OPINION

Pregnant pause

BY **EMILY SINGER**

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Pregnant women are faced with increasingly sophisticated tests capable of detecting problems in the fetus. Along with that potential come questions about how to use the sometimes complex and unpredictable information.

A large multi-center study published 5 December in the *New England Journal of Medicine* shows that chromosomal microarray (CMA) is **more sensitive at detecting genetic abnormalities** than karyotyping, the existing gold-standard method.

CMA can detect **copy number variations** (CNVs) — deletions or duplications of stretches of DNA — that are smaller than 100,000 base pairs. It is already used to **diagnose children with developmental delay** and other disorders. Karyotyping can only detect much larger variations that are visible under a microscope.

However, as lead investigator **Ronald Wapner** noted in Marchin a SFARI.org conference report on the study's **preliminary findings**, CMA's prenatal use raises a new set of questions.

"Interpreting that information prenatally is a very different discussion than when a parent brings in a child who already has an abnormality," said Wapner, director of reproductive genetics at Columbia University's New York Presbyterian Hospital. Prior to birth, "we don't know if there are going to be phenotypic [or observable] consequences, and that makes it more complex."

Wapner and his colleagues analyzed data from 4,400 pregnant women who were older than 35 or whose fetuses had some sign of abnormalities, and who underwent both karyotyping and microarray testing. (Both tests use samples from amniocentesis or chorionic villus sampling, invasive procedures that carry a small risk of miscarriage.)

CMA found clinically significant CNVs in 2.5 percent of fetuses that seemed to have a normal karyotype. That percentage was higher in fetuses with an abnormal ultrasound. In those cases, CMA identified six percent of clinically relevant CNVs (1 of 17 cases) that karyotyping missed.

Uncertain risk:

In an editorial accompanying the paper, **Lorraine Dugoff**, associate professor of obstetrics and gynecology at the University of Pennsylvania Perelman School of Medicine, suggests that the **new technology should be offered** to women who have an abnormal ultrasound.

Still, the benefits aren't big enough for most women, even those older than 35 or who have a positive screen for Down syndrome, she says.

That's because a small percentage — 1.5 percent — of the CNVs on prenatal microarrays are of 'uncertain significance,' meaning that it's unclear whether they are harmful.

That makes it difficult for clinicians to interpret the results for parents who may use the information to terminate the pregnancy. (The microarrays used in prenatal testing are much more limited, detecting a smaller set of CNVs, than those used in children, for precisely this reason.) Dugoff says the incremental value of the test doesn't outweigh the potential for uncertainty.

For example, a duplication or deletion on chromosome 16 called **16p11.2** can have **widely different effects**, including autism, developmental delay and speech problems, or no observable symptoms at all. This CNV is also sometimes linked to heart defects, the primary reason it's included in prenatal arrays.

The number of these uncertain CNVs is falling as researchers learn more about them. Wapner says that over the past five years, their proportion has dropped from 2.5 percent to 1.5 percent of CNVs identified.

Researchers hope to shrink that number even further with an effort to catalog this information, the **International Standards for Cytogenomic Arrays Consortium**.

A second paper in the same issue of the journal highlights the **latest prenatal technology** to come down the pike — a DNA sequencing approach the authors refer to as "jumping libraries." Researchers analyzed the genome sequence of selected stretches of DNA from a fetus revealed by ultrasound to have a heart defect.

They found that chunks of DNA from chromosomes 6 and 8 had been swapped, an unprecedented genetic variation that is not detectable by karyotype or microarray.

One of the breakpoints interrupts a gene called **CHD7**, which has been tied to CHARGE syndrome

— a complex pattern of birth defects that affects a number of organs — and to autism. After birth, the baby was diagnosed with CHARGE syndrome based on clinical symptoms.

The whole process took about 13 days, meaning it’s fast enough to be used in a clinical setting — and highlights the rapid pace of improvement in DNA sequencing technology.