, or even to the area of fetal chromosome analysis. In a study by Richards et al, the authors compared pregnant patients' perception of risk, anxiety, and worry based on a scenario in which they were faced with an uncertain finding on prenatal genetic testing versus a comparable uncertain finding on fetal ultrasound. The authors found no statistically significant differences between the 2 groups with respect to the patients' perceptions of risk or their emotional/psychosocial responses to these scenarios.⁹ With proper pre-test counseling to discuss the benefits and limitations of CMA, including detection rates for clinically significant and VOUS results, patients in both high and low risk populations are better able to make informed decisions related to their pregnancy management.

Another decision-making barrier when considering CMA versus karyotyping is cost. Historically, CMA has been widely perceived as being significantly more expensive than karyotyping. For this reason, CMA was considered less cost effective than karyotyping.¹⁰ However, as the diagnostic power of microarray has increased, updated cost-benefit approaches have been considered. Recent economic analyses of prenatal diagnosis by CMA versus karyotyping suggest that CMA is more cost effective for pregnancies in which there is a fetal ultrasound anomaly, which is consistent with current recommendations.¹¹ Such studies have not yet been performed for low/average risk pregnancies, which may factor into ACOG/SMFM's continued position of offering either karyotyping or CMA, rather than offering CMA to all women undergoing prenatal diagnosis, regardless of the indication.

4.2 | Limitations

Because our study relies on client-reported clinical data, it is possible that some cases were incorrectly classified into the CMA/karyotype group due to unreported ultrasound abnormalities.

TABLE 4 Breakdown of abnormal microarray data by group

	CMA Group (N = 257)	CMA/Karyotype Group (N = 156)
Detectable by karyotype	177	112
Aneuploidy	124	89
<i>Non-mosaic</i>	115	79
<i>Mosaic</i>	6	9
<i>Aneuploidy + deletion</i>	2	0
<i>Aneuploidy + ROH</i>	1	1
Deletion and duplication	15 ^a	7
>1 copy number variant	2	1
Deletions	16	6
Duplications	12	6
<i>Mosaic duplication</i>	2	1 ^b
Mosaic triplication	0	1 ^b
Triploidy	8	1
Complex structural abnormality	0	1
Possibly/partially detectable by karyotype	10	1
Deletion and duplication	6 ^c	1 (mosaic)
Duplication	1	0
Two duplications	1	0
Duplication + triplication	1	0
Mosaic deletion + mosaic aneuploidy	1	0
Not detectable by karyotype	70	43
Microdeletions	49	20
<i>Syndromic</i>	29	12
<i>Non-syndromic</i>	20	8
Microduplications	9	13
<i>Syndromic</i>	3	2
<i>Non-syndromic</i>	6	11
Mosaic aneuploidy + mosaic microdeletion	0	1 ^e
Microdeletion and microduplication	8	6
<i>Microdeletion and triplication</i>	1	0
>1 copy number variant	2 ^d	1
Single ROH	1	0
UPD	1	1
Complex structural abnormality	0	1

^aAll had karyotype/FISH that detected a structural abnormality.

^bKaryotype performed.

^c5/6 had karyotype performed that partially detected the abnormality and required array to clarify (ie, marker chromosomes, unknown bands involved); 1/6 was mosaic.

^dOne is mosaic.

^eNormal karyotype.

In addition, while CMA can detect a variety of clinically significant abnormalities that are not detectable by karyotype, it cannot detect balanced chromosome rearrangements. Previous reports suggest that 0.09% of prenatal samples undergoing diagnostic testing will have a balanced chromosomal rearrangement.¹² In our study, there was a single sample (0.3%; 1 out of 301 cases with karyotype analysis) that had an aneuploidy and a balanced translocation detected by karyotype. In this case, the aneuploidy was also detected by array and was consistent with the fetal anomalies seen, suggesting that the balanced translocation was an incidental finding. Because not every patient in our study had a karyotype performed, it is possible that there were additional cases of balanced rearrangements that were not detected

by CMA. Given that the majority of balanced chromosomal rearrangements have no overt clinical consequences (apart from the reproductive risk for having a child with an unbalanced translocation), the fact that microarray cannot detect truly balanced rearrangements is not offset by the gain in clinical diagnostic rate.

5 | CONCLUSION

In summary, our data demonstrate that a significant number of clinically relevant chromosome abnormalities would be missed if all women who were offered the option of either CMA or karyotyping

chose to have only a karyotype performed. Our study reinforces the diagnostic utility of CMA and supports its use in lieu of karyotyping for all women undergoing prenatal diagnostic testing regardless of the presence or absence of a fetal structural abnormality. These data also reaffirm the fact that more universal and uniform acceptance of CMA not only enables detection of submicroscopic chromosomal imbalances but also provides an opportunity for patients to make appropriately informed reproductive decisions after being made aware of possible fetal outcomes, management options and recurrence risks.

ETHICAL APPROVAL

The sample-related data analyzed for this manuscript was entirely retrospective with no patient or patient-related identifiers included in the analysis. No waivers or institutional approval was required.

CONFLICTS OF INTEREST

All authors are full-time employees at CombiMatrix, Invitae Corporation.

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