Deans, Z., & Newson, A. J. (2012). Ethical considerations for choosing between possible models for using NIPD for aneuploidy detection. Journal of Medical Ethics, 38(10), 614-618. DOI: 10.1136/medethics-2011-100180

Ethical considerations for choosing between possible models for using NIPD for aneuploidy detection

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Key words: Genetic Screening/Testing, Genetic Counselling/Prenatal Diagnosis; ethics; aneuploidy; Down syndrome.

Word count: 3,860

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ABSTRACT

Recent scientific advances mean the widespread introduction of non-invasive prenatal diagnosis (NIPD) for chromosomal aneuploidies may be close at hand, raising the question of how NIPD should be introduced as part of antenatal care pathways for pregnant women. In this paper we examine the ethical implications of three hypothetical models for using NIPD for aneuploidy in state-funded healthcare systems and assess which model is ethically preferable. In comparing the models we consider their respective timings; how each model would fit with current screening and diagnostic tests offered to pregnant women; the implications of offering NIPD at different stages of pregnancy; and the potential for each model to support reproductive autonomy and informed decision-making. We conclude by favouring a model that would be offered at 11-13 weeks gestation, alongside existing combined screening, provided that this is accompanied by measures to maximise informed decision-making, for example provision of adequate pre- and post-test counselling.

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INTRODUCTION

Non-invasive prenatal diagnosis (NIPD) is a type of prenatal testing that promises early and potentially definitive results relating to aneuploidy and genetic conditions in pregnancy by testing fetal DNA present in maternal blood.[1] The test involves analysis of cell free fetal DNA (cffDNA) present in maternal blood, thus avoiding the risk of miscarriage that accompanies current invasive methods of prenatal diagnosis. There is particular interest in using NIPD to detect aneuploidies such as Down syndrome (Trisomy 21) or the rarer conditions Patau syndrome (Trisomy 13) and Edwards syndrome (Trisomy 18). As prenatal testing using non-invasive methods develops further, the question of how it should be implemented in clinical practice and antenatal screening is surfacing.[2-4]

NIPD technology is developing quickly, but recent validation studies have shown that it is not yet fully accurate, only highly predictive, and that there is still a low false positive rate.[5-7] In view of this, the results from NIPD should be verified by invasive testing, and so for the time being it can only be regarded as an advanced screening test.[8] For the purposes of this paper we are assuming that NIPD is 100% accurate (with no false positives and no false negatives), and that from 10 weeks gestation it will be capable of diagnosing Trisomies 13, 18 and 21.

Debate is ongoing as to how NIPD for aneuploidy should be implemented.[9] In this paper we consider three hypothetical models for implementing NIPD for aneuploidy in the context

of a state-funded screening programme where combined screening is currently offered. Model One involves offering NIPD at around 10 weeks, accompanied by an ultrasound scan to date the pregnancy but does not include any other components of the combined screening test; Model Two involves offering NIPD at 11-13 weeks gestation alongside the combined screening test (in order to detect other conditions in addition to aneuploidies). Model Three involves offering NIPD, instead of invasive testing, to women in whom the combined test predicts a high risk of Down syndrome. The main practical differences between these models are in the timing, and how they would fit into the antenatal care pathway, as such they would significantly impact on how and in what context women would be offered NIPD.

We make a case for favouring Model Two, which varies from current practice by offering risk-free definitive information to all pregnant women, not just those whose fetuses are deemed to be at high risk of having a chromosomal abnormality. This model would mitigate concerns over inconvenient, extra ultrasounds and burdensome choices in Model One, and the false reassurance and limited access afforded by Model Three. However we also recognise the potential for Model Two to diminish informed decision-making through routinisation of prenatal testing subsequent to a possible loss of time to reflect. We suggest that these concerns could be overcome by well-implemented counselling and claim that the wider accessibility of definitive information to all pregnant women is important.[l]

[l] Financial costs are essential for determining the ethical acceptability any model, since state-funded healthcare budgets are limited and resources should be allocated fairly. However, an economic analysis is beyond the scope of this paper.

SCIENTIFIC AND CLINICAL ASPECTS OF NIPD

Many countries offer prenatal screening programmes for aneuploidy, most commonly during the second trimester, though increasingly in the first. For the purposes of this paper, we limit our discussion to offering NIPD within a state funded system where combined screening at 11-13 weeks followed by diagnostic invasive testing for pregnancies found to be at high-risk is currently offered. Combined screening incorporates the results of an ultrasound to measure nuchal translucency and a maternal blood test measuring biochemical markers to indicate the probability of the fetus being born with an aneuploidy. Women who receive a 'high risk' result are then offered invasive diagnostic testing, such as amniocentesis, which carries a small but significant risk of miscarriage (around 1%).[10]

One of the main advantages of NIPD is that it may be able to offer a definitive result without the miscarriage risk associated with current invasive testing. This offers a solution to the problem of women having to either settle for a probabilistic indication of aneuploidy, or putting their pregnancies at risk for definitive information. NIPD is based on the analysis of fragments of fetal DNA circulating in the pregnant woman's blood. One method of analysis involves detecting a higher amount of the chromosome of interest (such as 21, 18 or 13) in maternal blood through the use of massively parallel sequencing (also known as next generation sequencing). Research into NIPD for aneuploidies is ongoing and several large validation studies have been conducted using this sequencing approach.[II][5, 11] Indeed, NIPD is already commercially available in the United States,[12] but it should be noted that

[II] For example, positive predictive values for NIPD for Down syndrome are 98.6% for high-risk women. However full karytoping (visual examination of all chromosomes) remains the "gold standard" for aneuploidy diagnosis.[7]

this non-invasive test for aneuploidy is not yet considered to be fully diagnostic and a positive result must be confirmed by invasive testing.[8]

These developments are significant. Offering NIPD for aneuploidies may have important implications for the care of pregnant women and the choices they make. While current combined screening is safe, the initial set of results are probabilistic and require follow-up invasive testing for a definitive result. Invasive testing is, with the exception of rare technical problems, definitive but women face a small risk of miscarriage to determine whether her fetus has an aneuploidy. With NIPD, women could potentially choose to receive definitive information about aneuploidies earlier, without the risk of losing the pregnancy. Assuming there is good justification to introduce NIPD for detection of aneuploidies, an important question is how best to implement it in state-funded antenatal care pathways.

It is important to note that in the area of prenatal testing it is not only NIPD that is making rapid advances; other technologies are allowing the range of prenatal testing options to expand. Consequently other developments for NIPD and for prenatal testing in general may eventually supersede the models proposed here and challenge the ethical framework in which prenatal testing is based.[13]

POSSIBLE MODELS OF NIPD

Models for implementing NIPD for aneuploidy have already been suggested in the literature.[4] Here we formulate and discuss three hypothetical models. We recognise that how NIPD will be implemented depends on technological and economic considerations, but we have chosen these models because we believe them to be practically and clinically feasible in a state-funded antenatal care pathway. All are based on the assumption that

NIPD is 100% accurate, reliable from 10 weeks gestation and can only detect Trisomies 13, 18 and 21.

Model One: Instead of combined screening, NIPD would be offered to all pregnant women, regardless of age, and would be carried out following a dating scan at around 10 weeks gestation.

Model Two: NIPD would be offered to all pregnant women regardless of age and would be carried out at 11-13 weeks gestation alongside the current combined test to detect other conditions. Since we are assuming 100% accuracy for the purposes of this evaluation, there would be no need for further invasive tests for confirmation of Trisomies 13, 18, 21.

Model Three: Combined screening, which gives a probabilistic result, would still be carried out for chromosomal aneuploidies at 11-13 weeks gestation as it is now, and would be offered to all pregnant women regardless of age. For those women found to be at 'high risk' NIPD would be offered instead of invasive testing.

Model One

The most significant features of Model One are that the information about aneuploidies obtained through a screening programme would be definitive (rather than probabilistic, followed by invasive diagnosis, as with current testing), and would be received in the first trimester. This model would mean that every woman attending early enough for antenatal care (not just those deemed high risk) would be offered definitive information about whether her fetus had an aneuploidy. Furthermore, that information would be given earlier

in pregnancy. While early definitive information for all initially seems attractive, we suggest there are strong reasons why it might not be so good in practice.

i) Early, definitive results and informed decision-making

Under Model One, since women would receive definitive information earlier than if they underwent combined screening followed by invasive testing, they may in turn feel reassured earlier if the result is normal, and, if abnormal, they would either have more time to plan and prepare for raising a child with that condition or have more time to make a decision about ending the pregnancy.

The timing would also allow for earlier termination. For those who take a gradualist view of personhood and fetal rights, the moral implications of termination may be less troublesome at this earlier stage. For example, some religious groups regard termination as more acceptable before an early and specified gestational age. Earlier termination would also mean that the procedure could be carried out before the pregnancy became obvious to others. Evidence from women using NIPD for clinically indicated fetal sex determination from seven weeks gestation showed that they valued testing prior to the signs of pregnancy becoming obvious.[14] Further, some research shows that for some the termination procedure itself may be less physically and psychologically burdensome at this earlier stage,[15] though it should be noted that there is also evidence that this is not the case.[16]

Despite the advantages of earlier testing, there are several downsides to consider. There is evidence that some women would rather delay medical testing in pregnancy because they feel overloaded with information in the first trimester at a time when they already undergo

numerous tests, and would like to enjoy the 'honeymoon' period of the first few weeks of pregnancy and delay the onset of a period of worrying.[17]

For some time, there have also been concerns that prenatal screening has become routinised, and that in reality the choice to undergo testing is not as informed or freely made as it could be.[18] We make the assumption that a key motivation for introducing NIPD is that, as a prenatal screening and diagnostic technology, it will support reproductive autonomy,[19] and use this as a principle for differentiating between the models. We interpret reproductive autonomy as the power of pregnant women or couples to make free and informed decisions relating to reproduction, including pregnancy management. This requires that women have the opportunity and support to make fully informed decisions about their reproduction, rather than simply being allowed to make decisions without interference. We assume that reproductive autonomy can be expressed through informed decision-making in prenatal care and thus this is an important ethical discriminator between the clinical models. We do, however, recognise that the capacity for prenatal testing to promote reproductive autonomy has been challenged,[20] and that fully informed decision-making in prenatal diagnosis is difficult to achieve in practice.[21, 22] Existing psychological, social and institutional barriers will remain for each model of NIPD we discuss here. Even so, some models of care will be better than others at supporting informed decision-making.

Empirical evidence indicates that an erosion of informed decision-making is a real possibility with the introduction of NIPD,[23] and the challenge for each model is to mitigate this as much as possible. In Model One (and Two, which we will come to) there would be no initial risk assessment, and therefore the process of undergoing testing for aneuploidy would be

quicker. Since definitive results are derived from a single blood test, the ease of the test lends itself to routinisation. While the simple nature of NIPD is part of its appeal, it is disproportionate to the potential significance of the results. Routinely offering a test that gives definitive information at this point may mean women find themselves with information for which they had not been fully prepared. As Hall *et al* suggest in the context of Down syndrome screening:

> …a subsequent invasive diagnosis (as a separate test following a probabilistic result) currently provides another opportunity for reflection in the context of providing consent for that procedure (namely screening for aneuploidy). By potentially replacing the existing multi-step Down syndrome screening process with a single early highly predictive blood test, the use of cffDNA technology may reduce opportunities for exercising informed choice.[24]

Thus, the decision whether to undergo NIPD is arguably of greater magnitude than the decision to undergo combined screening. The need to build in time for reflection, deliberation, decision-making and thinking 'space'[25] to ensure informed decision-making for such a simple yet momentous test has been emphasised elsewhere in the literature.[26, 27]

These problems could perhaps be avoided by introducing a separate appointment to facilitate informed decision-making about NIPD prior to it taking place and ensuring there is appropriate counselling relating to the definitive nature of the results, but providing NIPD at 10 weeks leaves very little time for adequate counselling and reflection for such a significant test.

ii) Loss of information

Research has shown that combined screening can detect increased risk for other conditions, such as pre-eclampsia[28], intrauterine growth restriction,[29] and fetal abnormalities[30]. Because combined screening would not be offered under Model One, these other conditions identified by the screening blood test or ultrasound to measure nuchal translucency would not be detected. This could be addressed by modifying Model One to include screening for other conditions later in pregnancy, though for the reasons we outline below it would be problematic to include additional scanning and appointments.

iii) Early ultrasound

The dating scan in Model One is necessary to confirm gestation, viability and number of fetuses present. An earlier scan could not fully replace the usual 11-13 week scan. In addition, a scan at around 10 weeks would mean scanning pregnant women who may otherwise miscarry, since the first trimester is when pregnancy is most vulnerable to loss. The observed rate of natural miscarriage within the first twelve weeks of any pregnancy is 20%[31] and fetuses with chromosomal anomalies make up a large proportion of these spontaneous losses of pregnancy.[32]

iv) Vulnerable pregnancy and responsibility

Given the high rate of early miscarriage, Model One would present some women with difficult choices unnecessarily. The high rate of miscarriage in the first trimester means that offering NIPD at 10 weeks would cause some women to face a decision about termination

that they would otherwise not have had to make. While many of the differences between termination and spontaneous miscarriage relate to the process and associated medical implications, there are also important psychological and moral differences. With abortion, the woman has *chosen* to terminate her pregnancy; with miscarriage it has *happened to her*.[III] Thus establishing as a standard practice the offer of NIPD at this early stage, when a fetus with a chromosomal aneuploidy may miscarry naturally, could introduce a burden of choice,[4] and responsibility that may ultimately be more burdensome than empowering.

Model Two

The most notable feature of Model Two is that all women would be offered risk-free information that is definitive. Compared with Model One, in Model Two NIPD would be performed later and would be accompanied by screening for other conditions. This would mean women would be given fuller information about their pregnancy.

Under this model, only one standard ultrasound would take place, and this would be after the most vulnerable stage of pregnancy had passed, so the likelihood of women making a decision about whether to terminate a pregnancy that would otherwise miscarry naturally would be reduced.

As with the first model, Model Two could be subject to concerns about routinisation compromising informed decision-making. Although this is a problem for all prenatal screening, the ease of testing in NIPD could exacerbate the issue. One possible solution to

[III] Even in the case of spontaneous miscarriage a woman may feel responsible, culpable and guilty, perhaps because of the real or perceived possibility that her own behaviour or health played a part in causing the miscarriage.[32]

this would be to impose strict procedures for promoting informed consent that would encourage informed decision-making as much as possible. This would be easier under Model Two than Model One given that testing takes place later, offering women more 'thinking space' between the first appointment with a healthcare professional and the delivery of NIPD. Women would have had more opportunity to think about the impact of abnormal findings, as long as information about NIPD was given to and discussed with them at an early antenatal appointment. With good counselling procedures in place women and couples offered NIPD under Model Two could feasibly have the time to think about whether they would like to receive a definitive result as to the presence of an aneuploidy.

Model Three

The most notable feature of Model Three is that diagnosis of aneuploidy would be offered in two clinical stages: a probabilistic risk analysis (combined screening as is carried out currently) followed by an offer of definitive NIPD for those who receive a high risk result. It differs from current practice by removing the risk of miscarriage associated with current invasive diagnostic tests.

Model Three presents a step-wise process in the diagnosis of aneuploidy so that couples would first have the chance to reflect on a risk-based result before progressing to receive definitive information. This may potentially reduce the chances of women agreeing to definitive diagnosis without making a fully informed decision and suddenly finding themselves with information about which they had not given enough thought. This model

could reduce the problems around informed decision-making discussed above and maximise the chances that women were as aware as possible of the implications of a definitive test.

However, Model Three strikes us as an unnecessarily cautious approach, because instigating this level of prudency would require a trade-off with the lost opportunity for definitive information for those whose pregnancies were deemed to be low risk. Combined screening does not detect all cases of aneuploidy (for example the UK national benchmark detection rate for screening of Down syndrome is 90%).[34] When compared with Model Two, which includes time for reflection and offers definitive diagnosis to all pregnant women, this model that maintains a higher likelihood of false reassurance for one group of women.[IV] If reproductive autonomy is important, we would need good reason not to improve the chances of all pregnant women having the opportunity to receive definitive information about aneuploidy in pregnancy.

In addition, definitive information potentially serves, through any subsequent choice to terminate the pregnancy, to prevent the existence of a child who may suffer greatly, as might be the case with, for example, Patau and Edwards syndrome.[35] Model Three would be less capable than models One and Two of protecting a potential child from this fate.

COMPARING THE MODELS

Of the models we have discussed, Model One is most different to current screening programmes because all women would be offered a definitive test (not just those women deemed 'high risk' after combined screening); it would be carried out earlier, it would not

[IV] With thanks to Anita de Jong for the point about the problem with false reassurance in Model Three.

include an initial risk assessment, and it would not detect risk for as wide a range of conditions. Earlier testing has the attractions of reassurance or decision-making about continuing or terminating a pregnancy at an earlier gestational age.

An increase choice in and control for women, would present an unnecessary burden for many women because they will make a decision to terminate a pregnancy that would miscarry naturally. This is a significant concern, and the advantages of earlier testing are quickly outweighed when this is considered alongside the other draw-backs of Model One, namely the loss of information regarding other pregnancy complications and risk of exacerbating routinisation, and when compared with Model Two.

Model Three is most closely aligned with current practice. NIPD would be offered after combined screening and would replace the invasive methods currently offered to pregnant women when the screening result indicated a high risk. One of the most compelling aspects of Model Three is its two-stage structure. Giving women a risk result first builds in time for reflection and may be more conducive to ensuring women make informed decisions. However, because under Model Three NIPD would only be offered to those women assessed as high risk, many others would miss out on receiving definitive information about whether their fetus had an aneuploidy. In addition, there remains the possibility of women receiving falsely reassuring results at the screening stage. We therefore regard it as a mistake to include a risk assessment purely as an intermediary stage if good counselling could serve the purpose of preparing woman and couples for making an informed decision about definitive testing, as we believe could occur under Model Two. If reproductive autonomy is important (and it seems reasonable to suggest that it is), then we would need

good reason not to maximise the chances to achieve it for all pregnant women by offering Model Two.

Model Two would bring forward the time at which women would receive a definitive result, but testing would not be carried out at the most vulnerable period of pregnancy when many women would find themselves faced with an unnecessary burden of choice. Under Model Two all women would be offered definitive testing through NIPD. This would mean offering reassurance to all women whose fetuses did not have an aneuploidy. It would also mean that those women whose fetuses have an aneuploidy (but who would have been deemed 'low risk' with combined screening) could receive a definitive positive result.

There is, however, a remaining concern that, unless it is implemented with careful thought for the decision-making process, adopting Model Two may see a routinisation of NIPD and a loss of 'thinking space' for women to consider whether they would like to receive definitive information. Mechanisms would need to be in place to ensure that women were fully aware of the nature of the conditions covered by the testing process and that they had enough time to reflect on the offer of the test and how it sat with their own values. The most obvious ways to do this would be to increase counselling provision, to provide clear and helpful information, and to ensure that women were given sufficient time between being offered the test and accepting it. The nature of counselling would have to change with the move to definitive information; women and couples would need to think more about the condition rather than the nature of probabilities that the test will give rise to.

CONCLUSION

If it does become possible to use NIPD from as early as 10 weeks gestation for aneuploidy detection with an accuracy of near 100%, policy-makers will have to consider whether and how best to implement it. Ultimately, implementation will depend on the clinical possibilities and will necessitate balancing the practicalities of antenatal screening programmes, financial constraints and ethical considerations. Our reasons for favouring Model Two (offering NIPD with combined screening to replace current combined screening and follow-up testing) are that it gives choice to the greatest number of women, without introducing problems associated with very early testing and loss of potential benefits of combined screening. This would allow each pregnant woman the opportunity to find out whether her baby has one of the major trisomies. To safeguard against routinisation and erosion of informed decision-making Model Two would need to be underpinned with sound counselling and time for reflection.

As well as a comprehensive analysis of the necessary resources to implement Model Two, what is currently missing from this discussion is an indication of the preferences of pregnant women and couples. As an interim measure and to inform future practice, it may be worth offering women the choice between combined screening and NIPD (Model Two) and combined screening with follow-up NIPD for high-risk pregnancies (Model Three) and audit the choices they make.

Acknowledgements

The authors would like to thank members of the RAPID team, especially Mel Hill, and anonymous referees for helpful comments on earlier drafts of this paper. This paper presents independent research commissioned by the NIHR under the Programme Grants for Applied Research programme (the 'RAPID' project RP-PG-0707-10107). The views expressed in this article are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health.

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