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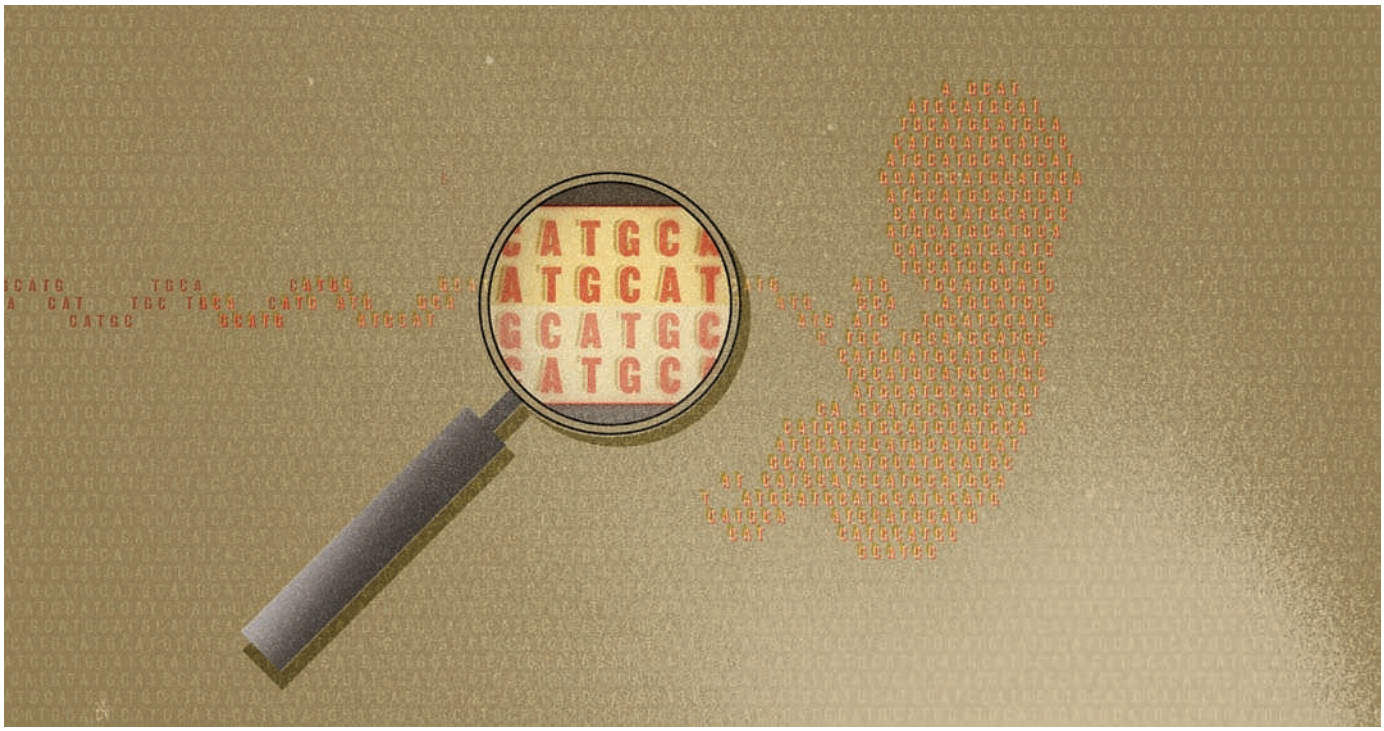

ILLUSTRATION BY GAVIN POTENZA

Get ready for the flood of fetal gene screening

Regulators, doctors and patients need to prepare for the ethical, legal and practical effects of sequencing fetal genomes from mothers' blood, says **Henry T. Greely**.

The world's news media was buzzing last week after researchers showed that a blood test for mothers could detect Down's syndrome in their fetuses[1]. Last month, two research groups independently published proof that the fetal genotype — the genetic status at a given locus — can be derived for thousands of sites from samples of fetal DNA with just a 10-millilitre blood draw from a pregnant woman[2,3].

The brave new world of widespread prenatal genetic diagnosis has been always 'arriving' since *Nature* published a paper by Danish researchers Fritz Fuchs and Povl Riis in 1956, reporting the first prenatal genetic testing in humans[4]. With non-invasive prenatal genetic diagnosis (NIPD) it may finally have arrived. Checking for hundreds or thousands of traits with one blood test, early in pregnancy, could move prenatal genetic testing from uncommon to routine.

That possibility challenges all societies to decide for which ends and by what means they want such tests to be used, raising hard questions about, among other things, abortion, disability rights, eugenics and informed consent.

Prenatal genetic testing has been clinically available since the late 1960s, but the costs, inconvenience and especially the miscarriage risks have limited its use. Each year, less than 2% of pregnant women in the United States undergo amniocentesis (in which a small amount of amniotic fluid containing fetal cells is taken for analysis) or chorionic villus sampling (CVS — in which fetal tissue is extracted from the placenta). Both procedures increase the risk of miscarriage. Until now, any given sample could be tested for only one or two conditions, typically chromosomal abnormalities such as trisomy 21, the cause of Down's syndrome.

These factors combined to limit recommended use of these methods to women with a higher risk of having a fetus with ▶

a particular disease. Most frequently this has meant women over the age of 35, whose chances of carrying a fetus with Down's syndrome are greater than the risk of a miscarriage caused by the procedure.

Biologists have known for decades that some fetal cells pass through the placenta and into the mother's blood stream. Technical problems have hampered attempts to isolate individual fetal cells and, even when such cells could be found, there was no guarantee that they were from the present pregnancy. Analysing the free-floating fragments of fetal DNA that exist in a pregnant woman's blood serum is proving more successful.

Blood contains billions of DNA fragments released when cells die and are broken up by enzymes. Even early in pregnancy, 5–10% of that 'cell-free' DNA in pregnant women comes from the fetus. Thanks to cheap and sensitive sequencing techniques, this DNA can be examined and aspects of the fetus's genome analysed. For some traits, such as paternally inherited dominant conditions, this can be done by looking for DNA variants — alleles — that the mother does not carry. For other traits, the number of copies of each variant can be used to determine how many copies of a chromosome the fetus carries, as well as how many copies of which alleles.

IN THE CLINIC

Non-invasive prenatal genetic diagnosis is already in clinical use for fetal blood-type screening. A woman of blood type Rhesus (Rh) negative can create antibodies against the red blood cells of a fetus of type Rh positive, injuring that fetus, or subsequent fetuses. In many countries, pregnant Rh-negative women routinely receive protective antibodies. Now, in several countries, including the United Kingdom, the Netherlands and France, cell-free DNA analysis is being used to determine the Rh type of the fetus and the antibody is only injected when needed.

"Commercial development of these methods seems likely within five years."

The potential of NIPD goes way beyond Rhesus screening. Two of the leading researchers in cell-free fetal DNA testing — Dennis Lo of the University of Hong Kong and Steve Quake of Stanford University in California — use different methods to analyse fetal cell-free DNA from maternal serum. Each has demonstrated the ability to detect aneuploidies — missing or extra chromosomes, such as in trisomy 21 (refs 5, 6). Last month, both researchers published proof that the fetal genotype could be derived for thousands of sites from cell-free fetal DNA[2,3] — demonstrating the possibility of using maternal blood to test for all fetal genetic traits.

There seems to be no technical barrier, given increasingly cheap genotyping and sequencing, to being able to test one sample simultaneously for chromosomal abnormalities; for single-gene diseases, such as cystic fibrosis, sickle-cell anaemia, and Tay-Sachs disease; and for various non-disease genetic traits such as sex.

Commercial firms are already interested. Sequenom in San Diego, California, is working with Lo; another, Artemis Health of Menlo Park, California, is working with Quake; and still others are also exploring the technology. For-profit development of these methods seems likely within five years, at least for chromosomal abnormalities, such as trisomy 21, and possibly for single-gene traits.

The scope and consequences of such testing will, of course, depend in large part on its accuracy. If NIPD is so inaccurate that it requires amniocentesis or CVS for confirmation, its influence will be limited. But the improving power, and decreasing cost, of DNA sequencing make it likely that the accuracy of these tests would be high. If necessary, samples can be genotyped or sequenced to greater and greater depth, particularly as costs drop, and additional samples, if needed, are just a blood draw away.

When such testing does take off — and it is when, not if — the public controversy will be about its uses. *In vitro* fertilization provides one precedent. More than 30 years from its first use, debates continue about whether it can be used by unmarried people, homosexuals and elderly women — and about who will pay for it. Preimplantation genetic diagnosis is a closer example, with strong disagreements about its use for sex selection, trait selection and the creation of 'saviour siblings'. With NIPD, abortion opponents will want little or no use of tests that will increase the number of pregnancies terminated. Some people will be concerned about technologies that prevent the birth of people with particular disabilities, both for the message that might send about the worth of those who are disabled and for its practical effects on research, treatment and support for those with disabilities.

And the spectre of eugenics will loom over the whole discussion. Some will oppose parental choices about the characteristics of their babies; others will worry that parental choice will be influenced, or trumped, by the decisions of governments, health-care systems or other institutions. Fears of eugenics will increase as such testing moves from fatal diseases to less serious medical conditions and then on to non-medical characteristics — sex selection today; skin, hair and eye colour tomorrow; perhaps, eventually, traits such as some cognitive or physical abilities. Still other kinds of uses will pose problems. Sometimes, for instance, parents with particular conditions, such as genetic forms of deafness, may want to ensure that their children have the same condition. Or some women, or the men in their lives, may want to move paternity testing *in utero*.

Some of these concerns exist today — witness for instance the dramatic skewing of live-birth sex ratios in China and India brought about by cheap and accessible ultrasound. But they will only become more immediate and more important with widespread NIPD.

Beyond these big questions lurk crucial operational details. Some involve the testing itself. Will such tests be regulated to ensure that they are safe and effective and, if so, how? Will the testing laboratories be subject to oversight that guarantees they perform the tests accurately? Who will pay for millions of genetic tests, and for the abortions that follow? The burgeoning controversies over the regulation of genetic testing, whether or not they are 'direct to consumer', provide one very contemporary example of these questions; the regulation of, and payment for, IVF and preimplantation genetic diagnosis provides another.

Much of the social impact — and the impact on the medical system — will depend on how widely such testing is used. Some of that will depend on those who fund health care and whether they see this testing as yet another cost or as a way to save money by avoiding the births of high-cost children. Part of the impact will depend on the legal system. If a test is clinically available and a physician does not offer it to a patient, at least in the United States, a physician could be liable through a 'wrongful birth' suit for the health costs of a child whose birth might have been prevented.

TIME TO TALK

In California currently, about two-thirds of pregnant women opt for non-invasive screening for Down's syndrome and neural tube defects. If the same fraction of pregnant women opt for NIPD, the United States alone would move from conducting fewer than 100,000 fetal genetic tests a year to about 3 million. Where will we find, or create, the professionals to provide genetic advice to these patients? And, of course, even if widely adopted, use of NIPD is unlikely to be uniform. It seems likely to vary between countries but also within countries, based on religion, ethnicity, education and other characteristics. In California, for example, it is thought that women with more education are more likely to accept screening and Hispanic women are less likely. What social issues will such disparities raise?

For parents who do choose NIPD, we will need to make sure they truly choose it. Today, amniocentesis and CVS are invasive procedures, typically prepared for over time. The parents and their physician decide that their fetus is at high risk of having a genetic disease, they go through genetic counselling and informed consent, and an invasive procedure

is scheduled for several days later. Confronted with a long needle or a transvaginal probe, few, if any, women will undergo either procedure without understanding that something serious is happening.

But if NIPD requires just one more tube of blood from the mother — and just one more signature on one more form — how can we ensure that parents understand what they are consenting to? Already some who get results of blood-based screening tests for the risk of Down's syndrome are shocked to learn they ever agreed to the test. NIPD greatly increases what is at stake; parents must not be surprised when genetic-test results arrive. And, of course, that consent will be even more complicated when hundreds of genetic traits can be tested, not just one or two.

"How can we ensure that parents understand what they are consenting to?"

These questions, and many others, have to be answered, and soon. Some of the answers may be the same across different cultures, others need careful national attention. Views and practices differ from country to country on abortion, on freedom of parental choice, on funding health care and on many other relevant considerations.

A few European groups have been studying NIPD. A European Union consortium called SAFE — the Special Non-invasive Advances in Fetal and Neonatal Evaluation Network — studied the scientific, medical and ethical issues around more limited NIPD applications for several years[7]; the PHG Foundation — the UK Foundation for Genomics and Population Health — convened a UK expert group that produced a report[8] on NIPD; and a more recent British project called RAPID — Reliable Accurate Prenatal non-Invasive Diagnosis — continues to work on the issues[9]. Little has been done in the United States[10] and almost nothing elsewhere.

Professional organizations, in medicine and in genetics, need to get involved, both in training their members about these technologies and in beginning to consider guidelines for their use, especially with regard to informed consent. Regulators, companies and consumer advocates need to be talking about pathways for assuring the safety, efficacy and quality of NIPD testing. In the United States, the Food and Drug Administration should start that process immediately. And it is time for ethics commissions, such as the US Presidential Commission for the Study of Bioethical Issues, to report on these issues.

Most importantly, we need to start conversations, between all those concerned, about the limits, if any, to place on this powerful technology. Whether we view NIPD gladly as a way to reduce human suffering, warily as a step towards a eugenic dystopia, or as a mix of both, we should agree that the better we prepare, the more likely we are to avoid the worst misuses of this potentially transformative technology. ■

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