Evolving applications of microarray analysis in prenatal diagnosis

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Purpose of review

Evaluation of copy number variation by microarray analysis has significant advantages over standard metaphase karyotyping and is quickly becoming the primary means of postnatal genetic evaluation for neonates and infants with dysmorphic features or cognitive difficulties. Before this technology is routinely used for prenatal diagnosis, further evaluation of its value and the clinical dilemmas it may introduce requires further study. This article reviews the recent literature on array technology use in prenatal diagnosis.

Recent findings

The use of microarray analysis for routine prenatal diagnosis is still being investigated. Use in certain prenatal situations such as the fetus with structural anomalies or those who are stillborn appears to add important, clinically relevant information. There are a broad range of array designs available and recent research has focused on the appropriate design for prenatal testing. Patient counseling may occasionally be difficult because of the uncertain phenotype associated with some array findings.

Summary

We present a brief overview of microarray technology including benefits and limitations. Previous research regarding use of microarray in prenatal diagnosis including specific scenarios of anomalous fetuses and abnormal karyotype is reviewed. Current guidelines and the authors' recommendations are presented.

Keywords

array-based comparative genomic hybridization, microarray, prenatal diagnosis

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Introduction

Evaluation of copy number variation by microarray analysis has significant advantages over standard metaphase karyotyping and is quickly becoming the primary means of postnatal genetic evaluation for neonates and infants with dysmorphic features or cognitive difficulties. Use in certain prenatal situations such as the fetus with structural anomalies or those who are stillborn appears to add important, clinically relevant information. There are a broad range of array designs available, and recent research has focused on the appropriate design for prenatal testing. Patient counseling may occasionally be difficult because of the uncertain phenotype associated with some array findings. Before this technology is routinely used for prenatal diagnosis, further evaluation of its value and the clinical dilemmas it may introduce requires further study.

Basic introduction to arrays

Metaphase karyotyping is the current gold standard for prenatal cytogenetic analysis and is able to detect whole chromosome aneuploidy as well as deletions, duplications and other chromosomal rearrangements that are 5–10 megabases in size or larger. Microarray analysis has recently become available and is able to detect deletions or duplications that are 100 times smaller (in the kilobase range) than those identified on karyotype [1•]. It has now become well known that deletions and duplications too small to be detected by karyotype (submicroscopic) can be easily identified by microarray analysis and can cause significant anomalies. Many of these smaller changes occur frequently enough to have well characterized microdeletion or duplication syndromes (e.g. DiGeorge syndrome), whereas others may occur only sporadically but have equally significant phenotypic consequences.

As a group these cytogenetic alterations, whether visible or submicroscopic, are referred to as copy number variations (CNVs). CNVs are regions of DNA usually larger than a kilobase (1000 base pairs) in size that are present at an altered copy number in comparison with a normal reference genome [2]. For the autosomes, each segment of DNA should have two copies, one on each of the homologous chromosomes. Deletions result in the presence of only one copy and duplications, including whole chromosome trisomies, result in three copies. Many small

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CNVs are benign, some are disease causing, and yet others are of unknown significance. In general, alterations that are greater than 1 Mb, involve gene-rich areas and are de novo have the greatest likelihood of being disease causing [1•].

Comparative genomic hybridization is a method for detecting deletions or duplications in the genome by directly comparing an unknown DNA sample to a normal sample and identifying those areas of the genome that are either under or over represented in the study sample. Therefore, only changes that cause deletions or duplications can be detected; point mutations, balanced translocations or inversions cannot be. For microarray analysis, DNA from a test sample and a normal reference sample are labeled with different fluorophores, mixed together, and hybridized to a glass slide printed with several thousand probes derived from most of the known genes and select noncoding regions of the genome. For any one probe, there should be equal amounts of DNA from both the patient and reference samples. Accordingly, the ratio of the fluorescence intensity of the test to that of the reference DNA is measured to determine the copy number changes for a particular location in the genome [2].

Array coverage: density/backbone/list of covered regions

The probes on an array can be created using short 30–50 base pair (bp) segments known as oligonucleotides (oligos) which are constructed directly on the array slide. Alternatively, the probes can come from slightly larger DNA constructs (150–750 bp) which are called bacterial artificial chromosome (BAC) probes because they originate from BACs. Rather than a single normal DNA sequence as a target, some arrays are now constructed using single nucleotide polymorphisms (SNPs).

Arrays can be differentiated by their probe composition. Targeted arrays are designed to maximize coverage of the parts of the genome that are known to be associated with phenotypic abnormalities and are intended to minimize findings of uncertain clinical significance. A targeted array can include as many or as few microdeletion and duplication syndromes as needed. Whole genome arrays screen the entire genome with the potential for more than 6 million probes including both those known to be associated with specific disorders as well as the rest of the genome.

The density of the probes in both targeted and whole genome arrays can vary. For instance, arrays can be designed with varying numbers of oligos dispersed across the genome. These oligonucleotides will be spaced so that critical regions have a limited number of kilobases between oligos (thus detecting small deletions) and backbone regions have a greater distance between oligos. In this way, it is possible to customize arrays for a specific list of critical regions associated with disease and with specific backbone coverage so that deletions outside of the critical regions are not detected if they are smaller than a given size.

Key points

- Evaluation of copy number variation by microarray analysis has significant advantages over standard metaphase karyotyping and is quickly becoming the primary means of postnatal genetic evaluation for neonates and infants with dysmorphic features or cognitive difficulties.
- Although it seems likely that microarray will become standard of care for prenatal testing, further evaluation of its value and the clinical dilemmas it may introduce requires further study.
- Pretest and posttest counseling are imperative whenever prenatal microarray testing is performed.

Construction of a prenatal microarray

The ideal construction of a prenatal array remains uncertain and is presently being evaluated in a study funded by the National Institute of Child Health & Human Development (NICHD) to be concluded this summer. As opposed to postnatal arrays used to evaluate infants with abnormal phenotypes, array designs for prenatal testing must minimize findings of uncertain clinical significance because the phenotype is incomplete or unpredictable in these cases and uncertain results can make counseling and parental decisions about pregnancy termination difficult. Presently, although not completely comparable, some guidance on the composition of a prenatal array is available from postnatal studies and a limited number of small series of prenatal cases.

Recent studies have suggested that 5–18% of children with multiple anomalies and/or developmental delay and a normal standard karyotype will have a disease causing CNV [3•,4–10]. Because of this diagnostic advantage, it has been suggested that microarray analysis should become the first-line approach to evaluating infants and children with suspected cytogenetic disorders [3•]. However, more than 95% of these cases will identify benign or uncertain CNVs when a high-density whole genome array is used potentially reducing their value in the prenatal setting [11].

Theoretically, low-density targeted arrays may identify fewer CNVs of unknown significance and hence be preferable for prenatal diagnosis [12••]. However, the recent literature argues that whole genome arrays provide superior identification of clinically significant syndromes without increasing findings of unknown significance [13].

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A further potential benefit of whole genome arrays is that the targeted regions may change as new syndromes are identified, so that constant editing of the array design will be required, whereas use of a whole genome array would reduce this need [14]. Further research and experience is needed before any design for routine prenatal use can be recommended.

Probe type may also vary between arrays. Oligo arrays may detect a significantly higher number of genomic alterations, whereas BAC arrays have a quicker turn-around time, better detection of mosaicism and have clear probes which allow for easy FISH confirmation [15]. Presently, it appears that oligo arrays are used most frequently for prenatal testing.

Current indications for microarray analysis in prenatal diagnosis

Microarray technology for prenatal testing is just transitioning into clinical care so that no well substantiated guidelines for its use exist. However, there is emerging information about its value in certain specific clinical scenarios.

Use of arrays in evaluation of ultrasound structural anomalies

As with postnatal use of microarray analysis, early prenatal experience has been in the evaluation of phenotypically abnormal cases. Overall, in fetal samples referred for standard indications including advanced maternal age, family history and ultrasound anomalies, among others, clinically significant CNVs, including those also seen on standard karyotype analysis, are identified in approximately 5–6% of cases with results of unknown significance occurring in approximately 1–1.5% of these [16•,17,18••]. When a fetal structural anomaly is present in these cases, microarray analysis will have a detection rate of approximately 1–3% beyond that of karyotype [16•,19,20]. The frequency of microarray specific findings in sampled pregnancies not having an ultrasound identifiable anomaly is not certain. Presently, based on expert opinion, in cases of anomalies identified on ultrasound, microarray analysis is recommended to identify microdeletion or duplication syndromes [1•,14].

Whether certain anomalies are more likely to be secondary to microdeletion or duplication is also being investigated. To date, the most common anomalies investigated have been cardiac, central nervous system, skeletal, urogenital, and renal. Increased nuchal translucency measurements and intrauterine growth restriction (IUGR) have also been evaluated [14,19,20]. These evaluations confirm the incremental value of microarray analysis compared to conventional cytogenetics or FISH [16•].

The potential of microarray analysis in evaluating fetal structural anomalies is illustrated in neonatal series [19]. Lu *et al.* demonstrated that 17.1% of 638 neonates with structural anomalies had CNVs. Of these, only 2.5% were whole chromosome aneuploidy. Of the remaining 93 anomalous neonates with genomic imbalances, 37 were well-known common findings, 44 were rare findings and 12 had mosaic results.

Delineating marker chromosomes

Arrays are also useful in interpreting karyotype findings, including marker chromosomes. The phenotype associated with a marker chromosome varies depending on the origin of the marker chromosome and its gene content. Empirically, nonsatellited markers have approximately a 15% risk of an abnormal phenotype whereas a satellited marker risk is approximately 11%. Similarly, whether or not the marker is from an acrocentric chromosome or contains heterochromatin versus euchromatin will modify the empiric risk. The characteristics, origin and content of marker chromosomes are not always fully determined by conventional cytogenetics. FISH can help identify their origin; however, prior knowledge of the region involved is required [21•]. Microarray analysis has the ability to specifically identify the region involved and the gene content. Although further experience is required to confirm the value of arrays in evaluating these cases, initial experience has demonstrated the potential value [16•].

Reciprocal balanced translocations

At present, the likelihood of phenotypic sequelae being associated with an apparently balanced de-novo reciprocal translocation on a prenatal karyotype is based on empiric data and is approximately 6%. This residual risk exists because the breakpoints are located within a gene disrupting its function or alternatively there is a submicroscopic imbalance unable to be identified by conventional karyotype. Recent reports have suggested that in up to 40% of individuals with apparently balanced rearrangements and phenotypic abnormalities, an imbalance involving one of the breakpoints will be identified by microarray analysis [22]. This high rate of imbalance has not been confirmed in prenatal cases. De Gregori *et al.* reported 14 balanced rearrangements (two with ultrasound abnormalities) identified from prenatal samples with no imbalances detected by array. At present, it is uncertain whether array evaluation of these rearrangements will be clinically valuable. Although it seems likely that confirming that a translocation is balanced by microarray analysis should reduce the residual risk and identifying an imbalance should increase it, further studies are necessary to confirm this.

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Use in the evaluation of stillborn infants

About 5% of structurally normal stillborn fetuses will have an abnormal karyotype as will 35–40% of stillbirths that are structurally abnormal or macerated. These numbers are likely to be underestimates because the quality of the karyotype in these cases is frequently poor and tissue culture is successful in only about 50% of cases; less in those with anomalies or maceration. Recently, Raca *et al.* [23] reported on the successful use of microarray analysis in the analysis of 15 phenotypically abnormal stillborns in which standard karyotyping was unavailable. In 13% microarray analysis revealed an abnormality.

Benefits of microarray in prenatal diagnosis

The primary advantage of microarray analysis over conventional karyotyping is the ability of an array to interrogate the genome at a higher resolution and therefore, array should have a higher sensitivity for identifying clinically significant abnormalities. This has already been illustrated in the prenatal setting in fetuses with structural anomalies including IUGR and increased nuchal translucency. It has also been demonstrated that microarray analysis can improve the genetic evaluation of balanced translocations and marker chromosomes which most likely will improve the ability to predict the phenotype.

Another important issue to consider is the turnaround time from prenatal sample collection to result availability. Currently, it takes 1–2 weeks for a karyotype result to become available, as cells must be cultured and scanned. For microarray analysis, cell cultures are not necessary because there is sufficient DNA in most villus and amniotic fluid samples from direct isolation. This is particularly true for analysis of stillborns in which cell culture may not be possible. In addition, microarray scanning is automated and does not require the same time and effort as scanning slides for karyotypes. Thus, turnaround times will be much shorter.

Limitations of microarray

As is the case with karyotyping and other technologies, microarray has limitations for prenatal testing. One of the most frequently mentioned limitations is that microarray analysis will not detect truly balanced translocations. Although this may not be clinically relevant for most prenatal cases, the knowledge of a translocation may provide important information for future generations and other family members. Also, some de-novo translocations may be balanced yet result in phenotypic consequence due to gene disruption. These cases would be missed. Standard microarray analysis will also not identify polyploidies because the relative gene content is balanced. Preliminary work suggests that use of SNP data, if present on an array, will identify these. Also, maternal cell contamination studies should reveal the majority of these. In both of the above instances, a karyotype performed in addition to the microarray analysis would solve these problems but whether this is cost-effective is uncertain.

Although microarray is more sensitive than karyotype for detecting small gains or losses, it does not always determine the exact size and location of the added or lost segments. Microarray has also been criticized for not being able to detect low-level mosaicism. However, a recent study by Hoang *et al.* [24] found that oligonucleotide array was able to detect mosaicism of 10% or greater and in some cases was able to detect mosaicism previously undetected by karyotype. It should also be remembered that standard karyotyping in which 15–20 cells are counted will only detect about 30–40% mosaicism with 95% certainty. Although it is clear that neither microarray analysis nor karyotype will identify all cases, the importance of such low-level mosaicism when found prenatally in an unselected population remains uncertain.

Another limitation of microarray analysis is the difficult counseling required when results of unknown clinical significance are discovered. As additional experience with microarray analysis is obtained, these should become much less frequent as many of these findings will be able to be reclassified as either benign or pathogenic. However, as with all prenatal testing, some findings will always be difficult to interpret because of their variable expressivity or incomplete penetrance. At present, a worldwide consortium (International Standards for Cytogenomic Arrays; ISCA) is collecting array findings and associated phenotypes and organizing them into a database within the National Institutes of Health (NIH).

Current guidelines

The American College of Medical Genetics has recently published guidelines that specifically endorse using arrays in cases where individuals show ‘multiple anomalies not specific to a well delineated genetic syndrome [such as] nonsyndromic developmental delay and intellectual disability and autism spectrum disorders.’ The guidelines recommend the use of arrays in other cases as well [25]. These include evaluation of the children with growth retardation, speech delay, and other less-well studied indications. These recommendations confirm the value of arrays in postnatal evaluation but do not give guidance for prenatal testing.

The American College of Obstetricians and Gynecologists (ACOG) suggests that the usefulness of microarray as the first-line test for prenatal evaluation of chromoso-

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mal abnormalities remains unknown and conventional karyotyping remains the primary cytogenetic tool. However, targeted arrays in combination with genetic counseling can be offered in the setting of an abnormal ultrasound finding and a normal karyotype result. In addition, it can also be offered in cases of fetal demise with congenital anomalies when conventional karyotype is unobtainable. ACOG stresses that couples who choose to undergo targeted microarray analysis receive both pretest and posttest genetic counseling. Couples should follow-up with their genetic counselors and discuss the results. They should understand that microarrays cannot detect all genetic pathologies and that a result of unknown clinical significance may cause anxiety. ACOG acknowledges that further studies are necessary to fully determine the clinical use of microarrays in prenatal diagnostics [26•].

Genetic counseling for prenatal microarray analysis

Perhaps the most difficult aspect of prenatal microarray use is the counseling dilemmas that can result. Generally, the microdeletion and duplication syndromes associated with severely abnormal phenotypes require counseling identical to abnormal karyotype results. Fetuses discovered to have less severe or later onset diseases (e.g. Charcot Marie Tooth Type 1A) may present a slightly more complicated counseling session. Where counseling is most difficult is when results are of unknown significance such as those involving array findings not previously reported. Counseling is equally difficult for array findings that may have a large spectrum of phenotypic consequences, show variable expressivity, or have reduced penetrance (e.g. the relatively frequent 22q11.2 deletion). In these cases, it may be helpful to determine if the array finding is inherited or de novo, although inheritance from a mildly or unaffected parent does not assure a similar fetal phenotype. One example of a particularly difficult result would be 16p13.11 deletions where both normal individuals and those with mental retardation, autism, seizures and schizophrenia have been found to have this deletion. There may also be affected children from an unaffected parent even when both carry the same deletion. Because of these dilemmas, comprehensive pretest and posttest genetic counseling is imperative in the use of prenatal microarray analysis.

Resources

Genome browsers such as the UCSC browser, DECIPHER, ISCA, dbVar, dbGaP, the European Cytogenetics Association Register of Unbalanced Chromosome Aberrations and Ensembl can help navigate which genes are included in the deleted/duplication region of an abnormal result. As described above, dbGap will be hosting the database of CNVs through ISCA. Groups such as Unique (www.rarechromo.org) can help as resources for patients and families of affected pregnancies.

Conclusion

The role of arrays in prenatal testing is evolving. It is already clearly demonstrated that microarray analysis has value in the evaluation of fetal anomalies identified by ultrasound and in the investigation of abnormal karyotype results. Their use in the evaluation of stillbirths also seems to be appropriate for clinical care. In the authors' opinion, it seems highly likely that microarray analysis will become the first tier test for all prenatal testing including structurally normal pregnancies. However, caution is needed in transitioning the use of microarray analysis into clinical care. Thought and study must be given to identify appropriate patient education and counseling. Equally important is the selection of the appropriate array design for prenatal testing. Such a design must balance the identification of pathologic imbalances against the number of uncertain and difficult to interpret results. Perhaps, more than one array choice will be required based on clinical findings and patient preferences. For instance, for patients who only want information on severe disorders, a low-density targeted array would be appropriate. For those patients with anomalies and those who want all available information, a whole genome array would be preferred. Regardless of which array type is chosen, it has become clear that pretest and posttest counseling regarding both normal and abnormal results is warranted.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:
- • of special interest
- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 139).

1 • Friedman JM. High-resolution array genomic hybridization in prenatal diagnosis. Prenat Diagn 2009; 29:20–28.
This review article describes the use of array genomic hybridization, its advantages and disadvantages. It highlights its importance for prenatal diagnosis only if the pregnancy is considered at high risk of having a pathogenic CNV.

2 Choy KW, Setlur SR, Lee C, *et al.* The impact of human copy number variation on a new era of genetic testing. BJOG 2010; 117:391–398.

3 • Miller DT, Adam MP, Aradhya S, *et al.* Consensus statement: chromosomal microarray is a first-tier clinical diagnostic test for individuals with developmental disabilities or congenital anomalies. Am J Hum Genet 2010; 86:749–764.
This paper presents evidence which strongly supports the use of microarray in place of G-banded karyotyping as the first-tier cytogenetic diagnostic test for patients with DD/ID, ASD, or multiple congenital anomalies.

4 Aston E, Whitby H, Maxwell T, *et al.* Comparison of targeted and whole genome analysis of postnatal specimens using a commercially available array based comparative genomic hybridisation (aCGH) microarray platform. J Med Genet 2008; 45:268–274.

5 Baldwin EL, Lee JY, Blake DM, *et al.* Enhanced detection of clinically relevant genomic imbalances using a targeted plus whole genome oligonucleotide microarray. Genet Med 2008; 10:415–429.

6 Pickering DL, Eudy JD, Olney AH, *et al.* Array-based comparative genomic hybridization analysis of 1176 consecutive clinical genetics investigations. Genet Med 2008; 10:262–266.

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7 Shevell M. Global developmental delay and mental retardation or intellectual disability: conceptualization, evaluation, and etiology. Pediatr Clin North Am 2008; 55:1071–1084; xi.

8 Xiang B, Li A, Valentin D, *et al.* Analytical and clinical validity of whole-genome oligonucleotide array comparative genomic hybridization for pediatric patients with mental retardation and developmental delay. Am J Med Genet A 2008; 146A:1942–1954.

9 Nowakowska B, Stankiewicz P, Obersztyn E, *et al.* Application of metaphase HR-CGH and targeted Chromosomal Microarray Analyses to genomic characterization of 116 patients with mental retardation and dysmorphic features. Am J Med Genet A 2008; 146A:2361–2369.

10 Lu XY, Phung MT, Shaw CA, *et al.* Genomic imbalances in neonates with birth defects: high detection rates by using chromosomal microarray analysis. Pediatrics 2008; 122:1310–1318.

11 De Vries BB, Pfundt R, Leisink M, *et al.* Diagnostic genome profiling in mental retardation. Am J Hum Genet 2005; 77:606–616.

12 •• Park JH, Woo JH, Shim SH, *et al.* Application of a target array comparative genomic hybridization to prenatal diagnosis. BMC Med Genet 2010; 11:102–109.

The authors describe the use of a designed target BAC-based aCGH platform as a prenatal diagnostic tool for detection of microscopic genomic imbalances and chromosomal aneuploidies. They conclude that their designed platform can be used in conjunction with conventional karyotyping and provides rapid and accurate results without the need to interpret regions of uncetain clinical significance.

13 Coppinger J, Alliman S, Lamb AN, *et al.* Whole-genome microarray analysis in prenatal specimens identifies clinically significant chromosome alterations without increase in results of unclear significance compared to targeted microarray. Prenat Diagn 2009; 29:1156–1166.

14 Faas BH, van der Burgt I, Kooper AJ, *et al.* Identification of clinically significant, submicroscopic chromosome alterations and UPD in fetuses with ultrasound anomalies using genome-wide 250k SNP array analysis. J Med Genet 2010; 47:586–594.

15 Neill NJ, Torchia BS, Bejjani BA, *et al.* Comparative analysis of copy number detection by whole-genome BAC and oligonucleotide array CGH. Mol Cytogenet 2010; 3:11–24.

16 • Van den Veyver IB, Patel A, Shaw CA, *et al.* Clinical use of array comparative genomic hybridization (aCGH) for prenatal diagnosis in 300 cases. Prenat Diagn 2009; 29:29–39.

This study evaluated the use of aCGH for prenatal diagnosis by analyzing 300 samples from women either undergoing amniocentesis or chorionic villus sampling. It was observed that although benign variants were detected in some cases, aCGH testing provided important new information in other samples without presenting major counseling difficulties.

17 Sahoo T, Cheung SW, Ward P, *et al.* Prenatal diagnosis of chromosomal abnormalities using array-based comparative genomic hybridization. Genet Med 2006; 8:719–727.

18 •• Maya I, Davidov B, Gershovitz L, *et al.* Diagnostic utility of array-based comparative genomic hybridization (aCGH) in a prenatal setting. Prenat Diagn 2010; 30:1131–1137.

Results of this article suggest that prenatal aCGH should be offered particularly in cases with abnormal ultrasound. They found the rate of detecting an abnormality by aCGH in low-risk pregnancies was 1 : 84.

19 Kleeman L, Bianchi DW, Shaffer LG, *et al.* Use of array comparative genomic hybridization for prenatal diagnosis of fetuses with sonographic anomalies and normal metaphase karyotype. Prenat Diagn 2009; 29:1213–1217.

20 Shaffer LG, Coppinger J, Alliman S, *et al.* Comparison of microarray-based detection rates for cytogenetic abnormalities in prenatal and neonatal specimens. Prenat Diagn 2008; 28:789–795.

21 • Fruhman G, Van den Veyver IB. Applications of array comparative genomic hybridization in obstetrics. Obstet Gynecol Clin North Am 2010; 37:71–85.

This paper concludes that the superior diagnostic power of aCGH far outweighs these concerns associated with prenatal use. They argue that such issues can be addressed during pretest and posttest counseling, and their impact will further diminish as the technology continues to develop and experience with its prenatal diagnostic use grows.

22 De Gregori M, Ciccone R, Magini P, *et al.* Cryptic deletions are a common finding in 'balanced' reciprocal and complex chromosome rearrangements: a study of 59 patients. J Med Genet 2007; 44:750–762.

23 Raca G, Artzer A, Thorson L, *et al.* Array-based comparative genomic hybridization (aCGH) in the genetic evaluation of stillbirth. Am J Med Genet A 2009; 149A:2437–2443.

24 Hoang S, Ahn J, Mann K, *et al.* Detection of mosaicism for genome imbalance in a cohort of 3,042 clinical cases using an oligonucleotide array CGH platform. Eur J Med Genet 2010. [Epub ahead of print]

25 Manning M, Hudgins L. Array-based technology and recommendations for utilization in medical genetics practice for detection of chromosomal abnormalities. Genet Med 2010; 12:742–745.

26 • ACOG Committee Opinion No. 446: array comparative genomic hybridization in prenatal diagnosis. Obstet Gynecol 2009; 114:1161–1163.

This is the ACOG opinion statement which recommends use of microarray analysis in specific prenatal clinical scenarios.

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