Non-Invasive Prenatal Testing – Facilitating Autonomy or Complicating Decision-Making?

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Introduction

All references to NIPT are to non-invasive prenatal testing. This term relates to the use and analysis of cell-free fetal DNA (cffDNA) in maternal blood. These tests can produce diagnostic outcomes (NIPD)[*1] and outcomes where further invasive diagnostic tests are required (NIPT).[2]

Aims

My research aims in this paper are:

1. To identify the aims and purposes of a publicly funded NIPT regime?
2. To consider how those aims/purposes might be realised?
3. To consider how increased information about the possible future child might impact on the complexity of parental and clinical decision-making during pregnancy?
4. To identify whether (& what) further research is required before the scope of NIPT is widened

Methods

I have conducted a critical narrative literature review that included a search against all major electronic academic databases and authoritative texts.[3] This paper draws upon and provides a synthesis of that review. I have made it clear where I am expressing my own views. My inclusion criteria included non-invasive prenatal testing; decision-making and

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[1] Fetal sex determination where genetic related factors; certain single gene disorders
[2] Eg NIPT for Aneuploidy (Trisomies 13,18 & 21)
[3] See appendix A and the separate list of references.

consent. I excluded invasive and ex vivo embryo testing and any literature pre 2013 from my search. There is relevant literature before this date but I have concentrated on material published after the commencement of (private) aneuploidy screening in the UK.

Results

1. Aims & Purposes

> '*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.*'[4]

Does prenatal screening/testing (invasive or non-invasive) promote reproductive autonomy when it is used to obtain data 'purely for information' or are these regimes really just about facilitating and/or enhancing a choice between the termination and continuation of the pregnancy? Much will depend on the information being sought. Searching for information about treatable or preventable conditions may allow parents to make important decisions that will safeguard the well-being of the pregnancy and the future child. Searching for untreatable genetic anomaly certainly highlights a choice between the continuation and termination of pregnancy[5] although there may be other reasons why that this information might be helpful to the future parents. It might allow those parents to prepare psychologically, practically and financially for the birth of a disabled child. Parents may not be seeking information for any one purpose: they may want to establish that their future child will be healthy and obtain a range of information that might include 'non health data'. Even where the explicit purpose is the discovery of anomaly, there may be public health considerations at play including health planning,

[4] Ravitsky, V., *'Non-Invasive Prenatal Testing (NIPT): Identifying key clinical, ethical, social, legal and policy issues'* (commissioned by the Nuffield Council on Bioethics) 2015, available from http://nuffieldbioethics.org/wp-content/uploads/Note-of-meeting-NIPT-meeting-18-Jan-2016-FINAL.pdfhttp://nuffieldbioethics.org/wp-content/uploads/NIPT-background-paper-8-Nov-2015-FINAL.pdf (accessed 22 April 2016), para 23

[5] See for example http://www.nhs.uk/conditions/pregnancy-and-baby/pages/screening-amniocentesis-downs-syndrome.aspx (last accessed 16/5/16) where this stark choice is highlighted in relation to aneuploidy screening. See also Strange, H, *Non Invasive Prenatal Diagnosis & Testing: perspectives on the emergence & translation of a new prenatal testing technology, 2015, p89, available from http://orca.cf.ac.uk/90887/ (accessed 26 May 2016).*

avoiding unnecessary and potentially harmful invasive tests and avoiding the inequity of a private sector only regime.[6]

One issue should be tackled head on: the argument that NIPT cannot be aligned with a choice to terminate a pregnancy when used as a contingent test.[7] The argument appears to be a simple and attractive one: NIPT is not diagnostic, and consequently, any results cannot directly present or inform a choice between the termination and continuation of the pregnancy in those cases. That argument clearly fails with diagnostic anomaly testing including NIPD. It also fails in situations where the parents treat the NIPT results as diagnostic,[8] or nonetheless, act on those results knowing that they fall short of diagnostic certainty. In many cases, a negative result will not be challenged through further invasive testing and there is some evidence of parents terminating a pregnancy on the basis of a positive NIPT testing alone. The argument also ignores the ultimate goal of the whole screening process – to rule in or rule out a particular feature, condition or anomaly in the developing child. In doing so there is an assumption that we can separate out the means from the ultimate ends of a process. NIPT can highlight a high probability of outcome (for eg, in relation to aneuploidies). Whether the test results feature directly or indirectly in subsequent parental decision-making, it is artificial to dispute any connection between the NIPT results and a subsequent parental choice to terminate the pregnancy related to a feature, condition or anomaly highlighted by those tests. I agree with Heather Strange that:

'*The limited scope for treatment of the fetus entails that in the majority of pregnancies,* ***when a diagnosis of 'fetal abnormality' is provided as a result of prenatal testing, this information may be used to guide decision making around a single intervention: whether to continue with a pregnancy, or whether to end that pregnancy through abortion'***[9]

The boundary between NIPT/NIPD can be problematic for clinicians in cases where the probability of outcome falls just short of diagnostic certainty, [10] but that does not mean

[6] Wale, J*, 'Don't forget the legal framework: the public provision of non-invasive prenatal testing in England & Wales'* (2016) Medical Law International available from http://mli.sagepub.com/content/early/2016/04/27/0968533216646154?papetocn (last accessed May 3, 2016), p6-7

[7] Strange (n5) at p107

[8] Ravitsky (n4) para 12

[9] Strange (n5) p89 (emphasis added). I would add as a direct or indirect result of testing

[10] The anxiety of clinicians about the closeness and possible alignment between NIPT and abortion is highlighted by Heather Strange (n5) p107.

there can never be a connection between NIPT and decisions to terminate. The final point against disconnection relates to the public narrative. Denying a connection between NIPT and the practice of abortion, suppresses the problems highlighted by prenatal screening generally;[11] runs contrary to patient experiences[12] and distorts reality in the context of anomaly screening.[13]

The literature identifies the following perceived benefits of NIPT:

a. **Empowering choice** – these tests are easy to perform (requiring only a standard blood test on the pregnant woman) and are consequently safe for both mother and fetus.[14] Although not diagnostic, NIPT reduces the need for invasive tests and the consequent (albeit small) risk of miscarriage.[15] Indeed, it is this absence of procedural risk that makes it potentially more acceptable to test purely for information.[16] The ability of parents to make risk free or at least risk reduced decisions ultimately empowers reproductive choice. NIPT provides options for the low risk pregnant population that were not available before and the options to test are likely to increase as we move to diagnostic certainty in a wider range of cases.[17]

   The RAPID evaluation report summary concluded that:

   '*Overall most parents felt that any additional anxiety and the length of time required for results were overcome by the benefits of the test, which were considered to include its safety, accuracy and simplicity, along with the reduced need for invasive procedures. Feedback from healthcare professionals has shown that NIPT was easily integrated into existing screening arrangements.*'[18]

   De Jong and DeWert[19] suggest that anomaly testing should not be understood as maximising choice per se and argue that public funding should only be available if the NIPT regime is understood to be about avoiding suffering related to living with a

[11] Strange (n5) p97
[12] Strange (n5)
[13] Wale (n6)
[14] Ravitsky (n4) para 19
[15] Approximately 0.5-1%
[16] Z. Deans, A.J. Clarke, and A.J. Newson, *'For your interest? The ethical acceptability of using non-invasive prenatal testing to test "purely for information"'* (2015) 29 *Bioethics* 19, at p24
[17] Strange (n6) p82
[18] RAPID = Reliable Accurate Prenatal Non-Invasive Diagnosis, p6 available from http://www.rapid.nhs.uk/wp-content/uploads/2016/01/RAPID_Executive_summary_6_May1.pdf (accessed 13/5/2016)
[19] De Jong A, de Wert GM, *'Prenatal screening: an ethical agenda for the near future'*. Bioethics, 2015; 29(1): 46-55 (available at http://www.ncbi.nlm.nih.gov/pubmed/25521973)

disabled child. This seems to be a case of splitting hairs, although as we shall see, the public narrative is particularly important in the context of public funding.

b. **Enhancing choice** – NIPT arguably enhances choice by facilitating early[20] and providing more reliable results than conventional screening.[21] However, in many cases the tests are not diagnostic and therefore not as robust or reliable as the traditional invasive tests.

c. **Facilitating choice** – in theory access to these tests should be simple (ie through traditional blood tests). However, increasing the range of information and data available to parents is potentially problematic and there is some degree of consensus that these tests should be made conditional on the basis of pre and post-test counselling. Again, the availability of NIPT should reduce the overall cost of invasive testing but there is a danger of looking at things in isolation and without knowledge of the likely uptake in NIPT testing[22] and the impact on State funded abortion services. Indeed, a wider discussion is required: should a State fund/facilitate these tests and if so, for what range of conditions/factors/purposes?

d. **Reducing risk** – I have suggested that NIPT is safe but have qualified this as a 'reduced risk' because the tests only reduce the potential need for invasive diagnostic tests and the associated risk of miscarriage. However, in cases where the results are not diagnostic, there might be a danger that NIPT offers false security to parents. There may also be undesirable consequences that flow from an increase in positive (untreatable) anomaly test results:

[20] Ravistky (n4) para 19 – results can be obtained in the first trimester and earlier abortions might be preferable in some cultures (para 46). However, any early abortion advantage might be lost if proper post-test counselling measures are in place (C Munthe, '*A New Ethical Landscape Of Prenatal Testing: Individualizing Choice To Serve Autonomy And Promote Public Health: A Radical Proposal*', Bioethics, 2015, 29(1), p43).

[21] In relation to the detection of Trisomy 21 see: http://obstetricsgynecology.eu/nipt-fetal-dna-maternal-blood?utm_source=e-alert&utm_medium=email&utm_content=button&utm_campaign=May%20update (accessed 23 March 2016). It should be noted that the UK RAPID study originally evaluated the reliability factor at 99% and the risk of false positives at 0.5-1% (see http://www.rapid.nhs.uk/wp-content/uploads/2014/01/NIPT-study-Participant-information.pdf (accessed 23 March 2016)

[22] O'Brien BM, Kloza EM, Halliday JV, Lambert-Messerlian GM, Palomaki GE, *'Maternal plasma DNA testing: experience of women counseled at a prenatal diagnosis center',* Genetic Testing and Molecular Biomarkers. 2014;18(10):665-9 (available at http://www.ncbi.nlm.nih.gov/pubmed/25137409)

'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.'[23]

e. **Preparing parents** - as discussed, early and reliable test results (even about anomaly) may enable the parents to prepare psychologically, physically, practically and financially for their future child and life with a disabled child.[24]

f. **Enabling remedial action** – early test results may enable remedial or preventable action to be taken during the pregnancy (eg testing for rhesus status). That has potential benefits for the pregnant women and her developing child.

g. **Realising a right to know**? Some parents may want to test 'purely for information' – to know whether a feature exists purely for its own sake.[25] In relation to pregnant women, Brownsword & Wale[26] have outlined a plausible basis for a qualified right to know in relation to personal health information - this would probably encompass information about the developing fetus to the extent that it touches or concerns the women's own physical and psychological well-being. Otherwise the mother's rights in relation to information about her developing child are potentially more problematic although clearly any such claims have to be taken seriously. The father also has a strong claim in relation to the health status of the developing fetus although we might expect the mother's interests to prevail over the fathers in the event of conflict. Ultimately society needs to decide what amounts to reasonable informational expectation in the context of pregnancy.[27]

Overall, it is probably fair to say that prenatal screening, and NIPT in particular, provides the potential for choice and wider reproductive freedom.

[23] Ravistky (n4) para 33
[24] Deans et al. (n16) p22
[25] Deans et al. (n16)
[26] Brownsword R & Wale J, 2016, *'The Development of Non-Invasive Prenatal Testing: Some Legal and Ethical Questions'*, Annual Review of law and Ethics (forthcoming)
[27] Deans et al. (n16) p25

2. Realisation of these purposes

a. Choices need to be real, meaningful & lawful

I have touched on the importance of public funding in securing access to these tests and the need for supportive pre and post-test counselling. The need for counselling is likely to be influenced by the range and complexity of information presented to the parents. Some information may be very clear and easy to interpret but some may present statistical risk relating to a current or future outcome or be qualified in terms of reliability. Factual identification of a genetic defect or anomaly is unlikely (by itself) to enable parents to make meaningful choices – they may require some degree of support to interpret that information. The degree of support and information required will also be dependent, to some degree, on education, culture and religious factors that will be context specific.[28] Some information may not enable any clear choice to be made – it may just tell the parents that there is an uncertain and potentially undesirable future for their child. It has to be asked whether society should be seeking to highlight information that cannot facilitate choice. Of course, there is also a debate to be had over whether any State should fund access to this type of information. It is clearly problematic for parents if these tests have the potential to generate uncertainty and anxiety rather than improving choice and reproductive freedom.[29] The pressure to expand the scope of NIPT and the risk of uncertain knowledge is a real one now that we have demonstrated the ability to map the human genome.[30]

And why are we doing the tests in the first place? Will parental purpose be known or will they the ends be conditional upon the test results? Further, if the purpose is to enhance reproductive choice, exactly what choice are we enhancing? If the primary purpose is to improve choice between the continuation and termination of pregnancy,

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[28] Michie M et al., '*Opinions & Informational needs about NIPT from Spanish & English speaking pregnant women in California'*, in P1-51 Poster Abstracts of ISPD 19th International Conference on Prenatal Diagnosis & Therapy, Washington DC, 12-15 July 2015, Prenatal Diagnosis 2015, 35, 27-109

[29] See Agatisa PK, Mercer MB, Leek AC, Smith MB, Philipson E, Farrell RM, *'A First Look at Women's Perspectives on Noninvasive Prenatal Testing to Detect Sex Chromosome Aneuploidies and Microdeletion Syndromes'*. Prenatal Diagnosis, 2015, (available at http://www.ncbi.nlm.nih.gov/pubmed/25800864)

[30] The pressure to provide wider information about the fetus is clearly demonstrated through the parental interviews discussed in Strange (n5).

those choices ought to be lawful and proper.[31] Proper in the sense of a choice that we think 'ought' to be made; and lawful in the sense that the law does not prohibit or otherwise restrict that choice. For example, if the core purpose of gender testing is to make a decision about the continuation of a pregnancy, is any subsequent termination a procedure that both ought to be allowed (proper) and is authorised by the law of the land?[32] We might just test for information about the fetus, although the difficulty will be in discovering whether this is a real or disguised purpose. Of course, parents may not formulate a purpose until the results are available or may have multiple reasons for undergoing the tests. Finally, in relation to testing 'purely' for information, we would need to address whether the State should fund and/or facilitate these types of tests and whether funding should extend to non-health related information.

b. **Alignment and convergence**

For the reasons highlighted, It is important that there is some degree of convergence /alignment between the regulatory frameworks relating to core purposes and the choices presented to parents. There also needs to be some congruence between the public narratives especially where public funding is engaged.[33] For example, it is problematic for a State to facilitate and encourage gender testing on the grounds of reproductive freedom and at the same time restrict terminations on the grounds of fetal sex. Certainly, this is not a black and white scenario but States should be careful not to introduce potential confusion into the public narrative around reproductive choice.[34]

c. Issues:

i. **Stark choice & mixed purposes** – anomaly testing can be seen in binary terms for untreatable conditions but as discussed it may be difficult to draw clear lines.[35]

ii. **Lawful & proper purpose** – Even if a State were to limit NIPT to lawful and proper purposes, there are practical problems. How do we know what are

[31] Brownsword & Wale (n26)
[32] For a fuller discussion of the arguments, see Wale (n6)
[33] Ibid.
[34] Ibid.
[35] Deans et al. (n16) p24; Wale (n6); Brownsword & Wale (n26)

true parental purpose(s) and how can latent (but improper and unlawful) purposes be enforced? There is also the practical difficulty around post-test formulation of purpose.[36]

3. *Increasing information about the future child – 'providing the means to choose well'*

Parental decision-making:

In this section, I will examine the issues connected with increasing information about the future child and ask whether expansion of testing categories will provide parents with the 'means to choose well'.[37] Some aspects have already been flagged:

a. **Trivial & routine**[38] - some commentators have associated the removal of risk with the potential to reduce the significance of these tests and any results.[39] Removing or limiting the miscarriage risk should not make the outcome of these tests any less significant for the parents.[40] There may be a risk that NIPT will be perceived as a routine and standard procedure - this may have important consequences to how clinicians handle consent procedures and to how parents react to particular results.

b. **Normality & lowering thresholds** - concern has been highlighted that NIPT may impact on our concept of normality – the fear being that it will raise our expectation of what is normal and consequently lower our threshold for terminating life that does not meet that criteria**.**[41] It raises the spectre of the designer baby and the potential for pressure on parents to produce entities of perfection. Concern has also been raised about the objectification of the future child/adult and the risks associated with parents expressing views about what they value as genetic traits in their children.[42]

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[36] Brownsword & Wale (n26)
[37] I have borrowed this phrase from Mairi Levitt, Empowered by Choice, Chp 6 in Chadwick, R., Levitt, M., Shickle, D., The Right to Know and the Right Not to Know: Genetic Privacy and Responsibility, 2nd edition, Cambridge: Cambridge University Press
[38] Ravitsky (n4) paras 27-28
[39] De Jong A, Maya I, van Lith JM. *'Prenatal screening: current practice, new developments, ethical challenges'*. Bioethics, 2015, 29(1): 1-8 (available at http://www.ncbi.nlm.nih.gov/pubmed/25521968); Ravitsky (n4); Nuffield Council on Bioethics, Note of Roundtable Meeting on Non-Invasive Prenatal Testing on 18 January 2016, available from http://nuffieldbioethics.org/wp-content/uploads/Note-of-meeting-NIPT-meeting-18-Jan-2016-FINAL.pdf (accessed 22 April 2016)
[40] Deans et al. (n16) p25
[41] Ravitsky (n4) paras 2 & 29
[42] Deans et al. (n16) p24

c. **Premature adoption[43] and false assurances** – there is a concern that where NIPT is not diagnostic, parents (and clinicians) may still treat the outcomes as such. There is already some evidence of this.[44] If diagnostic tests are foregone, there is a danger that NIPT will provide false assurances to the parents and create real dilemmas upon birth.

d. **Unnecessary decisions** – in some anomaly cases the pregnancy may spontaneously miscarry without the need for surgical/medical intervention.[45] Difficult decisions to terminate might be avoided if testing and results were delayed until a later stage in the pregnancy. So not only may NIPT increase the number of terminations based on anomaly identification, it may also do so if choices are presented prior to the usual cut off for spontaneous abortion.

e. **Potential confusion & undesirable options** - Mairi Levitt highlights that more choice does not necessarily give you the means to choose well.[46] Indeed Zuzana Deans et al. argue that:

'the ability to perform a test without risk is in fact something of a disadvantage as it is more likely to generate ethical difficulties and conflicts' [47]

Additional data and information about the developing child can produce unexpected and undesirable results and choices for the parents.[48] There may also be a risk that parents will attach too much significance to the results[49] or over watch for or interpret

[43] Because the tests are unnecessary (Ravistsky (n4) para 12) or because they are not diagnostic (Levenson D., *'Cell-free fetal DNA tests appropriately used by geneticists, often misunderstood by patients: survey finds many patients incorrectly think prenatal screening test is diagnostic'*. Am J Med Genet A. 2014 Apr; 164 A(4): vii-viii. (available at http://www.ncbi.nlm.nih.gov/pubmed/24639127); Horsting JM, Dlouhy SR, Hanson K, Quaid K, Bai S, Hines KA. *'Genetic Counselors' Experience with Cell-Free Fetal DNA Testing as a Prenatal Screening Option for Aneuploidy'*, J Genet Couns, 2013 Dec 19, [Epub ahead of print] (available at http://www.ncbi.nlm.nih.gov/pubmed/24352524))
[44] Levenson et al.; Horsting et al.(n43)
[45] Ravitsky (n4), para 35: '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'.
[46] Levitt (n37) p96 (& pp87-88)
[47] Deans et al. (n16) p21; similarly see Strange (n5) at p173
[48] Deans et al. (n16) p21
[49] Deans et al. (n16) p21

signs in their developing child because of those results.[50] There is also doubt that more information will facilitate choice in certain parental groups. For some, more information about the risk of genetic anomaly may be worthless irrespective of the available legal options because termination may be an unacceptable moral option based on their beliefs.[51]

f. **A right <u>not</u> to know?** So far we have proceeded on the basis that parents will want to know more information about their developing child. But what about those who do not want to know? If NIPT become routine, there must be a danger that this group of parents will be inadequately protected. Indeed, there are potential resource implications around incorporating a right not to know in any screening regime.[52] There may also be issues around incidental findings in the pregnant woman's blood (eg a finding of cancer) and her desire to know/or not know those results.[53]

g. **Constant evolution of technology** – the wider introduction of NIPT will have pros and cons for counselling.[54] Increasing levels of complex information, particularly in terms of statistical risk, is likely to require increased support and sophistication from counselling services. One of the principal challenges will be keeping those services sufficiently in touch with the evolving technology in this field - in terms of the range of conditions that are testable and the accuracy/reliability of any results.[55] Constant change may also have significant resource implications for any State that chooses to fund this type of testing regime.[56]

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[50] Deans et al. (n16) p22
[51] Wale (n6)
[52] Brownsword & Wale (n26); Deans et al. (n16); Skirton H, Patch C. *'Factors affecting the clinical use of non-invasive prenatal testing: a mixed methods systematic review'*. Prenat Diagn. 2013 Jun; 33(6): 532-41 (available at http://www.ncbi.nlm.nih.gov/pubmed/?term=23828950).
[53] Ravitsky (n4) para 14
[54] Ravistky (n4): '*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.*' (para 25)
[55] Ravitsky (n4) para 42; For a discussion on the difficulty posed by non-reportable results, see Borowski et al., *'Counselling required prior to NIPS for risk of unexpected findings', P1-57 in* Poster Abstracts of ISPD 19th International Conference on Prenatal Diagnosis & Therapy, Washington DC, 12-15 July 2015, Prenatal Diagnosis 2015, 35, 27-109
[56] Munthe (n20) p43: '*it will be very expensive to maintain the required adaptability of testing-kits and sufficient standards of counselling. Mere promotion of reproductive autonomy will hardly serve to justify such costs in a public priority- setting context'*.

Clinical decision making:

Many of the above points may apply equally to the clinician – NIPT could make patient interactions more complex - if, for example the data is unclear, equivocal or relates to uncertain outcomes. Expanding test criteria could make clinicians gatekeepers to non-health and trivial related data about the developing child. There must also be the risk that clinicians will be converted into mere technicians that are forced to respond to patient demands for information with little or any scope for clinical discretion.

4. *Widening scope* - what further research is required first?

a. Whole Genome Sequencing is on the distant horizon but the technology will come.[57] Although advance genetic data can be beneficial for prospective parents, it may also produce uncertainty around health or future outcomes. Some consideration therefore needs to be given to how we handle advances in knowledge and to address the type of knowledge: a) that we ought to know and b) that can be processed by parents and clinicians in a meaningful way. Observational and other qualitative studies on point b might be beneficial.

b. How might a State provide a suitably adaptable counselling framework, and at what cost?[58]

c. Further research is required around the public narration of anomaly screening and the choices these tests present:

'Although NIPT appears to bring many benefits, there does need to be clear and consistent public narrative in relation to the promotion and facilitation of parental choice in relation to any testing regime. If the facilitation of parental choice is a core purpose of testing, States should make that explicit and exercise caution before expanding the public funding and provision of NIPT without wider consideration of the connected regulatory frameworks.'[59]

d. What are the media perceptions of NIPT? So far the emphasis has been on the absence of risk and an informed media approach will be important in light of point c.

[57] NCOB (n38)
[58] Munthe (n20)
[59] Wale (n6)

e. If we increase the scope of NIPT– what will be the implications, for example in the demand for abortions/counselling/resource etc. Should the scope of testing expand incrementally[60] and then only after completion of proper evaluation studies? What are the implications around the State provision of access to non-health related data?

f. In relation to the availability of incidental genetic data '*there appear to be stronger arguments for not facilitating analysis of incidental data via additional public funding' but 'the public facilitation of such analysis (before and after birth) merits further consideration*.'[61]

Conclusions

This paper welcomes the arrival of NIPT but cautions against automatic widening of information categories without further inquiry and research.

Jeff Wale

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[60] For caution: see Alexander E, Kelly S, Kerzin-Storrar L.*'Non-Invasive Prenatal Testing: UK Genetic Counselors' Experiences and Perspectives'*, Journal of Genetic Counseling, 2015; 24(2): 300-11 (available at http://www.ncbi.nlm.nih.gov/pubmed/25315608)
[61] Wale (n6)

Appendix A

Summary of Key Publications

1. **Brownsword R & Wale J, 2016 -** right to know & right not to know – the latter might become more important in the future – reasonable to include a lawful & proper purpose requirement– burden should be on B (the screener)

2. **Nuffield Council on Bioethics – roundtable meeting, January 2016:**
    - Whole genome sequencing (WGS) on distant horizon
    - Broadening = complex decisions
    - Increased demand for NIPT – unclear if it means more abortions.
    - Routinisation
    - Difficulty in managing informed consent
    - Unnecessary worry/test (because of the likelihood of spontaneous miscarriage)
    - Implications for disabled.
    - Commercial options & issues
    - Cultural issues

3. **Wale J, 2016** – convergence in narrative & purposes. A state should only fund/facilitate lawful and consistent choices

4. **Ravistsky V, 2015, Nuffield Council of Bioethics Paper**
    - Para 2 implicit expression of what is normal
    - Para 12 premature adoption without a follow up diagnosis (6.2%)
    - Para 13 Whole Genome Sequencing – on distant horizon
    - Para 17 pre & post -test counselling, voluntary, negative effects of routinisation, diverse cultural/ethical needs
    - Para 19 Current benefits: safety, reliability, timing , access & ease/comfort
    - Para 21 Future cost savings if becomes diagnostic
    - Para 24 Constant evolution of reliability & implications for counselling
    - Para 27 In absence of procedure related risk, clinicians may perceive consent as less important than for invasive tests.
    - Para 28 Routinisation
    - Para 29 Lowering threshold in relation to minor conditions, late onset, non-medical traits, non-medical sex selection.
    - Para 42 Constant evolving accuracy/reliability

5. **Munthe C, 2015** – economic consequences of providing a suitably adaptive counselling model. Private vs public provision.

6. **Chitty L et al., 2015, Executive Summary of RAPID Evaluation** summary – recommends contingent use of NIPT for aneuploidy.

7. **Agatisa et al., 2015 Women's perspectives re NIPT for aneuploidies & microdeletion syndromes –** uncertain about utility and the actionability of receiving information about microdeletion syndromes with variable or unknown phenotypic expression.

8. **De Jong & De Wert, 2015, ethical agenda.** Anomaly screening leads to no other option but the choice between the continuation or termination of the pregnancy and can only be morally justified if its aim is to provide meaningful options for reproductive choice to PW & their partners. Anomaly screening should not be understood as maximising choice per se – there should be public funding only if understood as avoiding suffering related to living with a disabled child. Private sector funding is problematic – creates inequality between those who can and cannot afford these tests.

9. **Deans Z et al., 2015 - the ethics of testing purely for information**

10. **De Jong, Maya & Lith, 2015 – ethical challenges.** Risk is routinisation. If same test is used for different aims (detection of anomaly & pregnancy related problems) non-directive counselling can no longer be taken as standard.

11. **Alexander E et al., 2015 perspectives of genetic counsellors.** Concerns expressed about broadening NIPT in the routine antenatal setting.

12. **Chadwick et al., 2014, Right to know & not know (book); see in particular: Mairi Levitt, Empowered by choice? (Chapter 6):**
    - Choice does not automatically give you the means to choose well (p96)
    - Choice does not= equality
    - More choice=more confusion (p87)
    - More choice=undesirable options (p87)

- Responsibility for outcome (p88)
- Choice=self-expression (p89)
- More choice=more satisfaction
- Raising expectations (p89)
- Long & complicated menu at a restaurant – do we fall back on habit (p96)

13. **Skirton et al., 2014, easy test but hard decision.** Recommends a written record of parental consent in all cases.

14. **Obrien B et al., 2014, experience of counselled women**, Private sector costs were a barrier that if removed would increase uptake by 50%+. Nearly half did not want further testing.

15. **Levenson D, 2014, Many patients think NIPT is diagnostic**

16. **Horsting et al., 2014, Genetic counsellors experience with NIPT for aneuploidies.** Concern about how obstetricians and patients make use of tests.

17. **Skirton et al., 2014, PDT – European clinical guidelines.** Ease of testing may increase use of direct to consumer testing.

18. **RAPID Study patient info sheet –** patient information/ guidance probably more detailed than would be the position if implemented via the NHS.

19. **Skirton & Patch, 2013 – mixed methods review of NIPT –** there is a risk that these tests will be done without woman's knowledge.

20. **Wilkinson S, 2015, Reproductive Choice & Public Health –** pro-choice individuals cannot restrict the scope of these tests with risking inconsistency.

21. **Strange, H, 2015, Doctoral thesis,** ***Non Invasive Prenatal Diagnosis & Testing: perspectives on the emergence & translation of a new prenatal testing technology:***

    a. **P82 -** if NIPT becomes diagnostic – first time it enters the low risk population > danger of routinisation & normalisation of selective abortion.

b. **P86 –** direct talk of abortion & abortion experiences is very frequently absent from mainstream and/or public discussion of PNT in general as well as NIPD…often glossed over…presented instead as an essential element of reproductive choice.
c. **P88 -** explicit lack of public discussion re selective abortion as central to experiences/encounters with NIPD.
d. **P89 – '***The limited scope for treatment of the fetus entails that in the majority of pregnancies,* ***when a diagnosis of 'fetal abnormality' is provided as a result of prenatal testing, this information may be used to guide decision making around a single intervention: whether to continue with a pregnancy, or whether to end that pregnancy through abortion'***
e. **P97 -** by foregrounding THE discussion of individual reproductive choice – contains problems raised by PNT (including the underlying & centrality of selective abortion).
f. **P107 –** explores argument that because NIPT is not diagnostic it is not presenting a definite choice between termination/continuation – you still need invasive tests.
g. **P110 –** routinisation – no risk so why not test?
h. **P174 '***Whereas much emphasis was placed on 'knowing about' the test and 'getting information', the specific diseases and disorders tested for were positioned very much in the background and made 'symbolically invisible' (Thomas 2014, p.176).'*
i. **P174 '***The persistent presentation of women as autonomous, individual consumers and 'choice-makers' becomes quite clearly insufficient then, as we see that the very process of receiving information (however 'nondirective' it may be) - the process of becoming informed - entails some kind of local translation within relational, complex experiences of pregnancy, which are guided and shaped by both personal inclinations and established cultural norms'*

22. Poster Abstracts of ISPD 19th International Conference on Prenatal Diagnosis & Therapy, July 2015:

a. **P1-47, Kramer E et al.,** ***The changing landscape of prenatal screening,*** given the residual risk of anomaly after normal NIPS, clinicians must be aware of the limitations of NIPS & offer additional screening & testing options.
b. **P1-51, Michie M et al.,** ***Opinions & informational needs about NIPT from Spanish & English speaking pregnant women in California*****,** women value

NIPTS lack of procedural risk & its ability to help prepare for unexpected condition. Language and education barriers may be present & some women would value printed educational materials & to receive recommendations from a trusted advisor.

c. **P1-57, Borowski K et al., *Counselling required prior to NIPS for risk of unexpected findings*,** some chromosomal issues may be reported as non-reportable results (ie outside parameters of test) & produce anxiety for the pregnant women.
d. **P2-12, Griswold C et al., *Case of twin gestation affected with discordant aneuploidies, and a false negative non-invasive test result* (for T18) –** self-explanatory.
e. **P3-60, Sharma P et al., *Women's understanding of NIPT based on cell free DNA versus first trimester combined screening*,** 35% of women think NIPT & combined screening are equally reliable after counselling. Information given is complex and women would benefit from educational material specifically tailored to the integration of NIPT.
f. **P3-67, Strange H, *Patient & professional experiences with non-invasive prenatal diagnosis and testing: social & ethical issues raised*** (see above)

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