



Miller School Investigator's Commentary in Nature Medicine Describes Eye-Opening Prenatal Genetic Testing Flaws

Parents-to-be often turn to costly tests they believe will identify chromosomal abnormalities in embryos before implantation or in early pregnancy.

But these tests can be unreliable, and we are just beginning to understand how potentially misleading they can be, according to a recent commentary in Nature Medicine by Pasquale Patrizio, M.D., M.B.E., HCLD, FACOG, professor of obstetrics, gynecology, and reproductive sciences and chief of reproductive endocrinology and infertility at the University of Miami Miller School of Medicine, and an international group of coauthors.



Pasquale Patrizio,
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Dr. Patrizio and colleagues are leading research showing that pre-implantation genetic testing for aneuploidy (PGT-A), commonly used during in vitro fertilization (IVF), can result in false positives for abnormalities, when in fact these embryos would produce healthy babies.

Abnormal Cells May Not Indicate an Unhealthy Embryo

“This paper identifies new science about early embryology to make the scientific community aware that the placenta cells have high aneuploid load, and that does not mean the embryo is not healthy before an IVF transfer or even later on when the woman is pregnant,” said Dr. Patrizio.

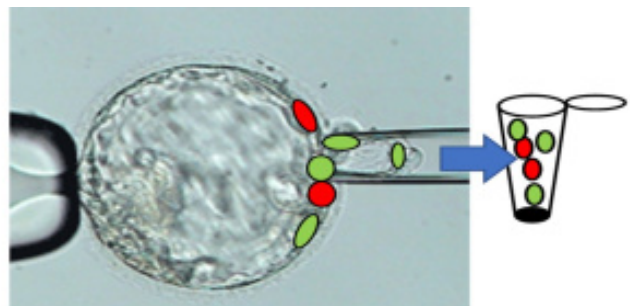
Among the novel findings described in the commentary is that the testing relies on very few cells – only five to six – biopsied from what will become the placenta, but not from the

embryo.

“In addition, there is an interesting biological process going on at this very early stage of development,” Dr. Patrizio said. “The embryo, to a certain degree, uses the placenta to get rid of abnormal cells. The future placenta compartment can be seen as a kind of reservoir and tolerates a lot of abnormal cells while still preserving a healthy baby.”

In essence, the embryo can self-correct. Therefore, identifying abnormal cells in the placenta might not be an indication of the embryo’s health at all.

“It is really a fascinating early developmental, biological phenomenon, and if it’s confirmed by additional ongoing studies, it may also shed new light on various pathologies of pregnancies,” Dr. Patrizio said.



Biopsy of placental cells with different mix of cells - “abnormal” cells depicted in red and the “normal” cells depicted in light green.

Plasticity of Placental Cells

In research conducted in 2017 and 2019, Dr. Patrizio and his team found that the future placenta has an average of 120 to



150 cells at the time that biopsies are performed. They also discovered that the future placenta has clusters of normal and abnormal cells (known as “mosaicism”). From this information, the team concluded that biopsies of five or so cells should not be regarded as representative of the entire placenta or cohort of cells.

“To make things even more complicated, placenta cells change, so this dynamic or genetic plasticity hinders the proper interpretation of results in a great majority of this testing,” Dr. Patrizio said.

The message to patients and the many IVF and other clinics still recommending the testing universally: In light of the reported inherent inaccuracy of results, limit use of PGT-A testing to only a few specific cases.

The more general issue of inaccuracy in genetic testing, particularly related to embryos, is not new, according to Dr. Patrizio.

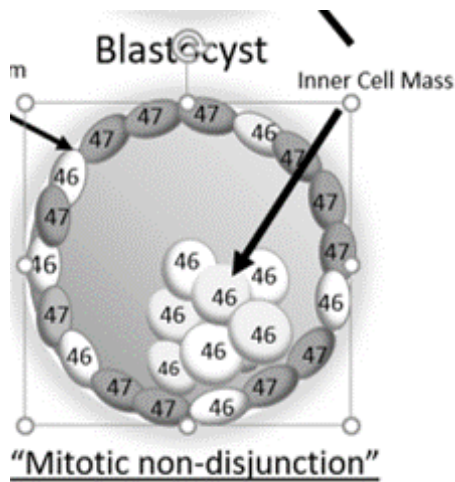
“Three years ago, my coauthors and I published a paper on the birth of many healthy children from the transfer of ‘abnormal’ embryos,” he said.

Limited Accuracy of a Widely Used Test

Despite this growing body of knowledge, the PGT-A test continues to be offered for about half of all IVF cycles in the United States, according to the paper.

Since placental cells are also sampled during early pregnancy with a test called CVS (chorionic villus sampling), the discovery of early placental plasticity suggests that abnormal test results should be confirmed with a more precise test,

such as amniocentesis, before important decisions are made about a pregnancy, according to Dr. Patrizio.



A mix of abnormal cells in the placental compartment (47 = abnormal, 46 = normal), are not representative of the embryo's inner cell mass showing all normal cells.

“We at the Miller School are extremely selective on when to apply embryo testing. There are several types of genetic testing,” he said. “The most unreliable ones are those that look for an abnormal number of chromosomes (PGT-A). But there are other genetic tests looking for genetic diseases, called PGT-M, that are very accurate and valuable, including those that can help diagnose for cystic fibrosis, muscular dystrophy, and many other diseases.”

PGT and PGT-A tests can cost thousands of dollars and can result in patients undergoing unnecessary additional IVF

cycles, costing tens of thousands of dollars.

Dr. Patrizio's coauthors include human reproduction experts from the Center for Human Reproduction in New York City; Rockefeller University; Medical University of Vienna in Austria; and the Infertility and IVF Unit at Tel Aviv University in Israel.

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