Nature Reviews Genetics | AOP, published online 23 June 2009; doi:10.1038/nrg2631

Ethics watch

AN OFFER YOU CAN'T REFUSE? ETHICAL IMPLICATIONS OF NON-INVASIVE PRENATAL DIAGNOSIS

Genetic prenatal diagnosis (PND) for fetal aneuploidies has been an integral part of prenatal medicine for over 30 years. It is usually performed as a combination of initial non-invasive risk screening (NIRS) strategies, and suspicious results are followed by invasive diagnostic procedures such as amniocentesis. Recently, however, several breakthroughs in non-invasive prenatal diagnosis (NIPD) indicate the upcoming clinical applicability of this procedure. In 2007, after years of largely fruitless efforts to enrich fetal cells in maternal plasma, Lo *et al.* reported the ability to correctly diagnose trisomy 21 in the fetus using quantitative analysis of cell-free fetal RNA in maternal blood[1]. And in 2008, Fan *et al.*[2] used shotgun sequencing of cell-free DNA in maternal blood to non-invasively diagnose fetal aneuploidy. Recently, at least two companies, using different technical approaches, have announced plans to introduce NIPD into health care: in February 2009, Lenetix, Inc. reported the launch of an Institutional Review Board-approved screening study on NIPD for Down's syndrome[3], and Sequenom, Inc. has revealed that NIPD will be available for clinical use in the fourth quarter of 2009 (REF. 4).

With regard to the clinical implementation of NIPD, three scenarios are possible: NIPD might replace current prenatal screening tests or be added to them; NIPD might be interposed between NIRS and invasive PND; or NIPD might replace invasive PND. Which of these options is followed will depend primarily on the technical accuracy of the NIPD strategies (in terms of sensitivity and specificity) but the third option seems to be the most attractive, especially in the long term.

What will the effects be of this third option, which sees invasive methods no longer being required for routine PND of aneuploidies? Depending on the NIPD method used three effects can be anticipated, which, especially in combination, might pose serious threats to the autonomous decision making of the pregnant woman. First, prenatal (cyto)genetic diagnosis will be achieved much earlier in pregnancy. From a medical perspective this is a positive development as termination-related risks for the mother are minimized at an earlier gestational age. But it is debatable whether such a shift would be ethically desirable, because early diagnosis could increase the proportion of pregnant women opting for termination, including for non-medical reasons (such as for 'unwanted' fetal sex). Second, uptake rates of NIPD might become as high as they are for NIRS strategies now, which in Germany, for example, could mean up to 85%[5]. Providing adequate pre-test counselling for such a high percentage of pregnant women would be challenging. Finally, the two-step approach of prenatal screening potentially followed by invasive diagnosis will be transformed into a one-step procedure. Although the abolishment of invasive PND has some positive aspects, as women who undergo prenatal testing would no longer have to risk fetal loss or their own health, the one-step diagnostic procedure might worsen current tendencies to neglect the reproductive autonomy of pregnant women. There will be only one contact between the pregnant woman and the physician to discuss the pros and cons of NIPD, which — if NIPD is implemented analogously to NIRS — might take place in a mass screening setting. It is therefore legitimate to ask whether this diagnostic 'offer' can be refused[6], and whether an autonomous decision-making process is still possible.

Reproductive autonomy, however, is of utmost importance in PND. This is because PND differs from other diagnostic procedures in medicine insofar as most of the conditions tested cannot be cured or substantially alleviated. In these cases, the mother's only option is to decide whether to accept the child's impairment or to terminate the pregnancy. Consequently, the main argument for offering prenatal genetic testing is to enhance the reproductive autonomy of the pregnant woman.

Studies have investigated the quality of informed consent in currently available multi-step procedures for PND. In a representative German survey, women were asked what prompted them to opt for PND: 25% stated that their physician wanted it; 36% thought that PND is an almost mandatory part of routine maternal care; and 16% had not given consent to the performed PND or could not remember giving consent[5]. Studies in many other countries have provided similar results. In France, a survey of 305 pregnant women — most of whom had undergone maternal serum screening — revealed that nearly half of the women were uninformed about the procedure[7]. There is already a need to improve the quality of informed consent for existing multi-step prenatal genetic examinations — a need that will be even more pressing if NIPD becomes a one-step procedure.

We argue that a new organizational setting for NIPD, which from the patient's point of view is clearly distinguishable from the setting for therapy-aimed prenatal care, could allow for a decision-making process to take place prior to NIPD and thus secure the reproductive autonomy of the pregnant woman. Women need to understand that there is a decision to be taken, that NIPD is not part of routine maternity care, and that the main aim of NIPD is to enable the pregnant woman to decide whether to live with an impaired child or to terminate the pregnancy. Therefore, a two-step approach with counselling in the first stage and decision-making and specific testing, where appropriate, in the second stage is essential for ensuring a value-consistent shared decision-making process that also takes into account the welfare of the unborn child.

Dagmar Schmitz, Christian Netzer‡ and Wolfram Henn§*

**Institute for History, Theory and Ethics in Medicine, RWTH Aachen University, Wendlingweg 2, 52074 Aachen, Germany.*

‡Institute of Human Genetics, University Hospital Köln, Kerpener Straße 34, 50931 Köln, Germany.

§Institute of Human Genetics, University Hospital, Saarland University, Building 68, 66421 Homburg/Saar, Germany.

Correspondence to D.S.
email: daschmitz@ukaachen.de

REFERENCES [1]Lo, Y. M. *et al.* Plasma placental RNA allelic ratio permits noninvasive prenatal chromosomal aneuploidy detection. *Nature Med.* **13**, 218–223 (2007) | [2]Fan, H. C., Blumenfeld, Y. J., Chitkara, U., Hudgins, L., & Quake, S. R. Noninvasive diagnosis of fetal aneuploidy by shotgun sequencing DNA from maternal blood. *Proc. Natl Acad. Sci. USA* **105**, 16266–16271 (2008) | [3]Bennani, H. Lenetix launches screening study of new Down syndrome test. *Reuters* [online], <http://www.reuters.com/article/pressRelease/idUS109286+05-Feb-2009+PRN20090205> (2009) | [4]UPDATE 2 — Sequenom delays Down Syndrome test; shares plunge. *Reuters* [online], http://uk.reuters.com/article/marketsNewsUS/idUKBNG44012820090429 (2009) | [5]Renner, I. (ed.) Experience of Pregnancy and Prenatal Diagnosis. *BZgA* [online], <http://www.bzga.de/?uid=25d093aacb9296ea646b087b68c27996&id=medien&sid=88&idx=1496> (2006) | [6]Clarke, A. Is non-directive genetic counselling possible? *Lancet* **338**, 998–1001 (1991) | [7]Favre, R. *et al.* How important is consent in maternal serum screening for Down syndrome in France? Information and consent evaluation in maternal serum screening for Down syndrome: a French study. *Prenat. Diagn.* **27**, 197–205 (2007)
FURTHER READING Wright, C. Cell-free fetal nucleic acids for non-invasive prenatal diagnosis. Report of the UK expert working group. *PHG Foundation* [online], <http://www.phgfoundation.org/download/ffdna/ffDNA_report.pdf> (2009)