Non-Invasive Prenatal Testing: Ethics and Policy Considerations

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Abstract

New technologies analyzing fetal DNA in maternal blood have led to the wide commercial availability of non-invasive prenatal testing (NIPT). We present here for clinicians the ethical and policy issues related to an emerging practice option. Although NIPT presents opportunities for pregnant women, particularly women who are at increased risk of having a baby with an abnormality or who are otherwise likely to access invasive prenatal testing, NIPT brings significant ethics and policy challenges. The ethical issues include multiple aspects of informed decision-making, such as access to counselling about the possible results of the test in advance of making a decision about participation in NIPT. Policy considerations include issues related to offering and promoting a privately available medical strategy in publicly funded institutions. Ethics and policy considerations merge in NIPT with regard to sex selection and support for persons living with disabilities.

Résumé

Les nouvelles techniques qui font appel à l'analyse de l'ADN fœtal dans le sang maternel ont mené à l'élargissement de la disponibilité commerciale du dépistage prénatal non effractif (DPNE). Nous présentons ici, à l'intention des cliniciens, les questions d'éthique et de politique qui sont associées à une option de pratique émergente. Bien que le DPNE offre des possibilités aux femmes enceintes (et particulièrement aux femmes qui sont exposées à des risques accrus de donner naissance à un enfant présentant une anomalie ou qui sont autrement susceptibles d'avoir recours au dépistage prénatal effractif), il donne lieu à des défis considérables en matière d'éthique et de politique. Les multiples aspects de la prise d'une décision éclairée (comme l'accès à des services de counseling au sujet des résultats possibles du test avant la prise d'une décision quant à la participation au DPNE) font partie des enjeux éthiques. Parmi les considérations en matière de politique, on trouve les questions liées à l'offre et à la promotion, au sein d'établissements subventionnés par l'État, d'une stratégie médicale offerte au privé. Les considérations en matière d'éthique et de politique s'entremêlent dans le cas du DPNE, pour ce qui est des questions relevant de la sélection du sexe et de l'offre d'un soutien aux personnes qui vivent avec des incapacités.

Key Words: Non-invasive prenatal testing, cell free fetal DNA, ethics, policy, prenatal diagnosis, prenatal screening

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INTRODUCTION

Recent advances in the detection and analysis of fetal DNA in maternal blood have led to the commercial availability of a new type of prenatal screening known as non-invasive prenatal testing.[1,2] NIPT promises the detection of a number of genetic and chromosomal conditions in the first trimester of pregnancy, obviating the risk of miscarriage that accompanies invasive prenatal diagnostic procedures such as amniocentesis or chorionic villus sampling.[1–3] While NIPT is not generally publicly funded in Canada, it is readily available to patients through a number of avenues, including placing information pamphlets and test kits in health care settings such as obstetrical units in hospitals and private clinics. NIPT has been shown to have a high negative predictive value, and it is plausible that Canadian jurisdictions may choose to provide public funding for NIPT in the future.[4–6]

NIPT has been recommended by the Society of Obstetricians and Gynaecologists of Canada[7] and professional bodies in several other countries[8–11] as a second level contingent screening test for women at risk for trisomy 13, 18, and 21, followed by amniocentesis to confirm positive tests. Scientists and professional bodies have clearly stated that while NIPT is significantly more accurate than existing screening methods, it is not sufficiently sensitive or specific to be considered a diagnostic test.[12,13] NIPT

has also been proposed as a replacement for a first level screening test in both high and average risk populations and as a diagnostic test of single gene disorders.[11,14,15] We provide here an overview of the science, health policy, and ethical implications that clinicians will want to understand regarding a new technology that they are increasingly being requested to engage with by patients and manufacturers.

CLINICAL SCIENCE

Non-invasive prenatal testing is a new type of prenatal screening test for genetic and chromosomal conditions. It is typically performed by measuring cell-free fetal DNA in maternal plasma, allowing the examination of fetal genetic material in a sample of maternal blood. Most of the current research and clinical application focuses on the use of NIPT for the detection of aneuploidy, in particular trisomies 13, 18, and 21, as NIPT offers a higher detection rate and lower false-positive rate than current screening modalities such as first trimester screening and integrated prenatal screening (Table).[13,16–29] Clinical research has suggested a wide variety of other potential uses for NIPT, with varying degrees of evidence to support the clinical effectiveness of these uses. There are clinical trial results supporting the use of NIPT for the detection of fetal RhD status,[30–32] selected gestational conditions (e.g., restricted growth),[31,33–35] and fetal sex determination.[31,36] Preliminary studies suggest that it has promise for detecting autosomal dominant paternally inherited disorders (e.g., Huntington disease),[31] conditions arising from a de novo mutation (e.g., achondroplasia),[37,38] and recessive conditions when parents carry different mutations (e.g., cystic fibrosis),[31,39–41] but large clinical trials have yet to be conducted for these uses. Applications in earlier stages of development include testing for recessive conditions when parents carry the same mutation (e.g., β-thalassemia).[42] Two teams have now sequenced an entire fetal genome, meaning that in the future any genetic condition might be identified by NIPT.[43,44]

Since 2011, more than 10 independent large-scale clinical trials have been published assessing the use of NIPT to detect trisomies 13, 18, and 21, with many additional studies currently underway.[19,28,45–58] Most trials used a population of women considered at high risk for trisomy; the results were consistent, with NIPT detection rates of more than 98% to 99%, and false-positive rates of less than 0.3%, for the detection of trisomy 21.[13,18–20,28] The cffDNA detection rate for trisomy 18 is 97% to 100%, with a false-positive rate of 0.07% to 0.8%.[13,18,19,28] These results suggest that NIPT is superior to existing prenatal screening modalities for trisomy testing in high risk populations (Table). Investigations are currently under way to assess the use of NIPT in average-risk populations.[52,53] The largest study published thus far of average-risk women who underwent routine prenatal screening for aneuploidies reported a detection rate of 100% and a false-positive rate of 0.1% for NIPT.[12] These authors concluded that NIPT is applicable to the general population, in which the prevalence of aneuploidy is much lower.[12] Studies in smaller average-risk populations have reported very similar results.[15]

Most commonly, NIPT measures cell-free fetal DNA in maternal blood. Cell-free nucleic acids, discovered in 1947, arise from degraded nuclear DNA from hematopoietic cells that have undergone programmed cell death.[47] Lo and colleagues first presented the diagnostic use of cell-free DNA in pregnancy, through the detection of cffDNA fragments of fetal Y-chromosomes in the blood of women carrying male fetuses.[59] NIPT techniques other than cffDNA measurement are currently being studied, but are still under development and have not been tested in clinical populations. Developing techniques for NIPT include placental microRNA analysis. Placental microRNAs are small single-stranded noncoding RNA molecules present in the maternal plasma. These molecules are being investigated for their potential to act as pregnancy-specific biomarkers for preeclampsia and fetal growth restriction.[18] Another potential avenue for NIPT is the analysis of genes known to be expressed in the extravillous trophoblasts that have been identified as potential fetal cell markers in maternal blood. Investigations into this possibility have examined the potential of using mutant enrichment amplification protocols or extremely sensitive microarray substrates to identify mutated fetal alleles in maternal plasma.[60–62] While cffDNA is the material most commonly measured in clinical applications of NIPT, this may change in the future. In this discussion, we use "NIPT" to refer to fetal genetic testing via maternal plasma, no matter what type or how fetal genetic material is analyzed.

CffDNA is primarily derived from the placenta, the fetal hematopoietic system, and the fetus itself.[63] The circulating cffDNA has a turnover half-life of 16.3 minutes (4 to 30 minutes), and is continuously released into the maternal circulation, providing a real-time snapshot of fetal DNA

ABBREVIATIONS

cffDNA	cell-free fetal DNA
CVS	chorionic villus sampling
FTS	first trimester screen
IPS	integrated prenatal screen
NIPT	non-invasive prenatal testing

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