PATIENT HANDOUT

CHROMOSOMAL MICROARRAY FOR PRENATAL DIAGNOSIS

Society for Maternal-Fetal Medicine

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Chromosomes are the organized DNA in each of our cells that direct structure, function, and personal characteristics. Almost all of our cells contain 23 pairs of chromosomes (46 total chromosomes). A loss or gain of chromosomal material can be associated with birth defects or developmental delay.

When they are studied in the laboratory, chromosomes are often stained and imaged using a microscope to determine whether there are any extra or missing fragments. This type of analysis is known as a *karyotype*. However, some losses or gains of genetic material are even smaller than what can be seen using a microscope. An enhanced test to detect these smaller changes is called a *chromosome microarray analysis,* or *CMA*. CMA is a technique that identifies gains (duplications) or losses (deletions) in genetic material that are smaller than those identified with a karyotype. CMA uses a gene chip to look at certain regions of the DNA to identify gains and losses in genetic material which are known as copy number variants (CNVs). CNVs may cause a wide range of human disorders, including developmental disorders and birth defects. CMA is currently recommended as the first-line test in the evaluation of congenital abnormalities and neurodevelopmental disorders in newborns.

With accumulating experience over the last decade, CMA is proving to be a valuable diagnostic tool during pregnancy. CMA can be performed during pregnancy to examine fetal DNA using samples obtained from chorionic villus sampling (CVS) and amniocentesis. CMA on a newborn is performed using a cheek swab or a blood sample from the baby.

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

A karyotype can detect abnormalities in chromosomes such extra or missing chromosomes (also known as aneuploidy), extra or missing smaller segments within the chromosomes (also known as deletions or duplications), and other rearrangements that are visible by a microscope. CMA has a higher resolution than karyotype, allowing for the detection of much smaller deletions and duplications. Several large-scale studies have compared prenatal use of chromosomal microarray to conventional karyotyping. These studies reported that compared with conventional karyotype, CMA can detect a potentially abnormal or disease-causing genetic variant in an additional 6%–7% of cases with fetal structural abnormalities seen by ultrasound, and in 1%–1.7% of cases with a structurally normal fetus by ultrasound.

Another advantage of CMA is that it does not require dividing cells as is required in conventional karyotyping, allowing the results to be returned rapidly. In addition, CMA can be performed on tissue obtained from fetal demise/stillbirth specimens, and this information can be used in subsequent counseling to prepare for the next pregnancy.

Q What are the limitations of CMA?

Because CMA looks for extra or missing genomic material, it cannot detect certain chromosomal rearrangements, such as translocations or inversions. The vast majority of these rearrangements, however, result in a normal newborns. Also, CMA will not detect CNVs that are very small and fall below the level of detection. In addition, CMA will not detect genetic changes within single genes, including those that cause disorders such as sickle cell anemia and cystic fibrosis.

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

Another disadvantage of CMA is the inability to precisely interpret the significance of previously unreported CNVs, or to predict the outcome for the newborn in these cases. CNVs are characterized as 1) benign; 2) clinically significant (that is, disease-causing); and 3) as a change that has not previously been described, known as a variant of uncertain significance (VUS). The overall likelihood of a VUS is approximately 1% to 2%. Fortunately, additional information on the classification of CNVs is rapidly accumulating, which should lead to a decrease in the incidence of VUS over time.

Patients in whom a fetal VUS is detected should receive counseling from experts, such as genetic counselors or clinical geneticists who have access to databases that provide updated information. Patients should be educated regarding the significance of the finding including the potential outcomes for the baby, and should be provided with resources and support. Further testing may be offered. It is important in the evaluation of a fetal VUS to

determine if either parent has the same CNV as was found in the fetus. Although CNVs that are found only in the baby and not the parents are more likely to be disease-causing, an abnormal neonatal outcome can sometimes still occur, even if a normal parent has the same CNV as the baby.

Q When should CMA be offered?

The American Congress of Obstetricians and Gynecologists (ACOG) and the Society for Maternal-Fetal Medicine (SMFM) recommend CMA when genetic analysis is performed in cases with fetal birth defects and/or a stillbirth. CMA replaces the need for fetal karyotype in these cases. ACOG and SMFM also recommend that either fetal karyotype or CMA be performed when invasive prenatal diagnosis (CVS or amniocentesis) is performed in cases with structurally normal fetuses regardless of maternal age.

Currently, some providers recommend CMA as a first-line test whenever fetal chromosomal analysis is planned, while other clinicians reserve CMA for cases in which there are fetal structural abnormalities to avoid the possibility of discovering a VUS.

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

Conventional karyotype may be more appropriate when a common chromosomal abnormality such as trisomy 21 (Down syndrome), trisomy 18, trisomy 13, or monosomy X is strongly suspected based on prenatal ultrasound findings. In these circumstances, a karyotype and/or a rapid turnaround test called prenatal FISH analysis is reasonable. A prenatal FISH analysis specifically looks at chromosomes 13, 18, 21, X, and Y or can be tailored to look for other specific abnormalities. A CMA can be subsequently performed in the event that the FISH or karyotype is normal. CMA is not currently recommended as a first-line test to evaluate first-trimester pregnancy losses.

Q How should patients be counseled prior to CMA?

Trained genetic counselors, geneticists, or other providers with expertise in the complexities of interpreting CMA results should counsel patients. Compared with conventional karyotype, CMA will detect a potentially abnormal or disease-causing CNV in an additional 6%-7% of cases with fetal structural abnormalities on ultrasound and in 1%-1.7% of cases with a structurally normal fetus and there is a 1.4%-2.1% chance that a fetal VUS could be detected. Particularly in cases with a structurally normal fetus on ultrasound, a fetal VUS may cause considerable stress and anxiety in parents. It may be difficult to interpret the significance of a CNV prenatally due to the limitations of fetal imaging and the limited information currently available correlating prenatal CNV findings with postnatal outcomes. CMA does not detect every genetic disease or syndrome, including disorders associated with single-gene mutations. CMA can detect consanguinity (whether parents are related in some way) and non-paternity in some cases.

Q What samples can be used for CMA testing?

CMA for prenatal diagnosis may be performed on DNA obtained from amniocentesis, CVS, fetal cord blood, and stillbirth specimens, including the placenta. Some labs require that a maternal blood specimen be sent with the original CMA specimen while other labs request parental samples only when a CNV is detected, in order to distinguish between an inherited CNV (from one of the parents) and a CNV found only in the fetus.

Q Are there differences between prenatal and postnatal CMA?

Prenatally CMAs are obtained to identify causes of malformations and predict neonatal outcomes. CMAs are recommended as the first diagnostic test for evaluating children with multiple congenital anomalies, developmental delay/intellectual disability, and/or autism spectrum disorders. Obtaining a diagnosis is important to parents for many reasons, including ending uncertainty, obtaining resources and caring for their child, and planning future pregnancies.

Q Is CMA expensive and will insurance pay for it?

The cost of chromosomal microarray is currently higher than conventional karyotyping but it is expected to decrease with increasing volumes and technical advances. Before undergoing testing, it may be best to check with your insurance carrier to find out if CMA will be covered.

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