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Microarrays and Next-Generation Sequencing Technology: The Use of Advanced Genetic Diagnostic Tools in Obstetrics and Gynecology

ABSTRACT: Genetic technology has advanced dramatically in the past few decades, and its applications and use in caring for and counseling pregnant women has been transformational in the realm of prenatal diagnosis. Two of the newer genetic technologies in the prenatal setting are chromosomal microarray and whole-exome sequencing. Chromosomal microarray analysis is a method of measuring gains and losses of DNA throughout the human genome. It can identify chromosomal aneuploidy and other large changes in the structure of chromosomes as well as submicroscopic abnormalities that are too small to be detected by traditional modalities. Prenatal chromosomal microarray analysis is recommended for a patient with a fetus with one or more major structural abnormalities identified on ultrasonographic examination and who is undergoing invasive prenatal diagnosis. Whole-genome sequencing analyzes the entire genome, including noncoding regions (introns) and coding regions (exons). However, because the introns are typically of little clinical relevance, there has been a focus instead on whole-exome sequencing, which examines the coding regions (exons) of the genome. The exons generally have greater clinical relevance and applicability to patient care. However, the routine use of whole-genome or whole-exome sequencing for prenatal diagnosis is not recommended outside of the context of clinical trials.

Recommendations and Conclusions

The American College of Obstetricians and Gynecologists (the College) and the Society for Maternal–Fetal Medicine make the following recommendations and conclusions for the use of chromosomal microarray analysis and newer genetic technologies in prenatal diagnosis:

- Chromosomal microarray analysis is a method of measuring gains and losses of DNA throughout the human genome. It can identify chromosomal aneuploidy and other large changes in the structure of chromosomes that would otherwise be identified by standard karyotype analysis, as well as submicroscopic abnormalities that are too small to be detected by traditional modalities.
- Most genetic changes identified by chromosomal microarray analysis that typically are not identified on standard karyotype are not associated with increasing maternal age; therefore, the use of this test can be considered for all women, regardless of age, who undergo prenatal diagnostic testing.
- Prenatal chromosomal microarray analysis is recommended for a patient with a fetus with one or more major structural abnormalities identified on ultrasonographic examination and who is undergoing invasive prenatal diagnosis. This test typically can replace the need for fetal karyotype.
- In a patient with a structurally normal fetus who is undergoing invasive prenatal diagnostic testing,

either fetal karyotyping or a chromosomal microarray analysis can be performed.

- Chromosomal microarray analysis of fetal tissue (ie, amniotic fluid, placenta, or products of conception) is recommended in the evaluation of intrauterine fetal death or stillbirth when further cytogenetic analysis is desired because of the test's increased likelihood of obtaining results and improved detection of causative abnormalities.
- Comprehensive patient pretest and posttest genetic counseling from an obstetrician–gynecologist or other health care provider with genetics expertise regarding the benefits, limitations, and results of chromosomal microarray analysis is essential. Chromosomal microarray analysis should not be ordered without informed consent, which should include discussion of the potential to identify findings of uncertain significance, nonpaternity, consanguinity, and adult-onset disease.
- The routine use of whole-genome or whole-exome sequencing for prenatal diagnosis is not recommended outside of the context of clinical trials until sufficient peer-reviewed data and validation studies are published.

Introduction

Genetic technology has advanced dramatically in the past few decades, and its applications and use in caring for and counseling pregnant women has been transformational in the realm of prenatal diagnosis. Cell-free DNA technology has already had an effect on prenatal screening paradigms, especially for women at high risk of fetal aneuploidy. In addition, for women who seek definitive diagnosis with amniocentesis or chorionic villus sampling, emerging genetic technologies offer testing options that exceed karyotyping of the fetus and delve deeper into the granularity of the genetic code. This Committee Opinion reviews and makes recommendations regarding the application of two of the newer genetic technologies in the prenatal setting: chromosomal microarray and whole-exome sequencing. For recommendations on prenatal testing for aneuploidy, see Practice Bulletin No. 162, *Prenatal Diagnostic Testing for Genetic Disorders* (1).

Chromosomal Microarray Analysis

Chromosomal microarray analysis is a method of measuring gains and losses of DNA throughout the human genome. It can identify chromosomal aneuploidy and other large changes in the structure of chromosomes that would otherwise be identified by standard karyotype analysis, as well as ***submicroscopic abnormalities*** that are too small to be detected by traditional modalities (Fig. 1). In contrast to the conventional karyotype, which primarily detects genetic abnormalities resulting from large changes in the number or structure of chromosomes, microarray analysis also can provide information at the submicroscopic level throughout the human genome. Duplicated or deleted sections of DNA at least 1,000 base pairs in size that differ from a representative reference genome are known as "***copy number variants***" (commonly known as CNVs) (2). The term copy number variant does not imply clinical significance and often is qualified as pathogenic or benign to clarify clinical relevance. Pathogenic copy number variants may account for a sizable portion of the human genetic disease burden; by some estimates they are as high as 15% (3). In the realm of prenatal diagnosis, the probability of finding a pathogenic copy number variant is highly correlated with the presence of structural fetal abnormalities, although significant copy number variants also can be identified in structurally normal fetuses. One difficulty that arises in

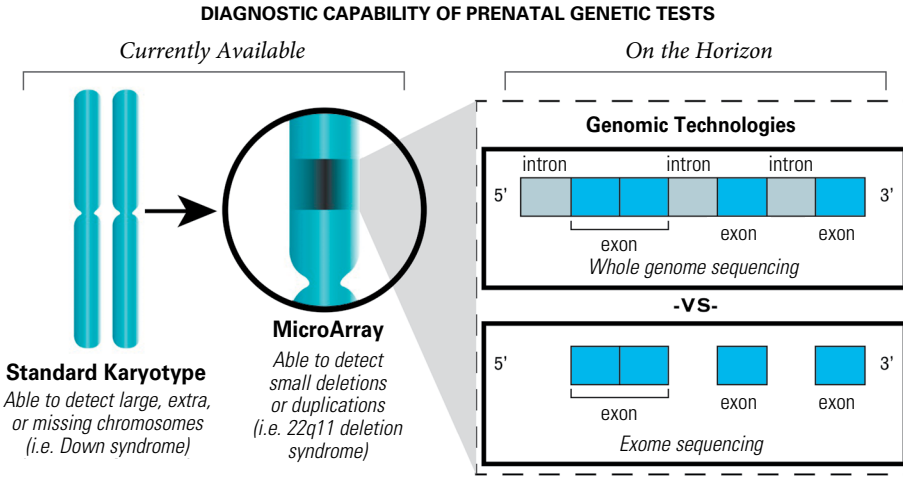

Figure 1. Diagnostic capability of prenatal genetic tests. (Reprinted from Hardisty EE, Vora NL. Advances in genetic prenatal diagnosis and screening. Curr Opin Pediatr 2014;26:634–8.) ⇦

using chromosomal microarrays is the detection of copy number ***variants of uncertain significance*** (sometimes abbreviated as VUS). Copy number variants of uncertain significance also may be referred to by the acronym VOUS or as variants of uncertain clinical significance (sometimes abbreviated as VUCS). Variants of uncertain significance are identified DNA changes that cannot be characterized reliably as benign or pathogenic at the time of the study because of limited data describing outcomes in association with the changes or that are associated with a variable phenotype (because of incomplete penetrance or variable expressivity). The interpretation of results is expected to improve over time as knowledge of the human genome grows. As the use of databases to link clinical findings with copy number variants becomes more robust, the number of variants of uncertain significance should decrease.

Another type of DNA alteration is a ***single nucleotide polymorphism*** (SNP). A SNP is a DNA variation in which a single nucleotide in the genome sequence is altered and may or may not cause disease. Copy number variants or SNPs identified using chromosomal microarray analysis do not appear to be associated with increasing maternal age (in contrast to the common trisomies that result from meiotic nondisjunction).

There are several limitations to chromosomal microarray. For example, microarray analysis cannot detect ***balanced chromosome rearrangements*** (eg, inversions or translocations), which do not result in deletion or duplication of genetic material, or cases of low-level tissue ***mosaicism***. Balanced rearrangements rarely are associated with disease unless there is disruption of a critical gene. Microarray may not identify low levels of tissue mosaicism in the fetus. In addition, as with any prenatal diagnostic technique, the presence or absence of mosaicism in the fetal cells evaluated may not represent the level of mosaicism present in peripheral blood, gonads, and other tissue. Although most microarrays currently in use are based on the analysis of SNPs, those that are not are unable to detect triploidy. Because chromosomal microarray is relatively new in the prenatal setting, insurance coverage may be variable. Some patients may wish to confirm insurance coverage or obtain preapproval before opting for microarray testing.

Chromosomal Microarray Versus Karyotype in Prenatal Diagnosis

Chromosomal microarray analysis has many advantages over the conventional karyotype in the realm of prenatal diagnosis. Chromosomal microarray yields more genetic information because of its higher resolution. In addition, because DNA can be obtained from uncultured specimens, results usually are available more quickly than with karyotyping, which requires cultured cells. Furthermore, because it does not require actively dividing cells, chromosomal microarray analysis of fetal tissue (ie, amniotic fluid, placenta, or products of conception) is recommended in the evaluation of intrauterine fetal death or stillbirth when further cytogenetic analysis is desired because of the test's increased likelihood of obtaining results and improved detection of causative abnormalities (4). Single nucleotide polymorphism-based chromosomal microarray of products of conception yields a higher rate of results compared with karyotyping, and it can identify maternal cell contamination, which is important in decreasing false-negative results (5). Additional information is needed regarding the clinical use and cost-effectiveness in cases of recurrent miscarriage and structurally normal pregnancy losses at less than 20 weeks of gestation.

In December 2012, researchers published the results of a large cohort study supported by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) that compared the efficacy of chromosomal microarray analysis with that of conventional karyotyping in prenatal diagnosis (6). In this study, microarray analysis identified all clinically significant aneuploidies and unbalanced translocations diagnosed with conventional fetal karyotyping (6). Consistent with previous studies (7), chromosomal microarray analysis identified additional clinically significant abnormalities in approximately 6% of fetuses with ultrasonographic abnormalities and a normal conventional karyotype result. Further, microarray analysis detected an abnormality in 1.7% of fetuses with an abnormal screening test result and a normal karyotype result (6). Of note, this study identified variants of uncertain significance in 3.4% of patients, of which 1.8% were classified as "likely benign" and 1.6% as "likely pathogenic based on data available at the time the study was conducted." When these variants were reanalyzed based on information available at the conclusion of the study in 2011, only 1.5% would have been classified as variants of uncertain significance. A subsequent pragmatic study demonstrated a similar rate of 1.6% (8).

Thus, based on the results of the NICHD multicenter trial and other studies, prenatal chromosomal microarray analysis is recommended for a patient with a fetus with one or more major structural abnormalities identified on ultrasonographic examination and who is undergoing invasive prenatal diagnosis. Examples of such major structural abnormalities include heart defects, brain abnormalities, cleft lip, and multiple congenital abnormalities. This test typically can replace the need for fetal karyotype. Microarray is unable to detect balanced chromosome rearrangements, but these are unlikely to be clinically significant for the fetus. An additional limitation of microarray that needs to be considered when counseling on recurrence risk is that the mode of transmission of the imbalance cannot be ascertained without a karyotype (ie, translocation versus trisomy).

In a patient with a structurally normal fetus who is undergoing invasive prenatal diagnostic testing, either fetal karyotyping or a chromosomal microarray analysis

can be performed. Most genetic changes identified by chromosomal microarray analysis that typically are not identified on standard karyotype are not associated with increasing maternal age; therefore, the use of this test can be considered for all women, regardless of age, who undergo prenatal diagnostic testing.

Need for Patient Counseling

In addition to the data regarding genetic testing results, the NICHD study raised several important considerations for the clinical application of chromosomal microarray analysis in the prenatal setting. The potential for detection of clinically uncertain and complicated findings with prenatal chromosomal microarray analysis can result in substantial patient anxiety (9, 10). Comprehensive patient pretest and posttest genetic counseling from an obstetrician–gynecologist or other health care provider with genetics expertise regarding the benefits, limitations, and results of chromosomal microarray analysis is essential for patients to make informed decisions. Chromosomal microarray analysis should not be ordered without informed consent, which should include discussion of the potential to identify findings of uncertain significance, nonpaternity, consanguinity, and adult-onset disease. Box 1 lists some key information that should be shared with patients who are considering prenatal chromosomal microarray testing.

In addition to copy number variants of uncertain significance, chromosomal microarray analysis can detect genetic abnormalities associated with adult-onset disorders (eg, Charcot–Marie–Tooth disease, which can be caused by a duplication), which may be inherited from an asymptomatic parent. As with many prenatal tests, some types of arrays also can identify evidence of consanguinity and nonpaternity. The type and amount of information reported varies depending on the specific array used as well as the policy of the laboratory that performs the analysis (11). This again underscores the need for adequate genetic counseling and informed consent before patients undergo testing with this technology.

Next-Generation Sequencing: Whole-Exome and Whole-Genome Sequencing

Although microarray analysis has increased diagnostic ability above karyotyping, most anomalous fetuses with a normal karyotype also have a normal microarray analysis and, thus, remain without a definitive diagnosis (7). ***Whole-genome sequencing*** (commonly known as WGS) analyzes the entire genome, including noncoding regions (***introns***) and coding regions (***exons***). However, because the introns are typically of little clinical relevance and the cost of whole-genome sequencing is high and the interpretation of the results very complex, there has been a focus instead on ***whole-exome sequencing*** (commonly known as WES), which examines the coding regions (exons) of the genome. The exons generally have greater clinical relevance and applicability to patient care. Whole-genome sequencing and whole-exome sequencing are considered next-generation sequencing (commonly known as NGS) technologies.

Whole-Exome Sequencing

Whole-exome sequencing has been used successfully in adults and children to diagnose mendelian inherited disorders (12) and to identify causes of intellectual disability (13). Whole-exome sequencing also is a broad molecular diagnostic approach to identify the etiology for fetal abnormalities, and whole-exome sequencing of fetal DNA obtained by amniocentesis, chorionic villi, or umbilical cord blood is being offered on a research basis in some laboratories and for specific clinical indications in other laboratories (14). Published data on the prenatal applications of whole-exome sequencing are limited to case series and case reports. However, these series suggest that a genomic abnormality may be identified in up to 20–30% of fetuses with multiple anomalies for which standard genetic testing results (ie, karyotype, microarray, or both) are normal (14). These cases illustrate how whole-exome sequencing potentially may be used to provide families with a definitive diagnosis, accurate estimates of recurrence risk, and even the options of preimplantation genetic testing or early prenatal diagnosis in a future pregnancy.

Box 1. Information to Share With Patients Before Prenatal Chromosomal Microarray Analysis ⇦

- Chromosomal microarray analysis will identify almost all of the abnormalities that are identified by fetal karyotyping and may identify additional specific 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 (a close blood relationship or incest) or nonpaternity.
- Genetic changes may be identified that may or may not cause disease. Samples of DNA from both parents may be required to help understand the significance of these 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 also may indicate that one of the parents has the same adult-onset disease but has not yet developed symptoms.

Prenatal exome sequencing may be reasonable in select circumstances, either in fetuses with multiple anomalies or in cases of recurrent fetal phenotypes with no diagnosis by standard genetic testing (eg, karyotype or microarray). The American College of Medical Genetics and Genomics recommends considering whole-exome sequencing when specific genetic tests available for a phenotype, including targeted sequencing tests, have failed to determine a diagnosis in a fetus with multiple congenital anomalies suggestive of a genetic disorder (15). However, the routine use of whole-genome or whole-exome sequencing for prenatal diagnosis is not recommended outside of the context of clinical trials until sufficient peer-reviewed data and validation studies are published. In general, at this time, whole-exome sequencing should be ordered only after consultation with a clinical genetics physician.

Often, the most efficient process for examining the exome in prenatal diagnosis involves sequencing the fetus as well as the biological parents (so-called ***trio sequencing***), which increases the diagnostic yield by filtering out thousands of uninformative genomic variants in a meaningful way. It is important to note that, like microarray testing, whole-exome sequencing of trios could reveal nonpaternity, consanguinity, and incidental findings in the parents' exomes that are medically actionable (16). For example, either a fetus with multiple anomalies or one of its parents may be found to have an inherited cancer gene mutation that is pathogenic but unrelated to the ultrasonographic findings.

Despite whole-exome sequencing's promise for increasing the ability to diagnose many diseases prenatally and in children or adults, there are important limitations to this technology. First and foremost, as of 2016, the use of whole-exome sequencing prenatally is hampered by long turnaround times because of the need to sequence and analyze the entire exome. As the ability to analyze the exome improves with state-of-the-art bioinformatics protocols and tools, this turnaround time is expected to decrease. The turnaround time in adults and children ranges from 5 weeks to 18 weeks (17). There are no consistent data for prenatal whole-exome sequencing, although the potential for long turnaround times limits the use of whole-exome sequencing for prenatal diagnosis, and especially for reproductive decision making. The second major limitation of this technology is the high number of variants of uncertain significance that can be found, which, as in the case of microarrays, may create enormous anxiety and be challenging for patients and obstetrician–gynecologists and other health care providers. Finally, the current cost of whole-exome sequencing and limited insurance coverage for this genetic technology may restrict its use and should be reviewed before ordering the procedure.

Because of the many complex issues that arise in using whole-exome sequencing clinically, the College and the Society for Maternal–Fetal Medicine recommend that all patients considering whole-exome sequencing receive counseling from an obstetrician–gynecologist or other health care provider with genetics expertise who is well versed in these technologies. Because of the aforementioned limitations and the current dearth of peer-reviewed data and validation studies proving the clinical utility of this technology, the College and the Society for Maternal–Fetal Medicine currently do not recommend whole-exome sequencing for routine use in prenatal diagnosis. In select circumstances (recurrent or lethal fetal anomalies in which other approaches have been noninformative), whole-exome sequencing may be considered as a diagnostic tool, but only after other appropriate testing has been noninformative and after extensive counseling by an obstetrician–gynecologist or other health care provider with genetics expertise who is familiar with these new technologies and their limitations.

Cell-free Whole-Genome DNA Screening

Some commercial laboratories have started offering cell-free DNA screening to screen for genome-wide gains or losses that include regions of DNA (7 ***mega base pairs*** or more) throughout the genome that may be associated with structural birth defects, intellectual disability, or both. This testing interrogates the entire genome and is designed to detect abnormalities larger than those evaluated on some of the cell-free DNA tests with targeted microdeletions. This goes beyond the information available from traditional applications of cell-free DNA screening, which evaluates for common aneuploidies and, potentially, several microdeletion conditions. This technology should not be confused with microarray, karyotype, or whole-exome sequencing, which specifically look at DNA sequence variants, not DNA copy numbers. Cell-free DNA screening is not a diagnostic test, and patients should be made aware of the limitations and benefits through pretest and posttest counseling. Genome-wide screening tests for genomic composition are only beginning to be validated for accuracy, clinical use and validity, and cost-effectiveness in peer-reviewed journals (18). Just as the College and the Society for Maternal–Fetal Medicine have recommended against routine screening for microdeletion syndromes by cell-free DNA screening, routine screening for genome-wide gains or losses with cell-free DNA is not recommended.

Glossary

Balanced Chromosome Rearrangement: A chromosomal rearrangement that does not result in deletion or duplication of genetic material, such as inversions and translocations.

Chromosomal Microarray Analysis: A method of measuring gains and losses of DNA throughout the human genome. It can identify chromosomal aneuploidy and other large changes in the structure of chromosomes

that would otherwise be identified by standard karyotype analysis, as well as submicroscopic abnormalities that are too small to be detected by traditional modalities.

Copy Number Variants: Duplicated or deleted sections of DNA at least 1,000 base pairs in size that differ from a representative reference genome. Copy number variants can be qualified as pathogenic or benign to clarify clinical relevance.

Exons: Coding regions of the genome.

Introns: Noncoding regions of the genome.

Mega Base Pairs: Equivalent to 1,000,000 base pairs.

Mosaicism: The presence of two or more populations of cells with different characteristics within one tissue or organ.

Single Nucleotide Polymorphism: A DNA variation in which a single nucleotide in the genome sequence is altered and which may or may not cause disease.

Submicroscopic Abnormality: Duplications and deletions smaller than what can be seen on conventional (microscopic) karyotype.

Trio Sequencing: Whole-exome sequencing of a fetus and its biological parents.

Variants of Uncertain Significance: Also known by the acronym VUS or VOUS or as variants of uncertain clinical significance (VUCS). Variants of uncertain significance are identified DNA changes that either cannot be characterized reliably as benign or pathogenic at the time of the study because of limited data describing outcomes in association with the changes or that are associated with a variable phenotype (because of incomplete penetrance or variable expressivity).

Whole-Exome Sequencing: A next-generation sequencing technology that analyzes only the coding regions of a genome.

Whole-Genome Sequencing: A next-generation sequencing technology that analyzes the entire genome, including noncoding and coding regions.

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