Non-invasive prenatal diagnosis for aneuploidy: toward an integral ethical assessment

Antina de Jong1,*, Wybo J. Dondorp2, Suzanna G.M. Frints3, Christine E.M. de Die-Smulders3, and Guido M.W.R. de Wert2

1Faculty of Health, Medicine & Life Sciences, Department of Health, Ethics & Society, and GROW, School for Oncology and Developmental Biology, Maastricht University, PO Box 616, 6200 MD Maastricht, The Netherlands/Centre for Society and Genomics, Nijmegen, The Netherlands 2Faculty of Health, Medicine & Life Sciences, Department of Health, Ethics & Society, and GROW, School for Oncology and Developmental Biology, CAPHRI, School for Public Health and Primary Care, Maastricht University, PO Box 616, 6200 MD, Maastricht, The Netherlands 3Department of Clinical Genetics, and GROW, School for Oncology and Developmental Biology, Maastricht University Medical Center, Maastricht University, PO Box 5800, 6202 Maastricht, AZ, The Netherlands

*Correspondence address. Tel: +31-43-3882145; Fax: +31-43-3670932; E-mail: at.dejong@maastrichtuniversity.nl

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ABSTRACT: The great promise of the pending introduction of non-invasive prenatal diagnosis (NIPD) for trisomy 21 (18 and 13) is that it enables one-step, early and safe testing for these abnormalities. The ethical debate so far has been limited to possible drawbacks of routine access to this type of testing: normalization of testing and abortion and adverse effects on autonomous decision-making. We address the ethical implications of the fact that routine NIPD affects the scope and strategy of current prenatal screening cascades. A decision is needed whether complementary (invasive) testing remains in place in order to avoid a loss of information as compared with current practice. If so, the supposed advantages of NIPD may be less significant than generally assumed. Accumulation of tests challenges informed consent and proportionality. Therefore, an ethical evaluation of the implications of NIPD for the prenatal screening strategy as a whole is needed.

Key words: ethics / cell-free fetal DNA / RNA / non-invasive prenatal diagnosis / aneuploidy / prenatal screening

Introduction

Screening for aneuploidies in the developed, primarily Western, world generally consists of two stages: (i) a risk assessment for trisomies 21 (Down’s syndrome), 18 (Edward’s syndrome) and 13 (Patau’s syndrome), based on the combination of maternal serum testing, fetal nuchal translucency (NT) measurement and/or maternal age; (ii) a diagnostic follow-up test in case of an increased risk, performed on material obtained through invasive procedures: amniocentesis (AC) or chorionic villus sampling (CVS) (Bui and Meiner, 2008; Saller and Canick, 2008). Trials with non-invasive prenatal diagnosis (NIPD) using cell-free fetal DNA and RNA in maternal blood are currently performed worldwide and focus primarily on NIPD for trisomy 21, although trisomies 18 and 13 may follow (Chiu et al., 2011; Ehrich et al., 2011; Papageorgiou et al., 2011). As a result, the current two-step testing may be replaced by a one-step diagnostic test targeted at these specific abnormalities (Go et al., 2011).

Although there has been some ethical debate about this prospect, the discussion has concentrated mainly on NIPD itself and on possible implications of routine access to one-step, early and risk-free prenatal diagnosis. The issues discussed include the perceived risk of normalization of testing and abortion, the fact that non-medical applications such as testing for fetal sex and paternity will become more easily available, and a possible negative effect on autonomous decision-making (Benn and Chapman, 2009; Schmitz et al., 2009).

Although these issues need to be addressed as well, we assert that the expected introduction of routine NIPD testing for trisomy 21 (and 18 and 13) urgently calls for ethical reflection on the overall scope and strategy of prenatal screening. A decision is needed whether complementary (invasive) testing remains in place in order to avoid a loss of information as compared with current practice. We discuss the practical and ethical implications of routine NIPD testing either for trisomy 21 only or for trisomies 21, 18 and 13.

Timing of NIPD-testing

Fetal DNA can be detected from 5 weeks of gestation and reliable NIPD may be feasible from 7 to 9 weeks of gestation (Wright and Burton, 2009). Therefore, it has been assumed in the literature that NIPD will take place rather early in the first trimester. This would...
have the advantage that test results are received early, leaving more
time for decision-making. Furthermore, possible termination of preg-
nancy in case of an adverse test result at this stage of pregnancy
can be emotionally less burdensome than in the current approach,
where diagnostic results are available after 11–14 weeks (CVS) or
16–20 weeks (AC) of gestation. Early testing is favourable from an
ethical point of view as well. According to the dominant account,
the moral status of the embryo/fetus is relatively low at the start
and increases with further stages of development (the gradualist
view) (de Wert, 1999). This notion of a gradually increasing moral
status implies that selective abortion early in pregnancy is morally
different from termination of affected pregnancies later in the first tri-
quarter or in the second trimester.

However, a serious disadvantage of early NIPD is that it may
increase the burden of choice for women, since abnormal fetuses
will be identified that would have miscarried spontaneously later in
pregnancy (Wright, 2009). Moreover, the timing of an NIPD test
offer will depend on how NIPD can best be integrated in the overall
screening strategy.

**Complementary testing: trisomies 18, 13 and NT measurement?**

A possible scenario is that NIPD will initially be introduced for diag-
nosing trisomy 21 only and replace current two-step testing for this
abnormality. This would maximize the benefits of NIPD at an early
stage of embryo development: the drawbacks of false-positive and
false-negative results generated by current risk assessment and the
miscarriage risk attached to current invasive diagnostic methods
would thereby be avoided (de Jong et al., 2010; Go et al., 2011). A
recent study by Susman et al. (2010) suggests that this procedure
would lead to 84% fewer invasive procedures, while diagnosing an
additional 7% of trisomy 21 cases (corresponding with the false nega-
tives in current risk assessment). However, this procedure would also
imply that about 50% of chromosomal abnormalities other than
trisomy 21, including trisomies 18 and 13, would be missed even
when follow-up detection by the mid-trimester fetal anomaly scan is
included (Benn and Chapman, 2010; Susman et al., 2010). So to
prevent testing being less informative than current practice, a solution
would be to leave risk assessment and invasive diagnostic testing in
place as a complementary screening trajectory for trisomies 18 and
13. Of course, the need for this does not arise as soon as these triso-
 mies can be included in the NIPD array.

Abolishing current risk assessment raises a similar question with
regard to NT measurement. Although offered as part of risk assess-
ment for common aneuploidies, this procedure may concurrently
lead to the early identification of pregnancies at a high risk of both
chromosomal and non-chromosomal disorders, such as congenital
heart defects and Mendelian disorders such as Noonan syndrome
(Sonek, 2007; Bilardo et al., 2010). Assuming that this information
has added value in terms of reproductive options, the question
arises what to do with NT measurement when introducing NIPD
for the three trisomies. Should NT measurement be left in place as
a separate screening test, complementary to NIPD? That would
have the benefit of avoiding a reduction of the scope of prenatal
screening and of the reproductive options that it is meant to
provide. It would then only be logical to also offer this separate NT
measurement to women who are currently not having risk assessment
testing for common aneuploidies or who do not opt for NIPD in the
future. However, separate NT testing must also be in line with the
requirements of proportionality and informed consent.

**Proportionality and informed consent**

First, offering complementary testing comes at the price of confronting
women with additional test offers shortly after NIPD has been per-
formed. This may add to the burden of testing, because screening
will increasingly become fragmented, leading to a series of moments of
choice for women and possibly to a prolonged period of anxiety.
To avoid this possible drawback of successive testing, NIPD and
complementary tests could be offered simultaneously at weeks
11–12 of gestation, which is the usual period for risk assessment
and gives the best performance for the NT measurement (Bilardo
et al., 2010). From a logistic point of view, such a combination
would also be advantageous. However, it may be challenging to ade-
quately inform women about those simultaneous, but very different
test offers. A targeted diagnostic test for trisomy 21, a risk assessment
test for trisomies 18 and 13, and NT measurement for a broad range
of abnormalities are very dissimilar in kind and scope. They also differ
with regard to the kind of test outcomes (risk versus diagnosis) and
decision-making consequences (follow-up testing versus termina-
tion/continuation of pregnancy). Furthermore, this 3-fold combi-
nation of tests would diminish the advantages of a ‘stand-alone’
NIPD as the moment of testing would be delayed. In contrast to
the promise of more simple counselling as a result of the conceptually
easy character of NIPD (Wright, 2009), counselling would in fact
become more complicated because of the heterogeneity of this com-
pound test offer. Although NIPD would still have the advantage of
being safe to perform, the other supposed advantages (early, easy)
would, in this scheme, be less significant than generally assumed.

Second, since prenatal screening also requires the just use of scarce
financial resources (distributive justice), the detection/cost ratio of
NIPD for trisomy 21 or for trisomies 21, 18 and 13 with or without
specific complementary testing has to be considered as well. A cost-
effectiveness analysis should take into account all the relevant
aspects of the test options, including costs for counselling, for
follow-up testing and for the lifetime provision of care for people
with abnormalities undetected by a stand-alone NIPD.

Third, the advantages of possible additional invasive testing for
trisomies 18 and 13 may not evidently outweigh the disadvantages
for participants, because its very limited target would negatively
affect the detection/miscarriage ratio (Health Council of the Nether-
lands, 2001).

Fourth, separate NT measurement would amount to turning current ‘incidental’ findings into a screening target and require that
informed consent be adapted accordingly. Presently, the possibility
of those ‘incidental’ (non-aneuploidy-related) findings is not always
included in pre-test information (Bilardo et al., 2010). As a conse-
quence, pregnant women may be confronted with findings that they
were not prepared for and that they might otherwise have indicated
that they did not want to receive (de Wert and Dondorp, 2006). It
is evident that pre-test information will have to cover these findings should NT measurement become a separate test. But given that an enlarged NT (≥3.5 mm) may indicate a risk for a wide range of abnormalities, this will not be possible on the level of specific abnormalities. As a form of more ‘generic consent’ (Elias and Annas, 1994) seems unavoidable here, the challenge is to offer not too much but yet enough information to enable women’s informed decision-making with regard to this testing.

**Conclusion**

The general opinion is that NIPD holds great promise to enable prenatal diagnostic testing earlier in pregnancy and in a one-step, easy and safe manner. However, as our ethical considerations of the pending introduction of NIPD for trisomy 21 (and then 18 and 13) suggest these expectations may well reflect a one-sided view that overlooks the broader context of prenatal screening in which NIPD has to be implemented. A decision is needed whether only NIPD or NIPD and complementary testing will be offered. This requires a proactive ethical evaluation to find out which approach is most in line with the principles of respect for autonomy and of beneficence, underlying the normative framework for prenatal screening.

**Authors’ roles**

The first draft of this article was conceived by A.J., W.D. and G.W. C.D. and S.F. had a role in supplying further clinical information and critical revision.

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