NUFFIELD COUNCIL ON BIOETHICS

BACKGROUND PAPER

Non-Invasive Prenatal Testing (NIPT)

Identifying key clinical, ethical, social, legal and policy issues

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Note
The author was commissioned by the Nuffield Council on Bioethics to write this paper in order to inform the Council's discussions about possible future work on this topic. The paper is intended to provide an overview of key clinical, ethical, social, legal and policy issues, but is not intended to offer any conclusions or recommendations regarding future policy and practice. Any views expressed in the paper are the author's own and not those of the Nuffield Council on Bioethics.

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Summary

1 This paper presents the current clinical status of Non-Invasive Prenatal Testing (NIPT) and its implementation. It presents key points from guidelines currently provided by professional societies. It then discusses key ethical, social and legal implications of NIPT and raises questions that the Nuffield Council may wish to consider to promote an ethically sound and socially responsible future implementation.

Context

2 Since its introduction, prenatal testing (PT) has been raising sensitive ethical and social issues. At an individual level, it touches on one of the most significant, intimate and challenging decisions in the life of a woman or a couple: what child to bring into the world. While some may choose to test in order to prepare for the arrival of a child with special needs, for some the decision to test is linked to the possibility of terminating a pregnancy based on an undesired result, creating links between PT and the abortion debate. At a societal level, PT raises a host of difficult issues and policy decisions: which tests should be allowed, offered or even publicly funded, based on what criteria, and for whom. These decisions reflect a societal assessment of when it may be justified to screen out certain conditions or disabilities. They can thus be seen as an implicit expression of what is - or should be - considered 'normal' and what constitutes an acceptable quality of life in a given society, creating links between PT and disability rights and even eugenic concerns.

3 Despite these challenging and sensitive issues, the social acceptability of PT remains high and it has become an integral part of prenatal care in most Western countries.[2] This is due in large part to the tremendous benefits it offers in promoting reproductive autonomy and in enabling the reduction of the incidence of certain hereditary conditions, an important public health benefit.[3]

4 Since 2011, NIPT is gradually being introduced into clinical practice around the world. By allowing genetic testing of fetal DNA through a maternal blood test, it eliminates the risk of miscarriage associated with current invasive procedures. By offering early and safe access to genetic information, it puts some of the challenges associated with PT in a new context and intensifies others.

State of the art: the current clinical status of NIPT

5 In recent decades, prenatal testing involves screening (combining blood tests and ultrasound for a risk estimate) followed by invasive diagnostic testing offered to women whose pregnancies are identified as being at high-risk for fetal abnormalities (CVS[4] typically at 10-12 weeks or amniocentesis[5] typically at 15-18 weeks). A particular focus of screening programmes is trisomy 21 (Down syndrome) that is a

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2 Press N, Browner CH. (1997) "Why women say yes to prenatal diagnosis." *Social Science and Medicine* 45(7): 979-89.

3 Wilkinson S. (2015). "Prenatal screening, reproductive choice, and public health." *Bioethics*, 29(1): 26-35.

4 Chorionic villus sampling tests placental cells.

5 Amniocentesis tests a small sample of the amniotic fluid that surrounds the fetus in the uterus.

prevalent condition (about 1 in 800 in Western countries), but they often include other aneuploidies (conditions stemming from an abnormal number of chromosomes), such as trisomy 18 (Edwards syndrome) and 13 (Patau syndrome), as well as other conditions.

6 The disadvantage of traditional screening approaches is their relatively low accuracy (for trisomy 21 detection rate is 82-95% depending on the test, and false positive rate is about 5%[6]), and the drawback of invasive diagnostic tests is about 1% associated risk of miscarriage. It was thus clear that a breakthrough in prenatal testing would require developing a non-invasive yet accurate test that would not pose any risk to the fetus, and ideally would also provide results in the first trimester of the pregnancy.

7 Initial research efforts that focused on identification of fetal cells in maternal blood were unsuccessful.[7] The hoped for breakthrough came in 1997 with the discovery by Lo *et al* of cell free fetal DNA (cffDAN),[8] comprised of small fragments of extracellular DNA originating from the fetus that circulate freely in maternal plasma. While all human beings carry their own cell free DNA, in pregnant women's plasma about 10% comes from the fetus. These fragments of fetal DNA become detectable at 7-10 weeks gestation. Their proportion in relation to maternal cfDNA is called 'fetal fraction' and is key to the success of NIPT, since a fetal fraction of at least 4% is required for adequate testing.[9] cffDNA rapidly clears from maternal circulation after delivery, preventing any risk of cffDNA persisting from previous pregnancies and confounding test results.

8 The potential of this discovery for prenatal testing was immediately apparent and the prospects of testing through a non-invasive simple maternal blood test generated much hope.[10] Researchers first assumed that before long NIPT would be accurate enough to replace current invasive diagnostic tests (calling it at the time NIPD - 'D' for diagnosis) and started cautioning about the possible effects of this one-stop risk-free approach on women's decision making and informed consent.[11]

9 It quickly became apparent that the introduction of NIPT needs to be gradual, as its accuracy did not match that of invasive tests and its performance varied for different conditions. Moreover, validation studies started in populations of women identified

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6 Song K, Musci TJ, Caughey AB. "Clinical utility and cost of non-invasive prenatal testing with cfDNA analysis in high-risk women based on a US population." *Journal of Maternal-Fetal & Neonatal Medicine*, (12): 1180-5.

7 Bianchi DW. (2010) "From Michael to microarrays: 30 years of studying fetal cells and nucleic acids in maternal blood." *Prenatal Diagnosis*, 30: 622–3.

8 Lo YM, Corbetta N, Chamberlain PF, *et al*. (1997) "Presence of fetal DNA in maternal plasma and serum." *Lancet,* 350(9076): 485-7.

9 Daley R, Hill M, Chitty LS. (2014) "Non-invasive prenatal diagnosis: progress and potential." *Archives of Disease in Childhood*, Fetal and Neonatal Edition*,* 99: F426-30.

10 Ravitsky V. (2009) "Non-Invasive Prenatal Diagnosis: An Ethical Imperative." *Nature Reviews Genetics*, 10(10): 733.

11 Dagmar S, Netzer C, Henn W. (2009) "An Offer you Can't refuse? Ethical Implications of Non-Invasive Prenatal Diagnosis." *Nature Reviews Genetics*, 10(8): 515.

as high-risk by conventional screening and the reliability of NIPT was thus established in this group, with validation for average-risk pregnancies lagging behind.[12]

10 In 2011, the first commercial offer of NIPT for trisomy 21 was released by Sequenom under the name "MaterniT21", followed by similar tests – performed using various technological and bioinformatics platforms – from other companies.[13] NIPT soon expanded globally and is currently offered in Europe, Asia, South America, Northern Africa and the Middle East.[14] Since blood samples can be shipped and analysed overseas, the global expansion of NIPT is crossing national and jurisdictional borders, raising complex challenges for regulators.

11 NIPT is now considered accurate and hence diagnostic for sex determination, fetal rhesus D (RHD) status and some single gene disorders.[15] It is also considered a highly accurate screening test for aneuploidies. NIPT has a false positive rate of about 0.09% and detection rate of about 99.2% for trisomy 21, a false positive rate of about 0.13% and detection rate of about 96.3% for trisomy 18, and a false positive rate of about 0.13% and detection rate of about 91% for trisomy 13.[16] Some companies currently offer packages that also include testing for sex chromosome abnormalities such as Turner or Klinefelter syndromes, microdeletion syndromes and single gene disorders. There is preliminary evidence of efficacy of NIPT in pregnancies with multiples, but at present it is recommended only for singleton pregnancies.[17]

12 Since the performance of NIPT has been validated more extensively for high-risk pregnancies (i.e. that have been identified as high-risk through traditional screening), it is currently recommended by some professional societies for use only in this population.[18] Some companies are now starting to offer NIPT to women with average-risk pregnancies[19] (i.e. the entire population of pregnant women), but the

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12 Gil MM, Quezada MS, Revello R, et al. (2015) "Analysis of cell-free DNA in Maternal blood in screening for fetal aneuploidies: updated meta-analysis." *Ultrasound in Obstetrics and Gynecology*, 45: 249-66.

13 "Harmony" from Ariosa, "Verifi" from Illumina, "Panorama" from Natera, "PrenaTest" from LifeCodexx, "Bambini" from Berry Genomics, and "Nifty" from BGI.

14 Allyse M, Minear MA, Berson E, *et al*. (2015) "Non-invasive prenatal testing: a review of international implementation and challenges." *International Journal of Women's Health*, 7: 113-26.

15 Daley R, Hill M, Chitty LS. (2014) "Non-invasive prenatal diagnosis: progress and potential." *Archives of Disease in Childhood*, Fetal and Neonatal Edition, 99: F426-30.

16 Gil MM, Quezada MS, Revello R, et al. (2015) "Analysis of cell-free DNA in Maternal blood in screening for fetal aneuploidies: updated meta-analysis." *Ultrasound in Obstetrics and Gynecology*, 45: 249-66.

17 Struble CA, Syngelakin A, Oliphant A, *et al*. (2014) "Fetal fraction estimate in twin pregnancies using directed cell-free DNA analysis." *Fetal Diagnosis and Therapy*, 35(3): 199-203.

18 Langlois S, Brock JA, *et al*. (2013) "SCOG Committee Opinion: Current status in non-invasive prenaatal detection of Down syndromw, Trisomy 18 and Trisomy 13 using cell-free DNA in maternal plasma." *Journal of Obstetrics and Gynaecology Canada*, 35(2): 177-83.

19 Heger M. (2015) "Sequenom to Shift Business Strategy to Focus on Average Risk as MaterniT21 Tests Decrease." *GenomeWeb*, Nov 05, 2015. At: https://www.genomeweb.com/business-

accuracy of NIPT in this population is a topic of ongoing debate. Regardless, it is currently recommended by all professional societies world-wide that a positive NIPT result be confirmed through invasive testing.[20] Pregnancy management, and particularly a decision to terminate a pregnancy, based on NIPT alone in considered clinically inappropriate, because the risk of a false positive exists and women may terminate an unaffected pregnancy. However, a recent large-scale study (of 28,739 women) showed that 6.2% proceeded to termination without confirmatory diagnostic testing,[21] raising the issue of a non-validated consumer-based premature adoption of a new technology. It also raises the issue of developing appropriate educational and counselling approaches for a technology that is evolving rapidly.

13 Whole Genome Sequencing (WGS) based on NIPT is technically possible[22] and researchers are working to develop this capacity.[23] If in the future fetal WGS becomes routine, any diagnosable genetic condition might be identified through NIPT. This would raise a host of challenging issues, from what information to disclose to prospective parents, through incidental findings, all the way to the use of this information after a child is born.

14 In 2015, it was revealed that NIPT detected potential cancer in pregnant women, leading to 26 confirmed cancer diagnoses.[24] Since NIPT looks at both maternal and fetal cfDNA, a test targeting the fetus inadvertently detected maternal genetic abnormalities.[25] This raises challenging issues related to the ethical obligation to disclose information that has great clinical utility on one hand, but for which there is currently no validated measures of false positives. Without such validation, some have argued that disclosure of this information raises the public health issue of over-diagnosis[26] regarding women who do not actually have cancer but will receive this information and go through unnecessary anxiety and diagnostic procedures. There are currently no professional guidelines regarding such findings and some have called for urgently revising consent forms and raising awareness of the possibility of such discoveries.[27]

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news/sequenom-shift-business-strategy-focus-average-risk-maternit21-tests-decrease (Last accessed November 7, 2015)

20 Dondorp WG, de Wert Y, Bombard DW, *et al*. (2015) "Non-invasive prenatal testing for aneuploidy and beyond: challenges of responsible innovation in prenatal screening. Summary and recommendations." *European Journal of Human Genetics*, 23(11): 1438–50.

21 Dar P, Kirsten CJ, Gross SJ, *et al*. (2014) "Clinical experience and follow-up with large scale single-nucleotide polymorphism-based noninvasive prenatal aneuploidy testing. " *American Journal of Obstetrics and Gynecology*, 211: 527-9.

22 Lo YM, Chan KC, Sun H, *et al*. (2010) "Maternal plasma DNA sequencing reveals the genome-wide genetic and mutational profile of the fetus." *Science Translational Medicine*, 2(61):61ra91.

23 Fan HC, Gu W, Wang J, *et al*. (2012) "Non-invasive prenatal measurement of the fetal genome." *Nature*, 487(7407): 320–4.

24 Oswald K. (2015) "Prenatal blood test detects cancer in mothers-to-be." *BioNews* 739. At: http://www.bionews.org.uk/page_503998.asp (Last accessed October 31 2015).

25 Amant F, Verheecke M, Wlodarska I, *et al*. (2015) "Presymptomatic Identification of Cancers in Pregnant Women During Noninvasive Prenatal Testing." *JAMA Oncology*, 1(6): 814-9.

26 Newson A, Carter S. (2015) "Prenatal testing, cancer risk and the overdiagnosis dilemma." BioNews 797. At: http://www.bionews.org.uk/page_515971.asp (Last accessed October 31 2015)

27 Bianchi D. (2015) "Prepare for unexpected prenatal test results." *Nature*, 522: 29-30.

Guidelines from professional societies

15 A number of professional societies world-wide have published guidelines or position statements regarding NIPT in recent years (see Table 1). The key points made in these documents are:

16 *How to use NIPT*:

(a) All documents state that NIPT is not a diagnostic test and that confirmatory invasive testing must be performed. Some add that clinicians must clearly counsel women that pregnancy management decisions should *not* be made based on NIPT alone.
(b) Six state that NIPT should be available to women carrying high-risk pregnancies (identified through traditional screening), but do not take a position regarding average-risk pregnancies due to unclear accuracy in this population.
(c) Three recommend considering cases where results are not reported, indeterminate or uninterpretable ("no call" test results) as high risk and offering in such cases genetic counselling as well as diagnostic testing. A failure to provide a result can stem from technical issues (such as problems with blood collection, transportation of samples, or assay failure) or from low fetal fraction, i.e. the percentage of fetal cfDNA in the blood (usually below 4%).[28] However, it is also suspected that in some cases such failure may stem from an increased risk of aneuploidy.[29]

17 *Counselling and consent*:

(a) Six discuss how pre-test counselling should be provided and two discuss also post-test counselling (reporting of results).
(b) Five explicitly address the issue of consent and recommend ensuring that women understand that testing is voluntary and can be declined. Two of these mention specifically concerns regarding the negative effects that routinisation of NIPT could have on consent and two recommend paying attention to and respecting diverse ethical, linguistic, educational, and cultural values and sensitivities when considering women's informational needs.

18 *Future research*: six call for further research to be conducted on NIPT, particularly in average risk pregnancies and in multiple gestation pregnancies.

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[28] Gil MM, Quezada MS, Revello R, *et al*. (2015) "Analysis of cell-free DNA in Maternal blood in screening for fetal aneuploidies: updated meta-analysis." *Ultrasound in Obstetrics and Gynecology*, 45: 249-66.

[29] Benn P, Cuckle H, Pergament E. (2012) "Genome-wide fetal aneuploidy detection by maternal plasma DNA sequencing." *Obstetrics & Gynecology*. 119: 1270.

Table 1: Professional Societies' Guidelines or Position Statements Regarding NIPT

Date	Source	Title
Nov 2012	***US***: National Society of Genetic Counselors (NSCG)	NSCG Practice Guideline: Prenatal Screening and Diagnostic Testing Options for Chromosome Aneuploidy
Feb 2013	***US***: American College of Medical Genetics and Genomics (ACMG)	ACMG Statement on Non Invasive Prenatal Screening for Fetal Aneuploidy
Feb 2013	***Canada***: Society of Obstetricians and Gynæcologists of Canada (SOGC)	Current Status in Non-Invasive Prenatal Detection of Down Syndrome, Trisomy 18, and Trisomy 13 Using Cell-Free DNA in Maternal Plasma
Apr 2013	***France***: Comité Consultatif National d'Ethique pour les sciences de la vie et de la santé (CCNE)	Questions éthiques associées au développement des tests génétiques fœtaux sur sang maternel
Apr 2013	***International***: International Society for Prenatal Diagnosis (ISPD)	Position Statement from the Aneuploidy Screening Committee on behalf of the board of the ISPD
May 2013	***Italy***: Italian College of Fetal Maternal Medicine (SIDIP)	Position Statement from the Italian College of Fetal Maternal Medicine: NIPT by maternal plasma DNA sequencing
Feb 2014	***Canada***: Canadian Agency for Drugs and Technologies in Health (CADTH)	NIPT: A Review of the Cost Effectiveness and Guidelines
Mar 2014	***UK***: Royal College of Obstetricians & Gynæcologists (RCOG)	NIPT for Chromosomal Abnormality using Maternal Plasma DNA
Mar 2015	***US and Europe***: American Society of Human Genetics (ASHG) & European Society of Human Genetics (ESHG)	NIPT for Aneuploidy and Beyond: Challenges of Responsible Innovation in Prenatal Screening (Position Document)
Jun 2015	***US***: American College of Obstetricians and Gynecologists (ACOG) and Society for Maternal-Fetal Medicine (SMFM)	Cell-free DNA Screening for Fetal Aneuploidy

Benefits of NIPT

19 The current benefits of NIPT are:

(a) Safety: the non-invasiveness of NIPT means that there is no risk to the fetus, making it much more attractive than current invasive tests which carry a small risk of miscarriage.
(b) Reliability: higher accuracy in comparison to current screening tests.
(c) Timing: allows obtaining results in the first trimester, earlier in the pregnancy than current tests.
(d) Access: a simple blood draw that requires little expertise, increasing access in comparison to procedures that require well-trained and experienced healthcare professionals.
(e) Ease and comfort: involves less pain and discomfort than invasive tests.

20 At a systemic level, the main benefit currently observed in places where NIPT is widely available is a drastic reduction in the number of invasive procedures performed.[30,31] As a screening test available to women with high-risk pregnancies, it allows many to proceed to NIPT rather than proceeding straight to an invasive test. For most of these women, a negative NIPT result is reassuring enough and they do not choose to confirm it with an invasive test. In Canada, for example, the introduction of NIPT as a screening for high-risk pregnancies is expected to reduce the number of amniocenteses performed per year from 10,000 to 300, reducing procedure-related fetal losses from 70 to 1.[32]

21 Future possible benefits include:

(a) Potential reduction in cost for the healthcare system: as NIPT drops in price and the number of avoided invasive procedures increases, the overall savings may become significant.
(b) In a more distant future NIPT may become reliable enough for certain conditions to replace invasive diagnostic tests. This will allow a one-stop test that provides accurate results early in the pregnancy without any risk to the fetus and at a lower overall cost to the system. It would also allow decisions regarding termination to be taken in the first – rather than the second – trimester of the pregnancy, making termination medically safer and for some

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30 Song K, Musci TJ, Caughey AB. "Clinical utility and cost of non-invasive prenatal testing with cfDNA analysis in high-risk women based on a US population." *Journal of Maternal-Fetal & Neonatal Medicine*, (12): 1180-5.

31 Larion S, Warsof SL, Romary L, *et al*. (2014) "Uptake of noninvasive prenatal testing at a large academic referral center." *American Journal* of *Obstetrics & Gynecology*, 211(6): 651.e1–7.

32 Pegasus ("PErsonalized Genomics for prenatal Aneuploidy Screening USing maternal blood") study data. At: http://pegasus-pegase.ca/ (Last accessed October 31 2015).

also emotionally and morally less burdensome.[33] Such a scenario will make NIPT what some have called the 'holy grail' of prenatal testing.[34]

Ethical and social implications of NIPT

22 The nascent literature on the ethical and the social implications of NIPT demonstrates that it raises many of the 'classical' concerns associated with previous prenatal testing techniques, while intensifying some of them. This section outlines the main themes explored in this literature.

Reproductive autonomy and informed decision-making

23 Prenatal testing is based on the notion of expanding and promoting reproductive autonomy by providing women and families with information that can assist in pregnancy management. In this context, NIPT is perceived as a positive development, allowing safer, easier and earlier access to such information. Indeed, empirical studies to date have shown that women's perceptions of NIPT are positive[35] and that expected uptake is high.[36]

24 At the same time, the rapid implementation of NIPT and the constant evolution of its reliability for different conditions (e.g. different aneuploidies) in different populations (e.g. high- and average-risk), raise concerns regarding the capacity of healthcare providers to appropriately counsel women.[37] The informational needs of women and of providers regarding NIPT need to be assessed[38] and educational materials need to be developed[39] to ensure decision-making regarding testing is informed.

25 The impact of NIPT on counselling may depend on how it is implemented. As a screening test for high-risk pregnancies, pre-test counselling may be less time consuming, because there is no need to discuss the procedure-related risk of miscarriage, as is the case of invasive testing. Moreover, by decreasing the number of invasive tests performed, NIPT will reduce the need for pre-test counselling for such invasive tests.

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33 Lewis C, Silcock C, Chitty LS. (2013) "Non-invasive prenatal testing for Down's syndrome: pregnant women's views and likely uptake." *Public Health Genomics* 16(5): 223-32.

34 Hewison J. (2015) "Psychological aspects of individualized choice and reproductive autonomy in prenatal screening." *Bioethics* 29(1): 9-18.

35 Hill M, Fisher J, Chitty LS, *et al*. (2012) "Women's and health professionals' preferences for prenatal tests for Down syndrome: a discrete choice experiment to contrast noninvasive prenatal diagnosis with current invasive tests." *Genetics in Medicine*, 14(11): 905-13.

36 Lewis C, Hill M, Silcock C. *et al*. (2014) "Non-invasive prenatal testing for trisomy 21: a cross sectional survey of service uses' views and likely uptake." *BJOG: An International Journal of Obstetrics and Gynaecology*, 121(5): 582-94.

37 Allyse M, Minear MA, Berson E, *et al*. (2015) "Non-invasive prenatal testing: a review of international implementation and challenges." *International Journal of Women's Health*, 7: 113-26.

38 Vanstone, M., C. King, B. de Vrijer and J. Nisker (2014). "Non-invasive prenatal testing: ethics and policy considerations." *Journal of Obstetrics and Gynaecology Canada* **36**(6): 515-26.

39 Chitty LS, Hill M, White H, et al. (2012) "Noninvasive prenatal testing for aneuploidy-ready for prime time?" *American Journal of Obstetrics and Gynecology*, 206(4): 269-75.

26 On the other hand, if implemented as a screening test offered to the entire population of pregnant women, NIPT will increase dramatically the number of women who require pre-test counselling. In the US alone, such a shift would expand the annual number from less than 100,000 to about 3 million.[40] Some have argued that the healthcare system would not be able to address such a demand[41] and concerns have been raised regarding women undergoing NIPT without fully understanding the meaning and implications of the test[42] and regarding the erosion of informed consent to be tested.[43] Some therefore suggested the development of innovative - and more resource efficient - models of counselling to allow for adequate pre-test counselling of the general population.[44]

The routinisation of NIPT

27 The prospect of the integration of NIPT as a routine part of prenatal care for all pregnant women may carry great benefits but it also raises concerns regarding the abovementioned possible erosion of counselling and consent. Some studies have shown that in the absence of procedure-related risk, clinicians perceive consent for NIPT as les s important than for invasive testing.[45,46] Concerns have also been raised regarding NIPT being performed without women being aware that a genetic screening is taking place, since NIPT only requires a blood draw and may thus be perceived as just another blood test performed among others during the pregnancy.[47,48]

28 Routinisation also raises concerns regarding the increased social and medical pressure women may feel to use NIPT in light of the fact that it carries no risk to the fetus. Some even expressed concerns regarding the stigmatisation of women who

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40 Hayden EC. (2012) "A newborn industry based on non-invasive genetic testing turns combative." *Nature*, 486: 454. At: http://www.nature.com/news/fetal-tests-spur-legal-battle-1.10894 (Last accessed October 30, 2015).

41 Leach MW. (2015) "Unjustified: The Imbalance of Information and Funding With Noninvasive Prenatal Screening." *AJOB Empirical Bioethics*, 6(1): 21-30.

42 Lewis C, Silcock C, Chitty LS. (2013) "Non-invasive prenatal testing for Down's syndrome: pregnant women's views and likely uptake." *Public Health Genomics* 16(5): 223-32.

43 van den Heuvel A, Chitty L, Dormandy E, *et al*. (2009) "Will the Introduction of Non-Invasive Prenatal Diagnostic Testing Erode Informed Choices? An Experimental Study of Health Care Professionals." *Patient Education and Counseling*, 78: 24-8.

44 Chitty LS, Hill M, White H, et al. (2012) "Noninvasive prenatal testing for aneuploidy-ready for prime time?" *American Journal of Obstetrics and Gynecology*, 206(4): 269-75.

45 van den Heuvel A, Chitty L, Dormandy E, *et al*. (2009) "Will the Introduction of Non-Invasive Prenatal Diagnostic Testing Erode Informed Choices? An Experimental Study of Health Care Professionals." *Patient Education and Counseling*, 78: 24-8.

46 Silcock C, Liao LM, Hill M, Chitty LS. (2015) "Will the introduction of non-invasive prenatal testing for Down's syndrome undermine informed choice?" *Health Expectations*, 18(5): 1658-71.

47 Hill M, Karunaratna M, Lewis C, *et al.* (2013) "Views and preferences for the implementation of non-invasive prenatal diagnosis for single gene disorders from health professionals in the United Kingdom." *American Journal of Medical Genetics*, 161A(7): 1612-8.

48 Skirton H, Patch C. (2013) "Factors affecting the clinical use of non-invasive prenatal testing: a mixed methods systematic review." *Prenatal Diagnosis*, 33: 532–41.

choose not to test as 'irresponsible'[49] and the exacerbation of the perception of prenatal testing as 'guaranteeing a healthy baby'. In light of the potential public health benefits of NIPT to reduce the burden of disease and disability on public healthcare systems, some are concerned that women who reject testing may be seen as responsible for the birth of a child with special needs and therefore as not entitled to social support or even public coverage of the health needs of their child.[50, 51] Some have emphasised the important distinction between the purpose of prenatal testing as "enabling autonomous reproductive choices by pregnant women and their partners" as opposed to "preventing the birth of children with specific abnormalities".[52]

29 Concerns are raised about the routinising of NIPT as lowering the threshold of socially acceptable prenatal genetic testing from severe untreatable conditions to conditions with a lower impact on morbidity or quality of life,[53] to late onset conditions,[54] to treatable conditions and even to non-medical traits.[55] This led to the argument that NIPT may lead society down a slippery slope towards 'designer babies',[56] allowing parents to select desired traits such as eye colour.[57] It also led to concerns regarding the potential use of NIPT for non-medical sex selection and early paternity testing.[58]

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49 Garcia E, Timmermans DR, van Leeuwen E. (2008) "Rethinking autonomy in the context of prenatal screening decision-making." *Prenatal Diagnosis,* 28(2): 115-20.

50 Sayres LC, Allyse M, Norton ME, Cho MK (2011) "Cell-free fetal DNA testing: a pilot study of obstetric healthcare provider attitudes toward clinical implementation." *Prenatal Diagnosis,* 31(11): 1070-1076.

51 Farrimond HR, Kelly SE (2013) "Public viewpoints on new non-invasive prenatal genetic tests." *Public Understanding Science* 22(6): 730-44.

52 Dondorp WG, de Wert Y, Bombard DW, *et al*. (2015) "Non-invasive prenatal testing for aneuploidy and beyond: challenges of responsible innovation in prenatal screening. Summary and recommendations." *European Journal of Human Genetics*, 23(11): 1438–50.

53 Verweij EJ, Oepkes D, de Boer MA. (2013) "Changing attitudes towards termination of pregnancy for trisomy 21 with non-invasive prenatal trisomy testing: a population-based study in Dutch pregnant women." *Prenatal Diagnosis,* 33(4): 397-99.

54 van Schendel RV, Kleinveld JH, Dondorp WJ, *et al*. (2014) "Attitudes of pregnant women and male partners towards non-invasive prenatal testing and widening the scope of prenatal screening." *European Journal of Human Genetics,* 22(12): 1345-50.

55 Minear MA, Alessi S, Allyse M, *et al*. (2015) "Noninvasive Prenatal Genetic Testing: Current and Emerging Ethical, Legal, and Social Issues." *Annual Review of Genomics and Human Genetics,* 16: 369-98.

56 van Schendel RV, Kleinveld JH, Dondorp WJ, *et al*. (2014) "Attitudes of pregnant women and male partners towards non-invasive prenatal testing and widening the scope of prenatal screening." *European Journal of Human Genetics,* 22(12): 1345-50.

57 *Op. cit*.

58 Newson AJ (2008) "Ethical aspects arising from non-invasive fetal diagnosis." *Seminars of Fetal and Neonatal Medicine,* 13(2): 103-8.

NIPT and eugenic social attitudes

30 The routinisation of NIPT raises concerns regarding the exacerbation of eugenic social attitudes.[59] The possible increased pressure on women to use a safe and easy test may lead to an increase in the number of detected conditions and therefore terminated pregnancies.[60] This, in combination with a lower threshold of testing, may decrease the overall presence of individuals with certain conditions in society and promote an expectation of 'perfect babies'.[61]

31 Such a reality may in turn lead to increased stigmatisation of individuals living with those conditions that NIPT can detect and their families. It may also lead to discrimination against such individuals and families,[62] although some have argued that sufficient legal protections are already in place to ensure this does not occur.[63] Finally, concerns are raised that eugenic social attitudes may lead to the adoption of policies that provide less support to individuals with special needs and their families,[64] and to decrease in the investment in research on conditions that are perceived as 'preventable' through NIPT.[65]

32 These concerns led to an emphasis on the importance of considering disability rights in policy making regarding the implementation of NIPT.[66] As highlighted by critics in relation to previous prenatal testing technologies, the inclusion of disabled citizens who are affected by such technologies in the debate surrounding their implementation is of utmost importance.[67,68]

NIPT and pregnancy termination

33 If and when NIPT is implemented for all pregnant women, it is expected to increase the rate of detection of fetal anomalies and with it, the number of terminated pregnancies. This creates a direct link between NIPT and the abortion debate, which

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59 Benn PA, Chapman AR (2010) "Ethical challenges in providing noninvasive prenatal diagnosis." *Current Opinion in Obstetrics and Gynecology*, 22(2): 128-34.

60 Allyse M, Minear MA, Berson E, *et al*. (2015) Non-invasive prenatal testing: a review of international implementation and challenges. *International Journal of Women's Health*, 7: 113-26.

61 Farrimond HR, Kelly SE (2013) "Public viewpoints on new non-invasive prenatal genetic tests." *Public Understanding Science* 22(6): 730-44.

62 Kellogg G, Slattery L, Hudgins L, Ormond K. (2014) "Attitudes of Mothers of Children with Down Syndrome Towards Noninvasive Prenatal Testing." *Journal of Genetic Counseling*, 23(5): 805-13.

63 Minear MA, Alessi S, Allyse M, *et al*. (2015) "Noninvasive Prenatal Genetic Testing: Current and Emerging Ethical, Legal, and Social Issues." *Annual Review of Genomics and Human Genetics,* 16: 369-98.

64 Vanstone M, King C, de Vrijer B, Nisker J. (2014) "Non-invasive prenatal testing: ethics and policy considerations." *Journal of Obstetrics and Gynaecology Canada,* 36(6): 515-26.

65 King JS. (2011) "And Genetic Testing for All... The Coming Revolution in Non-Invasive Prenatal Genetic Testing." *Rutgers Law Journal,* 42: 599-819.

66 Kaposy C. (2013) "A disability critique of the new prenatal test for Down syndrome." *Kennedy Institute of Ethics Journal,* 23(4): 299-324.

67 Kerr A, Shakespeare T. (2002) *Genetic Politics: From Eugenics to Genome*. New Clarion Press.

68 Shakespeare T. (1998) "Choices and Rights: Eugenics, genetics and disability equality." *Disability & Society* 13(5): 665-81.

raises concerns (particularly in the US context) that anti-abortion lobbyists may use it to justify strategies that restrict abortion.[69] For example, in 2015 a bill was proposed to the Ohio State Legislature that would make it illegal for a woman to terminate a pregnancy because her fetus was prenatally diagnosed with Down syndrome.[70]

34 Another concern is that, as mentioned above, the ease and safety of NIPT will make it more acceptable to test for minor conditions or even undesired non-medical traits, such as short stature. Considering that NIPT allows access to this information in the first trimester, concerns have been raised that this may lead to individuals deciding to terminate pregnancies for 'trivial reasons', leading over time to a 'trivialisation' of pregnancy termination.[71]

35 If and when NIPT reaches a diagnostic level, it will allow a decision regarding termination to be reached earlier in the pregnancy than current diagnostic tests. This would be an important benefit, as outlined above, but also raises a concern regarding the increased number of women who would face the emotional and moral burden of such a decision, considering that affected fetuses are sometimes miscarried spontaneously later in the pregnancy. The earlier access to information through NIPT could thus add stress and anxiety by creating a decision point for women in pregnancies that would have ended by nature taking its course.[72]

NIPT 'purely for information'

36 Due to the absence of risk to the fetus, parents may wish to use NIPT in order to prepare for the birth of a child with special needs. This use would be in line with the well-established goal of prenatal testing, which is to allow prospective parents access to information in order to promote their reproductive autonomy.[73] Other prospective parents may want to use NIPT out of pure interest in the results, without having any particular objective in mind. In any case where NIPT was performed, conditions that were detected prenatally would be known when the child is born. This raises concerns regarding the impact such knowledge might have on the future autonomy of the prospective child. Such concerns have led some to argue that NIPT 'purely for information' would be unacceptable if parents wish to test for adult-onset conditions, carrier status or minor genetic conditions with no health implication.[74]

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69 King J. (2012) "Politics and diagnostics collide." *Nature*, 491(7422): 33-4.

70 Short Title of the Bill: "Unborn child having Down Syndrome-prohibit abortion." At: https://www.legislature.ohio.gov/legislation/legislation-summary?id=GA131-HB-135 (Last accessed October 29, 2015).

71 de Jong A. de Wert GM. (2015) "Prenatal screening: an ethical agenda for the near future." *Bioethics,* 29(1): 46-55.

72 Hewison J. (2015) "Psychological aspects of individualized choice and reproductive autonomy in prenatal screening." *Bioethics* 29(1): 9-18.

73 Dondorp W, de Wert G, Bombard Y, *et al*. (2015) "Non-invasive prenatal testing for aneuploidy and beyond: challenges of responsible innovation in prenatal screening." *European Journal of Human Genetics*, 23: 1438-50.

74 Deans Z, Clarke AJ, Newson AJ. (2015) "For your interest? The ethical acceptability of using non-invasive prenatal testing to test 'purely for information'." *Bioethics*, 29(1): 19-25.

Justice and equity of access

37 At the present time, public funding of NIPT is still uncommon.[75] In the US, some insurers already cover certain uses of NIPT,[76] but in most countries that have universal health insurance it has not yet been integrated as a covered service, creating great disparities in access. In the UK, for example, such integration is currently under consultation with the National Screening Committee (as outlined below). With NIPT costing between £400 and £900,[77] this transitional reality is raising concerns regarding equity of access. These immediate concerns highlight the fact that cost is currently a barrier for women who are identified as high-risk through traditional screening and then cannot afford to pay for NIPT. This means that if they wish to obtain more accurate results, their only alternative is invasive testing, despite their expressed wishes to avoid the risk of miscarriage associated with such tests. Put simply, without public funding for NIPT, women with means can proceed to a safe and reliable screening test that would provide the great majority with peace of mind, while women without means can only proceed to a diagnostic test that carries a risk.

38 Beyond such immediate concerns, some are worried that a long term private/commercial availability of NIPT without public funding would exacerbate health inequities by allowing the better-off to terminate affected pregnancies and bring into the world children that are more likely to benefit from better health throughout their lives.[78]

The introduction of NIPT by private companies

39 To date, the introduction of NIPT into clinical use has been done by the companies that develop and sell the test. The bulk of the research that assesses the reliability of NIPT for various conditions has thus been performed by those who have a strong commercial interest in its implementation. With the global market for NIPT expected to reach 3.62 billion US dollars by 2019,[79] these commercial interests raise concerns about possible bias in the presentation of the data generated by private companies'

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75 Minear MA, Alessi S, Allyse M, *et al*. (2015) "Noninvasive Prenatal Genetic Testing: Current and Emerging Ethical, Legal, and Social Issues." *Annual Review of Genomics and Human Genetics,* 16: 369-98.

76 Allyse M, Minear MA, Berson E, *et al*. (2015) "Non-invasive prenatal testing: a review of international implementation and challenges." *International Journal of Women's Health*, 7: 113-26.

77 Morris S, Karlsen S, Chung N, Hill M, Chitty LS. (2014) "Model-Based analysis of costs and outcomes of non-invasive prenatal testing for down's syndrome using cell free fetal DNA in the UK national health service." *PLoS One,* 9(4): e93559.

78 Benn PA, Chapman AR (2010) "Ethical challenges in providing noninvasive prenatal diagnosis." *Curr Opinion in Obstetrics and Gynecology*, 22(2): 128-34.

79 "Non-Invasive Prenatal Testing (NIPT) Market Expected to Reach USD 3.62 Billion Globally in 2019: Transparency Market Research." *PRNewswire*, January 6, 2014. At: http://www.prnewswire.com/news-releases/non-invasive-prenatal-testing-nipt-market-expected-to-reach-usd-362-billion-globally-in-2019-transparency-market-research-238824411.html (Last accessed October 29, 2015).

research and about potential benefits being over-estimated.[80] Some caution that the commercial incentive to implement NIPT as a screening for the entire population of pregnant women (rather than limiting it to high-risk pregnancies) can lead to a premature use of the test.[81]

40 Companies have been using marketing strategies such as reaching out to pregnant women through social media or offering 'introductory pricing' specials to capture a market share.[82] The aggressive marketing of NIPT to healthcare providers and to women raises concerns regarding premature implementation of NIPT into routine practice in the absence of sufficient evidence of clinical utility.

41 The prospect of NIPT for fetal abnormalities being marketed direct-to-consumer (DTC) is raising serious concerns that this type of implementation will not allow women and families access to appropriate counselling and support to ensure their decision making is well informed.[83] Some have argued that to maintain minimum quality of practice, NIPT must be offered through health professionals with the expertise and training to provide the pre-and post-test information and counselling.[84]

Legal implications of NIPT

42 As an emerging technology, the introduction of NIPT raises some healthcare provider liability concerns. Are providers under obligation to inform eligible patients of the availability of NIPT as a part of prenatal care? And if not, how should they identify the point at which NIPT is considered standard of care and should be offered? Moreover, when NIPT is discussed, healthcare providers must disclose its limitations (e.g. regarding reliability for various conditions or the quality of the evidence for high versus average risk pregnancies). Failure to adequately communicate such limitations could mislead patients and distort their decision-making regarding testing, raising legal liability issues, particularly in cases where the pregnancy results in the birth of a baby with impaired health or a disability.[85] This requires that physicians remain informed regarding the constantly evolving accuracy and reliability of NIPT, a requirement that raises its own challenges considering the extremely rapid development of NIPT.

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80 Norton ME, Rose NC, Benn P. (2013) "Noninvasive prenatal testing for fetal aneuploidy: clinical assessment and a plea for restraint." *Obstetrics and Gynecology*, 121(4): 847-50.

81 Morain S, Greene MF, Mello MM. (2013) "A new era in noninvasive prenatal testing." *The New England Journal of Medicine*, 369(6): 499-501.

82 Morain *op. cit.*

83 Allyse MA, Sayres LC, Havard M, *et al*. (2013) "Best ethical practices for clinicians and laboratories in the provision of non-invasive prenatal testing." *Prenatal Diagnosis*, 33: 656-61.

84 Dondorp W, de Wert G, Bombard Y, *et al*. (2015) "Non-invasive prenatal testing for aneuploidy and beyond: challenges of responsible innovation in prenatal screening." *European Journal of Human Genetics*, 23: 1438-50.

85 Toews M, Caulfield T. (2014) "Physician liability and non-invasive prenatal testing." *Journal of Obstetrics and Gynaecology Canada*, 36(10): 907–14.

43 The companies developing NIPT technologies[86] have been embroiled in legal battles over intellectual property since the introduction of NIPT into the market in 2011.[87] While the social purpose of the patent system is to encourage innovation by providing the owner of an invention with a temporary exclusive right of control, concerns arise regarding increase in price, lower availability and limited access while patents are in force. A particular concern is that a single company would achieve market monopoly on NIPT by successfully getting injunctions against all its competitors.[88] Such a company could dictate the initial price of the test and potentially make it out of reach for government programmes while the patent is in force. It could also reach agreement with a limited number of insurance companies or healthcare providers, which would restrict the access of certain women.

44 Another concern is that patents on NIPT technology will limit the possibility of research and development. Reduced market competition can lead to limited quality assurance, to reduced cost effectiveness and to a decrease in the availability of cheaper options.[89]

Global implementation of NIPT

45 NIPT is expanding globally at a fast pace and is now available in 61 countries.[90] The introduction of NIPT in low- and middle-income countries (LMICs) carries particular benefits but also some unique challenges that should be addressed for an effective and ethically sound global implementation.

46 Benefits:

(a) Requiring only a blood draw, NIPT reduces the need for trained healthcare providers to perform invasive diagnostic procedures and makes testing more accessible in resource poor areas.
(b) Better detection of genetic abnormalities in the fetus can allow the mobilisation of resources for better care of newborns in areas where such resources are not widely available.[91]
(c) Earlier detection means that a decision regarding termination can be made earlier, making termination safer and also more acceptable in some cultural/religious contexts.[92]

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86 The US companies who own the majority of NIPT patents are Sequenom Inc., Natera Inc., Illumina's Verinata Health Inc., and Ariosa Diagnostics Inc.. Other major players are the Chinese companies BGI and Berry Genomics.

87 Hayden EC. (2012) "A newborn industry based on non-invasive genetic testing turns combative." *Nature*, 486: 454. At: http://www.nature.com/news/fetal-tests-spur-legal-battle-1.10894 (Last accessed October 30, 2015).

88 Agarwal A, Sayres LC, Cho MK, *et al*. (2013) "Commercial landscape of noninvasive prenatal testing in the United States." *Prenatal Diagnosis,* 33(6): 521-31.

89 *Op. cit.*

90 Chandrasekharan S, Minnear MA, Hung A, *et al*. (2014) "Noninvasive prenatal testing goes global." *Science Translational Medicine,* 6(231): 231fs15.

91 *Op Cit*.

47 Concerns:

(a) Regulatory issues: in most LMICs there is little or no regulatory control of the content and quality of NIPT, raising concerns regarding the reliability of the technology that is being used.

(b) Access: a recent survey of 28 countries to assess global trends in the clinical implementation of NIPT demonstrated great variability both across and within countries.[93] Access to NIPT currently depends greatly upon a woman's location, with more barriers present in LMICs where large disparities in access to prenatal testing already exist. Implementing NIPT equitably would require investment in sequencing capacity and training of healthcare providers.

(c) Cost: the abovementioned survey reported NIPT prices as ranging globally from $350[94] to $2,900.[95] In most LMICs NIPT is not covered by private or public insurance and women must pay for it out of pocket, putting NIPT out of reach for most families. This may exacerbate existing inequities in access to prenatal care. For example, in China the median monthly household income in 2013 was $515 and NIPT was sold at $457-$587 while amniocentesis was covered by most public programs. In Brazil the unaffordability of NIPT was even more apparent, with median monthly household income in 2013 at $626 and NIPT costing $1,492.[96] An equitable implementation of NIPT would require including it in public programmes or at least subsidising it substantially, which could remain unaffordable for many governments of LMICs.

(d) Informed decision making / provider and patient education: the provision of NIPT in LMICs may pose greater challenges to informed decision making than in developed countries due to low genetic literacy and paucity of trained genetic counsellors and medical geneticists. This poses challenges particularly regarding understanding the current limitations of NIPT and may thus compromise women's informed decision making.[97]

(e) Sex selection: NIPT can provide accurate fetal sex determination as early as seven weeks of pregnancy,[98] earlier than previous methods. In countries with a strong cultural preference for boys, earlier access to this information through NIPT may increase the rate of sex selective pregnancy terminations. In areas of the world where sex ratios are already significantly skewed this possible use of

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92 Haidar H, Rispler-Chaim V, Hung A, Chandrasekharan S, Ravitsky V. (2015) "Non-Invasive Prenatal Testing: Implications for Muslim Communities." *American Journal of Bioethics - Empirical Bioethics*, 6(1): 94-105.

93 Minear MA, Lewis C, Pradhan S, Chandrasekharan S. (2015) "Global perspectives on clinical adoption of NIPT." *Prenatal Diagnosis*, 35: 959-67.

94 All prices are in US dollars.

95 Minear MA, Lewis C, Pradhan S, Chandrasekharan S. (2015) "Global perspectives on clinical adoption of NIPT." *Prenatal Diagnosis*, 35: 959-67.

96 Chandrasekharan S, Minnear MA, Hung A, *et al*. (2014) "Noninvasive prenatal testing goes global." *Science Translational Medicine,* 6(231): 231fs15.

97 Allyse M, Minear MA, Berson E, *et al*. (2015) Non-invasive prenatal testing: a review of international implementation and challenges *International Journal of Women's Health*, 7: 113-26.

98 Devaney GE, Palomaki JA, Scott DW, Bianchi D. (2011) Noninvasive fetal sex determination using cell-free fetal DNA: A systematic review and meta-analysis. *Journal of the American Medical Association*, 306: 627–36.

NIPT raises serious concerns. While in China and India it is illegal for healthcare providers to disclose fetal sex to prospective parents, the effectiveness of these laws is already questionable. NIPT may further exacerbate the incapacity of states to control parents' access to this information because samples could be sent abroad for analysis.[99]

NIPT in the UK

48 In the UK, NIPT for Down syndrome and other conditions is currently available commercially but not as part of the National Health Service (NHS). The NHS's Fetal Anomaly Screening Programme (FASP) currently includes combined screening for Trisomy 21, 18 and 13 from 10-14 weeks of pregnancy[100] and a detailed anomaly ultrasound scan around18-21 of pregnancy.[101]

49 To be included in the programme, NIPT - like any other new technology - has to go through a review process[102] performed by the UK National Screening Committee (UK NSC), to assess whether there is clear and compelling evidence that it would be beneficial.[103] The Committee makes new recommendations or updates existing ones based on reviews of the best quality evidence available at the time.[104] This evidence review process has four main steps:

- stakeholder identification based on The National Institute for Health and Care Excellence (NICE) guidance;
- literature search and scoping to identify relevant new research, based on the key priorities of the evidence review;
- external review that results in a detailed report based on which conclusions are made, and a public consultation period of three months during which the identified stakeholders, or anyone else, can comment on the report; and
- a UK NSC recommendation regarding the proposed screening based on the external review and any stakeholder submissions, and based on determined criteria.[105]

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99 Chandrasekharan S, Minnear MA, Hung A, *et al*. (2014) "Noninvasive prenatal testing goes global." *Science Translational Medicine,* 6(231): 231fs15.

100 At: http://www.nhs.uk/Conditions/pregnancy-and-baby/pages/screening-amniocentesis-downs-syndrome.aspx#close (Last accessed October 18, 2015)

101 At: http://www.nhs.uk/Conditions/pregnancy-and-baby/Pages/anomaly-scan-18-19-20-21-weeks-pregnant.aspx (Last accessed October 18, 2015)

102 At: https://www.gov.uk/guidance/evidence-and-recommendations-nhs-population-screening (Last accessed October 18, 2015)

103 John Marshall, "General information, UK National Screening Committee", 13 August 2015. At: https://phescreening.blog.gov.uk/2015/08/13/evidence-update-new-consultation-on-non-invasive-prenatal-testing-and-latest-uk-nsc-recommendations/ (Last accessed October 18, 2015).

104 At: https://www.gov.uk/guidance/evidence-and-recommendations-nhs-population-screening#evidence-review-process (Last accessed October 18, 2015).

105 https://www.gov.uk/government/publications/evidence-review-criteria-national-screening-programmes/criteria-for-appraising-the-viability-effectiveness-and-appropriateness-of-a-screening-programme (Last accessed October 18, 2015).

50 The UK NSC is currently in the process of reviewing NIPT. As part of this process it commissioned a systematic review of the published scientific and cost evidence related to NIPT[106] and considered the results of a pilot study undertaken in 4 hospitals as part of the RAPID study (Reliable Accurate Prenatal non-Invasive Diagnosis).[107] Both documents are available at: http://legacy.screening.nhs.uk/fetalanomalies (last accessed 18 October 18 2015).

51 Based on the evidence produced by these studies, the UK NSC is currently consulting on whether NIPT should be introduced as a second-stage screen for trisomies 21, 18 and 13 following a risk score of 1:150 or higher (as a result of the current combined screen), while advising women that NIPT is not diagnostic and requires invasive testing for a definitive diagnosis. The UK NSC suggests that if introduced in this way, NIPT could provide a much better risk estimate, which means that many women will be able to avoid invasive diagnostic testing and its associated risk of miscarriage. Modelled data estimate that this could mean a decrease from 46 to three test-related miscarriages per year.

52 The review began in February 2015 and is estimated to be completed by December 2015, with the consultation period ending on 30 October 2015. The Nuffield Council's interest in NIPT is therefore particularly timely. If NIPT is implemented through the NHS in 2016, as expected, many of the issues raised in this background paper may become more relevant than ever for the UK healthcare system.

Questions the Nuffield Council may wish to consider

53 *Uses of NIPT*

(a) Should certain uses of NIPT be banned (e.g. testing for non-medical sex determination, for non-medical physical traits or for adult-onset diseases)?
(b) How should NIPT be handled when testing is 'purely for information' and the information will be available to parents and possibly to insurers after the child is born? Should such testing be banned or limited? Should it exclude non-treatable or adult onset conditions? What regulations are required to protect the autonomy of prospective children born after NIPT has been performed?
(c) Should whole-genome sequencing (WGS) through NIPT be allowed/encouraged/covered? What information should be disclosed? Under what conditions? How should clinical utility be determined in this context? Who should pay for consultations to follow up on WGS when testing for done privately?
(d) How should possible maternal cancer as an 'incidental finding' of NIPT be treated? Should this information be disclosed to pregnant women? And if so, under what conditions? How should possible benefit to the pregnant woman be

[106] Taylor-Phillips S. *et al.* "Systematic review and cost-consequence assessment of cell-free DNA testing for T21, T18 and T13 in the UK – Final report." July 2015.
[107] Chitty L. *et al.* "RAPID Non-invasive prenatal testing (NIPT) evaluation study: Executive summary." May 2015.

balanced against considerations of public health and concerns regarding over-diagnosis?

54 *Commercial implementation of NIPT*

(a) Should states regulate the commercial implementation of NIPT? For example, should the marketing and the advertising of NIPT be evaluated and approved to ensure that information provided to pregnant women and to healthcare providers is accurate and non-biased?
(b) Should states regulate the direct-to-consumer (DTC) sale of NIPT by companies? And if so, should such regulation be limited to certain conditions/traits? For example, should the DTC sale of trisomy testing be regulated differently than that of sex or paternity?
(c) Is regulation required to protect the privacy of women and prospective children from possible unapproved use of samples held by private companies?

55 *Public implementation of NIPT*

(a) How should decisions be made regarding public funding / coverage of NIPT in countries with universal health insurance? How should decisions be made regarding new conditions that NIPT becomes reliable for? Can the UK model (i.e. the process of evaluation developed by the National Screening Committee) be useful for other countries? Does it need to be adapted to better address the rapid development of NIPT?
(b) How should considerations of cost-effectiveness be balanced against considerations of equity of access?

56 *Global implementation of NIPT*

(a) How should NIPT be implemented in mid-lower income countries? What are the unique considerations as NIPT expands globally?
(b) How should cultural perspectives and various value-systems be considered in the implementation of NIPT? For example, what will be the impact of NIPT on sex selection in societies with a strong cultural preference for boys, where sex imbalance (stemming from previous techniques of prenatal testing) is already causing social unrest? Or the implications of NIPT in societies that value performance, where societal/cultural pressure to choose 'the genetically best prospective children'[108] already exists?

57 Education and counselling

(a) What are the most pressing needs in terms of provider and patient education in relation to NIPT? What tools and resources are required to address these needs?

[108] Savulescu J. (2001) "Procreative Beneficence: Why We Should Select the Best Children." *Bioethics*, 15(5/6): 413-26.

(b) How should pre- and post-test counselling for NIPT be provided? Should new models be developed to prepare for the drastic increase in demand when NIPT becomes first-tier screening offered to all pregnant women?

58 *Social considerations*

(a) Should the introduction of NIPT be accompanied by public policy that:
- enhances the protection of women from pressure to test?
- enhances the protection against discrimination of individuals living with disabilities or medical conditions that could have been 'eliminated' through NIPT?
- enhances support systems for families with children who have conditions that can be detected by NIPT, to ensure that women's choices regarding testing and termination are truly free?

(b) How should the public be engaged in discussing questions raised by NIPT? How should public debate regarding the social and ethical implications of NIPT be informed and promoted?

(c) How should policy regarding NIPT take into consideration the values, opinions and preferences of various stakeholders, e.g. families, healthcare providers, professional societies, and disability advocates?

59 *Future research*: what future empirical and conceptual research is required for an ethically and socially sound implementation of NIPT? What methodologies and approaches are best suited for the required research?

Appendix

NIPT in the UK: additional information

The RAPID NIPT Evaluation Study was set up with input from the UK NSC in order for the results to inform its review of NIPT. RAPID's objectives were:

- to investigate the use of NIPT to detect fetal aneuploidy as part of the NHS Down syndrome (DS) screening pathway
- to establish the optimal method of using NIPT in the NHS DS screening pathway
- to assess whether the test performance in an NHS study population is comparable with published data
- to assess the acceptability of the test to patients and health professionals
- to assess the benefits and costs of implementing NIPT in the screening programme
- to assess the implications of implementation of NIPT at a population level.

The study ran from November 2013 to February 2015 and included 1,164 women carrying an aneuploidy risk of between 1:2 and 1:1000 for either trisomy 21 and / or trisomy 18 or 13. It showed that NIPT can be provided safely and effectively as part of the NHS DS screening programme in the four clinics involved and presented "a strong case for the implementation of NIPT as part of the NHS DS screening programme to improve the quality of care for pregnant women and the performance of the programme as a whole".[109]

RAPID compared the implications of offering NIPT to women with a risk of up to 1:150, 1:500 and 1:1000 and the results are summarised in Table 1 below.

The commissioned review of the published scientific and cost evidence[110] constructed an economic model to compare NIPT as a second-stage screen for women with a risk higher than 1:150 to its use as the first-stage test offered *instead* of the current screen test (i.e. for women with any risk score). The model showed that NIPT as a second-stage screen would result in similar numbers of trisomies detected, 43 fewer miscarriages of unaffected pregnancies (because fewer women would choose invasive testing than currently do) at approximately the same cost as currently; whereas NIPT as a first-stage screen test would cost an extra £105 million to the NHS, and would result in more invasive tests than NIPT as a second-stage screen.

Based on this evidence, the UK NSC believes that at this time it is justified to implement NIPT into the fetal anomaly screening programme (FASP) only for women with a risk of 1:150 or higher, for five reasons:

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[109] Chitty L. *et al.* **"**RAPID Non-invasive prenatal testing (NIPT) evaluation study: executive summary." May 2015.

[110] Taylor-Phillips S. *et al.* "Systematic review and cost-consequence assessment of cell-free DNA testing for T21, T18 and T13 in the UK – Final report." July 2015.

- While the benefit of offering NIPT to 'high-risk' pregnancies (higher than 1:150) is clear, because it would markedly reduce invasive testing, this benefit is less clear if it is offered when the risk threshold is reduced (lower than 1:150). Although more trisomies would be detected, this benefit does not outweigh the effect on the number of invasive tests offered.
- This approach would not reduce the number of detected trisomies compared to current screening.
- Since the availability of NIPT in the UK is limited, this approach would not exceed the current capacity for offering NIPT in the UK.
- Evidence showed that this approach - compared to the alternatives - would have a minimal effect on the expenditure on the screening programme, which makes it more pragmatic, especially in light of current uncertainties.
- Retaining the current 1:150 risk threshold minimises changes to the current pathway, allowing the offering of NIPT to those at the highest risk without disrupting the screening programme and while providing an opportunity to explore current uncertainties such as impact on testing uptake.

Table 1: Summary comparisons of the outcomes for the proposed screening pathway including NIPT compared to the current NHS DS screening pathway in the England and Wales population[111]

Testing strategy	DS detected compared to current	Less Invasive Testing compared to current	Less Invasive Testing related miscarriage compared to current	Additional cost of implementing NIPT testing strategy (test cost - £250)
>1:1000 (No direct invasive testing offered)	176 more	4,805 less	24 less	£7,809,000 more
>1:500 (No direct invasive testing offered)	152 more	4,826 less	25 less	£3,365,000 more
>1:150 (No direct invasive testing offered)	102 more	4,870 less	25 less	£337,000 less

[111] Chitty L. *et al. Op cit.* Page 6.