Review

Challenges in Prenatal Cytogenomic Microarray Reporting: Balancing Laboratory Findings, Clinical Utility and Patient Anxiety

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Cytogenomic microarray has been increasingly applied in prenatal diagnosis with the advantage of higher resolution and faster turn-around time compared with conventional karyotyping. However, the greater information offered by this technology also leads to special challenges and ethical dilemmas for laboratory cytogeneticists, obstetricians, and patients. These issues are most apparent in reporting results of uncertain clinical significance, which are frequently found by cytogenomic microarray. The reporting of such variants may lead to significant obstetrician unease and patient anxiety, particularly as the results of cytogenomic microarray may often be the primary factor in determining whether to terminate a wanted pregnancy. However, cytogeneticists often feel an obligation to report such variants due to laboratory guidelines or avoidance of future legal liability. Here, we discuss several issues specific to interpreting array results in the prenatal setting, including copy-number-variant size and gene content, penetrance, inheritance, region of homozygosity, mosaicism, maternal cell contamination, and clinical correlation. We propose a practical approach for cytogeneticists to balance complete reporting of laboratory findings with predicted clinical utility and minimization of patient anxiety. Our discussion also highlights the importance of establishing a prenatal array database with longitudinal studies to determine phenotypic outcomes related to variants identified on array, and the central role of genetic counseling in the use of prenatal cytogenomic arrays. Incorporation of these elements and a universal reporting framework will be crucial for more seamlessly integrating cytogenomic array analysis into prenatal care.

[N A J Med Sci. 2014;7(4):148-155. **DOI:** *10.7156/najms.2014.0704148]*

Key Words: *prenatal diagnosis, cytogenomic microarray, copy number variant (CNV), variants of uncertain significance (VUS), array reporting*

INTRODUCTION

Banding-based (or conventional) cytogenetic analysis has been the gold standard for prenatal diagnosis since the 1970s, typically offered to pregnant women with advanced maternal age, positive maternal serum screening, abnormal fetal ultrasound findings, or parental anxiety.[1] Although conventional cytogenetic analysis is essential for the quality of prenatal care, this approach has limitations. The most prominent are limited genomic resolution, such that many submicroscopic disease-relevant chromosomal aberrations cannot be detected, and requirement of metaphase chromosomes from cultured cells, leading to long turn-around times and the potential for no results due to culture failure. In contrast, cytogenomic microarray technology allows for the robust and efficient detection of genomic submicroscopic imbalance from uncultured cells, overcoming many of the limitations of conventional cytogenetics in prenatal diagnosis. Given these advantages, demand for microarray testing in the prenatal setting is quickly growing.[2-4]

Received: 08/29/2014; Revised: 09/29/2014; Accepted: 09/30/2014
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Currently, there are two major platforms of cytogenomic microarray: comparative genomic hybridization (CGH)-based array (aCGH) and single nucleotide polymorphism (SNP)-based array.[5] The former compares the genomic content of a test DNA sample with that of a normal reference DNA sample, detecting submicroscopic gains and losses known as “copy number variants” or CNVs at different resolutions depending on the array platforms and design. The latter detects CNVs by measuring both probe signal intensities and allelic frequencies, and has the ability to detect additional genomic changes, such as triploidy, region of homozygosity and maternal cell contamination or chimerism in prenatal samples. Because of these advantages, SNP-array is the preferred platform in prenatal cytogenomic microarray testing.

With the ability to detect submicroscopic pathogenic CNVs that were otherwise undetectable by conventional cytogenetic methods, cytogenomic microarray has been established as a first-tier test for the postnatal evaluation of individuals with intellectual disability, autism spectrum disorders, and/or multiple congenital anomalies. A corresponding reporting guideline has been published by American College of

Medical Genetics and Genomics (ACMG) in 2011.[6] In contrast, the clinical utility of cytogenomic array in prenatal diagnosis was not well defined. To address this issue, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) funded a multicenter clinical trial to compare cytogenomic array with conventional karyotyping in prenatal studies.[7] This trial demonstrated that array is most beneficial over conventional karyotyping in fetuses with abnormal ultrasound findings. In this study, array revealed clinically significant CNVs in 6% (45/755) of this group of fetuses.[7] Consistent with this finding, in a 2013 systematic review of four large studies (n = 12,362), array revealed clinically significant CNVs in 6.5% (201/3090) of fetuses with abnormal ultrasound findings and a normal karyotype.[8] Based on these studies, the American College of Obstetricians and Gynecologists (ACOG) and Society for Maternal-Fetal Medicine recommend use of array over conventional karyotyping when fetal congenital anomalies are identified on ultrasound.[9]

The downside of the higher diagnostic yield of array is the detection of CNVs of uncertain clinical significance (VUS), which have not been reported previously and thus have unknown phenotypic effects. In the NICHD trial, array detected VUS in 3.4% (130/3822) of all cases that were normal by karyotype.[7] How to interpret those CNVs and how to appropriately apply this information in clinical practice is the major challenge of applying array in prenatal diagnosis. The ACMG reporting guidelines for postnatal arrays may not be fully applicable to the prenatal array studies due to the unique status of prenatal testing. One major difference is that array findings are typically used to explain *existing* phenotypes in postnatal analysis, but instead must often *predict* fetal phenotypes in prenatal analysis. This consideration is especially true as prenatal array becomes offered by some providers in the setting of advanced maternal age, positive maternal serum screening, or parental anxiety, in the absence of ultrasound abnormalities which may give some indication (though often non-specific) of fetal phenotype.[10] In this context, it is important for cytogeneticists to remain mindful that the prenatal array diagnostic report may be the critical data that informs the patient decision to either terminate or maintain a wanted pregnancy.

As found in the above studies, a laboratory performing this test should expect that a substantial portion of CNVs detected by cytogenomic array would be classified as VUS. Yet ultimately many of these CNVs will not be clinically significant. Obstetricians and patients do not have sufficient additional guidance to make the critical and irreversible decision about whether to proceed with the pregnancy. Furthermore, patient anxiety caused by findings other than normal is a substantial challenge for genetic counseling. As a result, compared to postnatal analysis, prenatal array testing carries significantly higher risk and potential legal liability for alleged misdiagnosis. This caution is particularly warranted given potential cases where a variant is identified prenatally in the laboratory but not reported, and a child is subsequently born with a phenotypic abnormality.

In this article, we will discuss several considerations specific to the classification of CNVs in the prenatal setting, including CNV size and gene content, penetrance, inheritance, reference database and clinical correlation. We will also touch upon other related issues including reporting regions of homozygosity, detection of maternal cell contamination and low-level mosaicism. A reporting strategy is proposed to balance identified laboratory findings with clinical utility in obstetrical practice and minimization of patient anxiety.

CLASSIFICATION OF CNVS IN THE PRENATAL SETTING

An established guideline from professional governing organizations (such as ACMG and ACOG) for interpretation and reporting CNVs in the prenatal setting is currently not available. Therefore, in practice, cytogeneticists and laboratory geneticists adopt an evidence-based approach to interpret the clinical relevance of a CNV, primarily relying on standards and guidelines for postnatal constitutional CNVs.[6,11] In essence, a CNV is classified into one of three main categories of significance: (1) clinically significant or pathogenic, (2) uncertain clinical significance, which may be further divided into three subcategories of (a) likely pathogenic, (b) uncertain, and (c) likely benign, and (3) benign. This classification is made on the basis of CNV size, genomic content, review of the literature, and information in available databases. However, these guidelines may not be fully adaptable to the prenatal setting. Interpretation and reporting of prenatal CNVs require additional considerations that we will discuss below.

Consideration of CNV Size and Gene Content

In general, larger CNVs are more likely to be clinically significant than smaller CNVs. However, very large CNVs can be benign and very small CNVs can be pathogenic.[12] Therefore, while genomic size is one of the factors to establish a practical cut-off for CNV calls, gene content of a CNV and any available literature related to the CNV or included genes must be crucial parts of the interpretive consideration. Exclusion of CNVs based solely on a defined minimal size may miss clinically significant findings. If a CNV involves a pathogenic gene that is known to be dosage-sensitive to the copy number change, it should be reported regardless of size.

However, if a CNV is best classified as a variant of uncertain significance, in particular likely benign variants based on available information, reporting such an unclear finding with little known predictive value regarding the fetal health will almost certainly cause increased parental anxiety. It is estimated that new CNVs occur in a rate of approximately 1.2×10^{-2} per haploid genome per transmission at a median resolution of 150 kb, amounting to about 2.5 CNVs/100 live births,[13] significantly higher than the rate of genetic disorders identified perinatally. Thus, the majority of *de novo* CNVs are likely benign in nature, especially in the case of small CNVs (< 500kb) without known pathogenic genes. It is conceivable that establishing a reasonable size cut-off, in the range of 500-1000 kb, for reporting CNVs of uncertain

clinical significance will reduce patient anxiety regarding likely benign CNVs, but not miss large CNVs of potential clinical significance. This approach stands as long as CNVs below this size limit are examined and interpreted appropriately by laboratory geneticists to not reduce the diagnostic yield of known pathogenic CNVs.

Consideration of Penetrance and Expressivity

An increasing number of CNVs are being identified as susceptibility loci or risk factors for a variety of genomic disorders including developmental delay, intellectual disability, autism and psychiatric disorders.[14,15] Enrichment of these CNVs among affected individuals in comparison with healthy controls implicated them as pathogenic. However, these susceptibility CNVs show incomplete penetrance and variable expressivity, with outcomes ranging from normal to severely affected individuals.[16-18] When such a CNV is identified in a pediatric patient with related phenotypes, it is justified to report it as "pathogenic" because it explains at least one part of the genetic etiology of the disorder in the patient. Reporting susceptibility CNVs as pathogenic also adheres to ACMG guidelines for postnatal array reporting, in which pathogenic CNVs are defined as "documented as clinically significant in multiple peer-reviewed publications, even if penetrance and expressivity of the CNV are known to be variable".[6] In the prenatal setting, however, the associated neurodevelopmental phenotypes cannot be ascertained and it is difficult to quantify the risk to the fetus. Therefore, a testing laboratory may choose not to report an inherited susceptibility CNV (a 15q11.2 BP1/BP2 deletion, for instance) to the patient based on "the lack of any family history of neurodevelopmental or psychological abnormalities, the low penetrance risk, and a lack of evidence for a link to the increased nuchal translucency observed".[19] This case illustrates the dilemma in prenatal array reporting and raises the issue of whether it is ethical to withhold such information from patients.[20] The penetrance of 15q11.2 BP1/BP2 deletion was estimated to be about 10%,[17] which may not seem high from a population perspective, but it may be intolerable for the future parents considering the disease burden of developmental disabilities.

Even for known variants, however, the precise degree of penetrance is often unclear. In the absence of this data, it can be argued that the identification of a susceptibility CNV has predictive value related to the child's future health. It may therefore be reasonable for a testing lab to report such susceptibility CNVs as pathogenic following ACMG guideline for postnatal array reporting. On the other hand, given the uncertainty of the outcome, we would consider it more appropriate to report such susceptibility CNVs as "VUS", or "VUS likely pathogenic" (in variants where the estimated penetrance is high) in the prenatal setting. Importantly, results should be delivered to patients in the context of genetic counseling along with information currently available about the condition, including estimation of penetrance[17,21] and range of phenotypes.

A more challenging case is the identification of CNVs with conflicting evidence for clinical significance (such as 15q11.2 duplication)[22,23] in the prenatal setting. To avoid arbitrary decisions regarding the communication of such CNVs, a recently published Belgian prenatal array reporting guideline listed seven susceptibility CNVs for reporting.[24] These guidelines were based on the criteria of a sufficiently high risk of a severe phenotype and/or associations with structural abnormalities that can be ascertained by ultrasound. Such an approach provides a useful framework for a national consensus on prenatal array reporting and can be adopted by other countries. However, such a pre-determined list must be reviewed and updated periodically to ensure its timeliness in this rapidly developing field.

Consideration of Inheritance

Parental studies are important for prenatal diagnosis and may provide additional information regarding the inheritance, penetrance and other features of a CNV identified in the fetus. As a general rule, an uncommon *de novo* CNV is more likely to be a pathologic change, while an inherited CNV from a phenotypically normal parent is more likely to be a benign event.[25] However, the inheritance of a CNV may not determine or change its clinical significance. It is particularly true for the CNVs with incomplete penetrance and variable expressivity, as well as with late onset phenotypes. Indeed, many susceptibility CNVs are inherited from an apparently healthy parent.[16] Even in the absence of evidence suggesting incomplete penetrance and variable expressivity of a particular CNV, such possibilities cannot be ruled out. Therefore, it is important to interpret CNVs based on the genomic content and available literature instead of overemphasizing inheritance patterns. Nevertheless, parental testing should be routinely performed for pathogenic CNVs and CNVs of uncertain significance, as this information is useful for counseling of the parents, management of the pregnancy, and defining the recurrence risk for future pregnancies (see below: "Confirmation and parental studies").

Consideration of the Reference Databases

Searching a CNV in internal and external databases, including public databases that collect data from the general population (Database of Genomic Variants), or from patients with multiple congenital anomalies and/or developmental disabilities (DECIPHER, ECARUCA, ISCA, SFARI, etc.) is a critical step for classification of the CNV.[10] However, the interpreting cytogeneticists should be aware that use of databases consisting of mainly postnatal cases may introduce ascertainment bias in interpretation of CNVs identified prenatally. Thus, it is critical to develop appropriate CNV databases for prenatal studies and to follow up with the child in postnatal growth to better understand genotype-phenotype correlations. For each testing laboratory, it is also important to maintain an internal database to track identified CNVs as certain CNVs may be specific to the laboratory procedure, platform used, and/or the population served. These laboratory-specific CNVs may not be reported at a frequency high enough in the public databases to be classified as benign, however, a high frequency (>5%) in the internal database indicates such a CNV could be benign or likely benign in nature. As collective knowledge in this field

continues to grow, interpretation of CNVs is expected to improve and thereby the frequency of CNVs classified as VUS is expected to decrease.

Consideration of Clinical Correlation and Incidental Findings

When interpreting an array result, it is important to correlate the detected CNV with clinical findings in the patient. Obviously, this is difficult in the prenatal setting, where not all clinically significant phenotypes can be clearly revealed by current technologies such as ultrasound. Even if a structural abnormality is present, it is often nonspecific, thus limiting our ability to correlate clinical findings with detected CNVs in fetus. As illustrated in the above example of 15q11.2 BP1/BP2 deletion, part of the challenge in reporting is that it is not clear whether this deletion correlates with the clinical finding of increased nuchal translucency observed in the fetus. If determined that the genotype and phenotype are not related, this deletion may be considered a “non-actionable incidental finding” and thus not reported.[19] Because our current knowledge of genotype-phenotype correlation is limited in the prenatal period, restricting clinical reporting criteria to the observed fetal structural abnormalities may lead to the erroneous conclusion that many of the pathogenic CNVs associated with neurodevelopmental phenotypes in childhood, but with no known fetal structural abnormalities, are not clinically significant. Reporting prenatal CNV results based on such reasoning will inevitably result in discrepancies between prenatal and postnatal array results, if later the child is found to have neurodevelopmental issues and referred for postnatal array testing.

The primary clinical reasoning for prenatal microarray testing is typically to determine childhood disability due to a genetic disorder. Therefore, it can be argued that CNVs associated with neonatal and pediatric phenotypes are clearly related to the testing indication; whereas CNVs related to late onset phenotypes (such as cancer risk) are not directly related and may be considered as incidental findings. However, such incidental findings may nevertheless have significant clinical consequences to the future child, even if only later in life. Whether to report such findings must be agreed upon between testing laboratories, referring clinicians, and patients as part of the pretest counseling and consent process. Future guidelines for array-based testing, such as those released by the ACMG for incidental findings in whole exome sequencing,[26] may advise whether there are genomic regions that should be routinely analyzed to assess late-onset disease risk, but currently this must be done on a laboratory-by-laboratory basis.

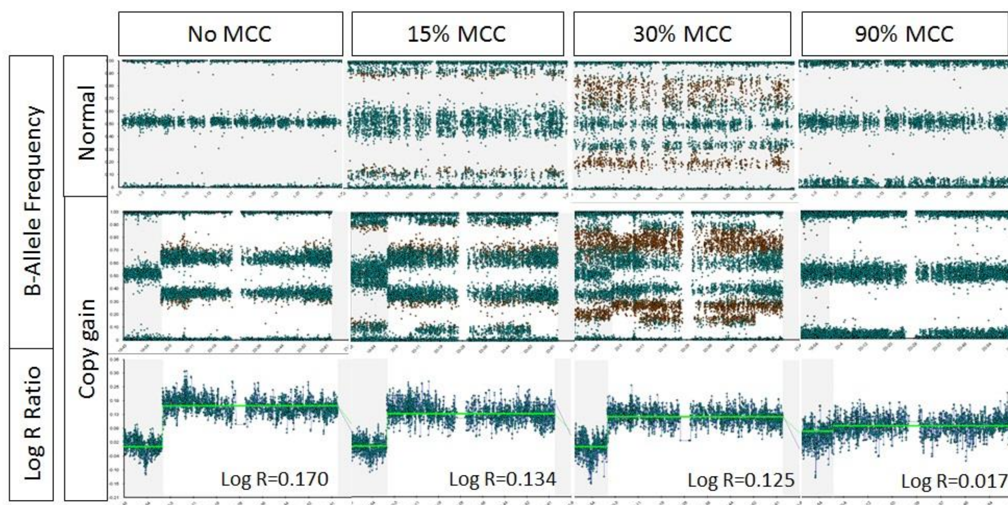

Figure 1. Detection of MCC on SNP-array. MCC can be detected on SNP-array by the appearance of additional tracks on the B-allele-frequency chart (top panels). Copy gains and copy losses may still be called depending on the percentage of MCC (lower panels). The bottom two rows are an example of trisomy 20 in the presence of different percentages of MCC, illustrating B-allele-frequency and log R ratio, respectively.

OTHER CONSIDERATIONS IN PRENATAL ARRAY REPORTING

Region of Homozygosity (ROH)

Regions of homozygosity (also referred to as loss of heterozygosity and absence of heterozygosity) may also be detected by SNP array platforms.[27] In constitutional specimens, ROH may be indicative of uniparental disomy (UPD) or regions of the genome demonstrating identity by descent.[28] The finding of ROH alone is not diagnostic, but can suggest an area of concern that would require additional testing. For instance, ROH leads to an increased risk of disorders caused by recessive mutations, and UPD involving imprinted regions may result in imprinting disorders. However, reporting and interpreting ROH should be approached with caution, since it may also reveal unexpected or unacknowledged parental relationships, such as consanguinity and inbreeding.[29,30] In addition, with a background of consanguinity, ROH in a known imprinted region may result from consanguinity and not truly represent UPD of the region. Therefore, any potential pathogenic UPD

indicated by ROH must be verified by other methods, such as methylation testing.[31] Balancing the benefit for the patient in terms of knowing the potential clinical significance of identified ROH and ethical/legal issues of revealing unexpected consanguinity must be well-considered before reporting ROH findings.

Maternal Cell Contamination (MCC) and Chimerism

Prenatal array analysis requires particular quality assurance of the test specimen beyond that needed for postnatal arrays. MCC in amniotic fluid and chorionic villi sampling cell cultures is well documented, and therefore represents a potential source of error in prenatal diagnosis. Adequate measures to minimize the inclusion of maternal cells in prenatal samples should be part of the laboratory quality assurance program as specified in ACMG standards and guidelines for clinical cytogenetics laboratory (section E3.3 of reference[32]). In addition, ACMG guidelines for cytogenomic microarray (revision 2013) requires MCC analysis be performed on all prenatal samples, unless contamination is otherwise excluded.[33] It should be noted that when SNP-array is used, MCC may be detected during interpretation as additional tracks appearing in the allelic frequency (**Figure 1**). Therefore, separate MCC analysis may not be necessary for SNP-array platforms. Whether a given CNV can be detected in the presence of MCC depends on the CNV type (gains and losses) and size (small vs. large). For example, the whole chromosome duplication in Figure 1 may be detectable against a background of < 30% MCC, but a 1 Mb deletion or duplication will be much more difficult to be detected. Determining array sensitivity against a background of increasing MCC must be part of the analytical validation process in each performing laboratory. If a performing laboratory intends to report CNV findings in samples with MCC, it must further establish a validated cut-off for a reportable level of MCC. In addition, the laboratory should be aware that samples with 30% or 70% MCC cannot be distinguished by allelic tracks. Therefore, clear documentation of sample morphology and quality during sample setup stage is critical for interpreting results of samples with MCC. The documentation is also valuable in concert with SNP array for identification of potential fetal chimerism that shows two different genomic profiles, similar to MCC. It is difficult to distinguish between MCC and fetal chimerism based on SNP array findings alone. When MCC findings are ambiguous or fetal chimerism is suspected, verification of the findings using a different method with maternal samples must be performed.

Detection of Mosaicism

Cytogenomic arrays have a variable ability to detect mosaicism. Most CGH arrays typically detect mosaicism at 20%~30% of cells [34] and SNP arrays can detect lower levels of mosaicism at ~10%.[35] When mosaicism is detected, verification should be performed on an independent culture as mosaicism may represent an artifact of culture due to relative overgrowth of non-fetal cellular populations.[33] Alternatively, mosaicism may represent true fetal mosaicism or confined placental mosaicism in chorionic villi sampling cells. The significance of mosaicism in chorionic villus sampling may differ based on the distribution of the abnormal cells in the direct and cultured preparation, as well as the chromosomes involved.[36] Similar sample processing procedure and cautions of reporting, as used in conventional cytogenetic analysis (E4.3.1 in reference[32]), should be adopted.

In the context of evaluating a sample for mosaicism, laboratory cytogeneticists must also be cognizant that array provides an *average* copy number signal across the entire tested sample. However, reciprocal duplication and deletion of the same region caused by unequal post-zygotic mitotic recombination (or unequal sister chromatid exchange) in an individual may not be detected by array analysis, as these genetic changes would only be detected on a cell-by-cell basis using FISH or conventional cytogenetic methods. If there is a suspicion of such a condition, cell-by-cell-based studies should be carried out to investigate this possibility. In addition, mosaicism may not be detectable (at a low level) or distinguished (at a high level) in specimens with MCC.

CONFIRMATION AND PARENTAL STUDIES

Confirmation and parental studies are recommended for prenatal array findings with pathogenic CNVs and CNVs of uncertain significance to verify and assess recurrence risks in future pregnancies. Karyotyping (if detected CNVs are > 5Mb) or metaphase FISH (if appropriate FISH probes are available) should be the first-line confirmation test as array and other molecular methods (such as quantitative PCR) will likely not detect structural changes associated with the detected CNVs. For example, a CNV may result from unbalanced segregation during meiosis in a balanced carrier parent. Therefore, normal parental arrays will not be sufficient to define a CNV as *de novo*. Follow-up karyotyping and metaphase FISH are useful for detecting such changes, which is critical for understanding the abnormalities and recurrence risks in future pregnancies.

On the other hand, these additional studies will increase the cost of prenatal array testing. A carefully considered category of reportable significant prenatal array findings established in the testing laboratory may help reducing unnecessary additional studies while keeping the risk of missing real pathogenic findings to the minimum.

IMPORTANCE OF GENETIC COUNSELING AND PRETEST CONSENT

Comprehensive pre- and post-testing genetic counseling is essential for prenatal array testing. The purposes, expectations, benefits, limitations and risks should be discussed with patients during pre-testing counseling, and patient's informed consent is required for prenatal array testing.[9] A list of important pretest counseling issues for prenatal array is provided by a working group of European Society of Human Genetics.[37] It is particularly important that genetic counselors, obstetricians, and, by extension, patients are well educated as to the limitations of the array-based testing. They must first understand that array-based testing cannot detect all pathogenic genetic changes that may lead to phenotypic abnormalities (for instance, point mutations or

balanced translocations). More importantly, they must understand that the laboratory has established criteria to minimize reporting of variants of uncertain significance in favor of a strong focus on reporting known pathogenic variants that clearly guide clinical decision-making. However, establishing these criteria necessarily means that some CNVs that may ultimately lead to abnormal phenotypes will not be reported due to limited available information at the time of reporting. While this will likely occur infrequently, it must be acknowledged by patients during the pre-test counseling and consent process that this "missed diagnosis" is a possibility. Additional data collected as this testing becomes more widespread will lead to more robust statistics to weigh the likelihood of this outcome to assist patient decision-making. Furthermore, it must be well explained to patients before testing that in 1-7% of cases,[7,38-41] they may receive an array report with a VUS, but without significant further guidance to make a straightforward decision regarding their pregnancy. This possibility may be one that some patients find unacceptable and may cause them to decline testing. Ideally, a robust consent and pre-test counseling process will reduce the legal liability to laboratory and obstetric providers regarding prenatal array analysis. The testing laboratory may provide a reporting protocol/standard to its clinical clients to help them understand the array findings as well as considerations regarding the establishment of reporting criteria (as discussed above). This documentation and communication will assist both the pre- and post-testing counseling.

Although genetic counselors are familiar with prenatal diagnosis and the associated uncertainty, counseling for cytogenomic array presents a new challenge. Several recent studies of the experience of prenatal genetic counselors showed that the majority were uncomfortable to deliver results with uncertain clinical significance, suggesting that more training and education is required.[42,43] Reporting uncertain prenatal array results may lead to counseling dilemmas initially, as adaptation of any new technology into clinical use. However, as our knowledge of the human genome grows and more data collected in clinical practice, these dilemmas should become less frequent.

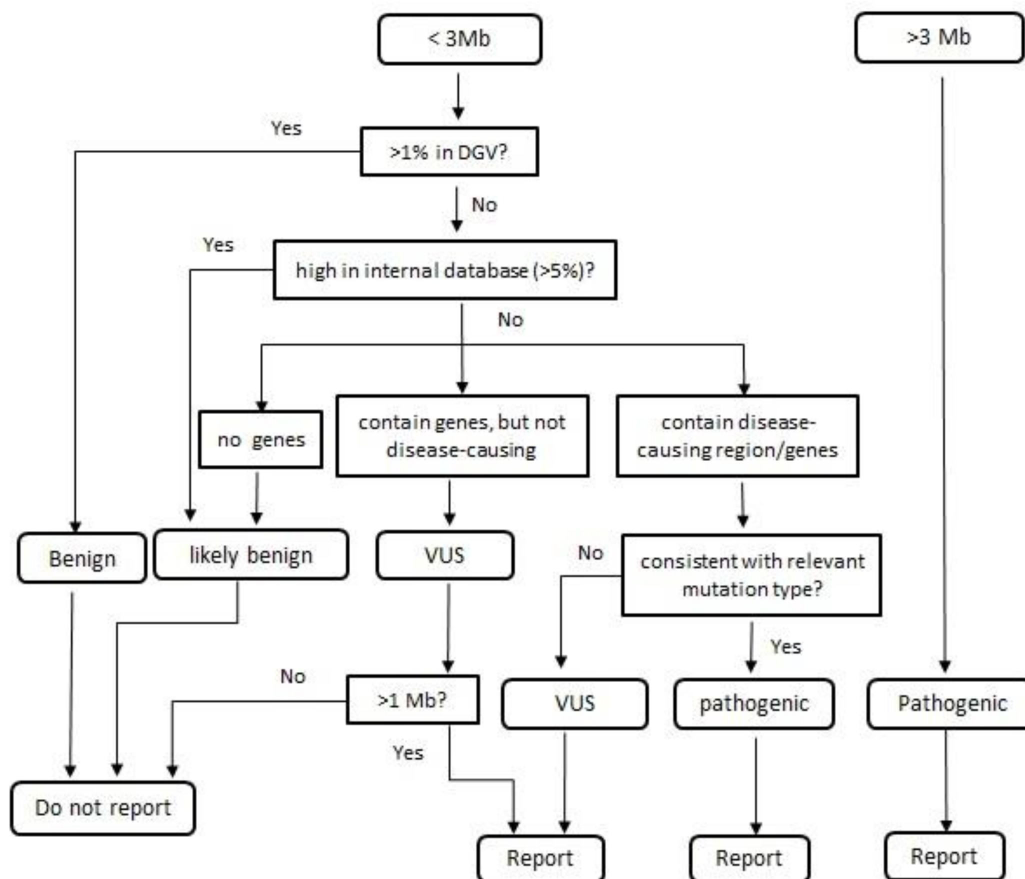

Figure 2. A flow-chart of classification and reporting of CNVs in prenatal cytogenomic microarray. CNVs with clear clinical significance, including large CNVs detectable with conventional karyotyping (>3 Mb), and CNVs that include known disease-causing regions/genes are reported either as pathogenic or VUS depending on the mutation type. A size cut-off of 1 Mb is applied to VUS with annotated genes but without known disease-causing genes, while likely benign VUS and benign CNVs are not reported.

CONCLUSIONS

There is a growing clinical demand for cytogenomic microarrays in prenatal diagnosis. While laboratory geneticists and cytogeneticists are familiar with array technology and interpretation of array result in pediatric patients, in the prenatal setting we are confronted with special challenges and ethical dilemmas, in particular how to report CNVs of uncertain clinical significance. Here we discussed several issues including CNV size, penetrance, inheritance and clinical correlation in the prenatal setting and proposed our approach to balance laboratory findings with clinical utility and patients' anxiety. An example of reporting strategy is given in **Figure 2**. In this strategy, CNVs with clear clinical significance, including large CNVs detectable with conventional karyotyping (> 3 Mb), and CNVs that include known disease-causing regions/genes are reported (either as pathogenic or VUS depending on the mutation type). A size cut-off of 1 Mb is applied to VUS with annotated genes but without known disease-causing genes, while likely benign VUS and benign CNVs are not reported. A similar strategy, including a set of pre-determined target regions and a size cut-off for backbone variants, has been tested in a laboratory setting to show that this reporting strategy detected all CNVs of clear prognostic value and did not miss any CNVs of clear clinical significance.[44]

Our discussion also highlights the importance of developing a large database of CNVs identified prenatally. Ideally, the database should contain information about the detected CNV, interpretation, decision of whether the result is reported, as well as postnatal follow up with the child. Such a prenatal microarray database will provide a useful measurement of consensus among different laboratories regarding difficult cases to decrease the subjectivity in reporting.

Finally, pre- and post-test genetic counseling is critical for the implementation of prenatal array testing. With patient education and advancing knowledge of phenotypic consequences of identified variants, prenatal array analysis is expected to become an important diagnosis tool in obstetric practice.

CONFLICT OF INTEREST
None.

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