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Ethical, legal and social issues arising from cell-free fetal DNA technologies

Appendix III to the report:
Cell-free fetal nucleic acids for non-invasive prenatal diagnosis

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Disclaimer: The field of non-invasive prenatal diagnosis is extremely dynamic and technology is developing very rapidly; this report is accurate as of 7th January 2009.

Executive Summary

Ethical, legal and social issues arising from cell free-fetal DNA technologies

This paper provides an analysis of ethical, legal and social issues raised by the introduction of cffDNA technology for non-invasive prenatal testing. We recognise the clinical benefits of cffDNA technology in terms of a reduction of invasive procedures (amniocentesis and CVS) as well as better targeting of pregnancy-related interventions. However, these benefits notwithstanding, the introduction of this technology is not necessarily ethically unproblematic if seen in the context of broader debates about prenatal testing, and if one considers the particular characteristics of cffDNA technology. The paper also examines a range of potential applications for the technology within the context of clinical genetics services, routine antenatal care, and direct-to-consumer testing.

Use of cffDNA technology within existing specialist clinical genetics services provides a valuable tool for earlier and safer determination of fetal sex relevant to inherited (sex-linked) disorders. However, the availability of non-invasive tests using cffDNA could also lead to an increase in prenatal testing and to selective terminations of pregnancy in circumstances currently only possible in the highly regulated context of preimplantation genetic diagnosis (PGD). The ability to test earlier in pregnancy could influence the choices made by parents to continue with the pregnancy and could even make it a more difficult choice to continue with an affected pregnancy. More generalised use of non-invasive testing could facilitate selective terminations of pregnancy in a range of conditions hitherto not diagnosed prenatally and where the arguments for and against termination may not have received sufficiently scrutiny.

In antenatal care, cffDNA technology has already been introduced for the management of RhD[1] in high risk sensitised pregnancies. However, test parameters and the appropriate scope for the general application of cffDNA testing in antenatal care remain to be established. With respect to antenatal screening for aneuploidies such as Down's syndrome, the introduction of cffDNA or cffRNA analysis could replace current screening methods with testing programmes that allow for non-invasive and highly predictive diagnostic testing. Albeit likely to be 3-5 years in the future, the prospect of the introduction of cffDNA technology in routine antenatal care underlines the importance of informed consent in the design and evaluation of antenatal screening programmes.

In the light of these issues, we suggest that it may be useful to consider the introduction of cffDNA technology as part of a more general shift towards non-invasive prenatal testing. One area of potential concern is the application of the technology for fetal sex determination for non-medical reasons, for example by means of tests already available from commercial providers via the internet, with a view to sex selective abortion. We examine some of the arguments that could be made for and against such uses and review some possible implications for the NHS. More importantly, however, this illustrates that the introduction of cffDNA

1 RhD blood antigen, commonly known as Rhesus (Rh) factor D.

technology raises questions about the adequacy of existing legal frameworks and about appropriate policy and regulatory interventions that transcend health care providers.

Consideration of these ethical, legal and social issues should play an important role during the introduction of cffDNA technology, and below we identify a number of related avenues for further research. We have not dealt in any length in this report with technical, application-specific questions (such as specificity and sensitivity, the potential for contamination, or the fact that certain nucleic acid-based tests may be sensitive to ethnic differences), although these technical questions should also be considered prior to the implementation of cffDNA testing.

1.0 Introduction

The use of cffDNA for non-invasive prenatal testing was discussed at a meeting of the Joint Committee on Medical Genetics of the Royal College of Physicians, the British Society for Human Genetics, and the Royal College of Pathologists in 2007. This led to the decision that the involvement of a wider group of stakeholders was needed to form recommendations about the key issues in implementation of this technology across the UK. The PHG Foundation, an organisation dedicated to the application and evaluation of genome-based technologies for the benefit of health, volunteered to set up a working group, consisting of a steering committee and a wider group of stakeholders, and run two workshops that would explore the issues further. The results of this process are available in the main report, *Cell-free fetal nucleic acids for non-invasive prenatal diagnosis*.

The provenance of this review of ethical, legal and social issues raised by the use of cell-free fetal DNA (cffDNA) and RNA (cffRNA) from a maternal blood sample for non-invasive prenatal testing (NIPD) was as a briefing paper for the working group. As a consequence, the content and scope of the review has in part been dictated by the scope of the main project (to focus upon the development and implementation of the technology in the UK). Many of the issues raised below (e.g. assumptions about the scope of the technology, timing of the introduction of different applications, and specific ethical, legal and social arguments) have subsequently been taken up in the main report: this paper has not been amended to reflect the revised content of the main report, but is intended to supplement those findings.

In this review we summarise the most significant issues and indicate potential areas for further in-depth analysis. Overall, we suggest that although the technology has the potential to offer clinical benefits, its implementation should be considered together with broader issues and developments in this area. One of the advantages of the technology is that it allows for non-invasive testing earlier in pregnancy, and we review how this feature of the technology interfaces with existing care pathways. One may also ask how the availability of earlier, safer testing will change the management of pregnancy and how this may be linked with changes in rates of termination of pregnancy. The interface between clinical care and the regulatory framework relating to abortion emerges as a theme. The implementation of cell-free fetal DNA technology may also be regarded as part of a more general shift towards non-invasive prenatal testing, both via medical and non-medical intermediaries as well as direct-to-consumer, and as such raises a host of broader issues. Although there is an increasingly globalised traffic for medical care, particularly in the area of reproduction where national laws may differ substantially, our discussion mainly focuses on the ethical, legal and social issues raised by use of the technology in the UK.

2.0 Does cffDNA technology raise new issues?

In this section, we suggest that cffDNA technology, despite being amenable for safer and earlier prenatal testing, raises a distinct set of ethical, legal and social issues. This argument is based on a number of assumptions about the likely implementation of the technology, which admittedly also introduce uncertainties into our discussion overall. However, these uncertainties seem preferable to discussing the technology in general terms that is as NIPD, without taking account of its particular characteristics. Once we have established that cffDNA technology raises a distinct set of ethical, legal and social issues, we discuss these in more detail with respect to termination of pregnancy in the following section.

2.1. Assumptions

This analysis is based upon a number of assumptions about the likely implementation of the technology. Some of these relate to the scope of the technology (Section 2.4). We have sought to take account of and differentiate between what is actually currently possible with cffDNA technology, what is likely to be possible in future, and the prospect of generalised NIPD, which is often appealed to in public discussions of this technology.

- Current cffDNA testing relies upon a range of different technologies. The most reliable and most developed analytical methods rely upon measuring a quantifiable systematic difference between fetal and maternal DNA;
- Where systematic differences are measured, this limits the application of the technology primarily to the detection of paternally inherited DNA sequences.[2] In the immediate term, this will include the use of technology for sex determination and the diagnosis of conditions in which there are differences between maternal and paternal DNA, such as rhesus D status (RhD);
- The technology is predicated upon the presence of DNA from the fetus in the maternal bloodstream, which is in the form of short fragments. The small size of the fetal DNA fragments limits the range and applicability of the technology, since it cannot be used to examine lengthy mutations or deletions;[3]
- Within a clinical genetics setting, the technology is likely to be adopted most quickly for sex determination to identify fetuses at risk of an X-linked disease and certain endocrine disorders. To a lesser extent it may be used for the diagnosis of fetuses at risk of autosomal dominant diseases, such as Huntingdon's disease and achondroplasia, and for identifying paternally derived mutations indicating fetal carrier status in autosomal recessive diseases caused by compound heterozygosity, such as cystic fibrosis and ß-thalassaemia.[4] It is currently not possible to identify fetuses that are homozygous for autosomal recessive disorders, since maternally derived DNA from the fetus cannot be distinguished from maternal DNA; in this respect, the potential

2 Shotgun sequencing methods described recently are not dependent upon differences between paternal and maternal DNA. Fan H. C. *et al.* Noninvasive diagnosis of fetal aneuploidy by shotgun sequencing DNA from maternal blood PNAS0808319105, (2008).

3 Norbury G. & Norbury C.J. Non-invasive prenatal diagnosis of single gene disorders: How close are we? *Seminars in Fetal and Neonatal Medicine* 13(2): 76-83 (2008).

4 *Cell-free fetal nucleic acids for non-invasive prenatal diagnosis* report, chapter 4.

application of the technology is likely to be limited;

- Once the technical specifications of the test technology are well-established, it might be routinely integrated into clinical genetics services for some conditions within 2-3 years;
- The reliability of the cffDNA technology in the context of managing RhD has already led to it being adopted routinely for high risk sensitised pregnancies and could become the norm for all RhD-negative pregnancies within the next 2-3 years;[5]
- Further utilisation of the technology within Down and other aneuploidy screening programmes (such as Edward's and Patau's syndrome) is likely within 3-5 years. However, (as discussed in more detail in the main report) there remain considerable uncertainties as to how exactly the technology will be implemented in this area, that is whether as an addition to existing screening tests or as a stand alone screening/ diagnostic test;
- Determined consumers may access cffDNA technology from private companies via the internet (already available for the purposes of sex determination) immediately without medical support. The number seeking direct-to-consumer testing is likely to increase over time as awareness of the science and its potential applications grow;
- Some of the limitations that apply to cffDNA technology do not apply to the analysis of cffRNA of feto-placental origin. Research in this area is currently less well established than cffDNA-based technology, but is developing very rapidly;
- The non-invasive[6] nature of cffDNA technology offers significant advantages over current clinical protocols. It is expected that cffDNA analyses will allow a considerable reduction of invasive genetic testing, which carries a risk (~1%) of miscarriage regardless of the genetic status of the fetus, for example for sex determination in pregnancies at high risk of X-linked conditions,[7] and that cffDNA technology will also allow for better targeting of interventions to pregnancies affected by certain conditions, for example for RhD and other conditions;[8]
- This review is directed primarily at the UK, rather than countries where the healthcare systems are substantially different (in terms of available resources and technologies).

2.2 Does cffDNA technology raise new ethical problems?

The ethical basis for prenatal testing is well established and the similarity between this type of test and pre-existing prenatal test technology might suggest that there are unlikely to be any substantive new ethical issues raised by this technology. Indeed, given that cffDNA

5 *Cell-free fetal nucleic acids for non-invasive prenatal diagnosis* report, chapter 6.

6 Note that the 'non-invasive' tag is historical and was acquired through comparison with other diagnostic procedures such as CVS and amniocentesis. CffDNA technology is invasive in the sense that a maternal blood sample is required.

7 Norbury, G. & Norbury C.J. Non-invasive prenatal diagnosis of single gene disorders: How close are we? *Seminars in Fetal and Neonatal Medicine* 13(2): 76-83, (2008).

8 Finning, K. M. & Chitty. L. S. Non-invasive fetal sex determination: Impact on clinical practice. *Seminars in Fetal and Neonatal Medicine, Non-Invasive Prenatal Diagnosis: Implications for Antenatal Diagnosis and the Management of High-Risk Pregnancies* 13(2): 69-75 (2008).

testing is likely to be safer than current, more invasive techniques, it might seem that if current techniques are ethically acceptable, then we should think that cffDNA testing is not only ethically acceptable, but preferable to current techniques. However, two issues make this inference problematic. **First**, the broad agreement on the legal and ethical acceptability of current techniques for prenatal diagnosis does not mean that they are necessarily ethically unproblematic: their acceptability should be kept under consideration, and legal acceptability should be distinguished from ethical acceptability. **Second**, the very fact that cffDNA testing is likely to carry a significantly lower risk to the fetus than other forms of prenatal testing, might itself create ethical problems; some people might be encouraged to use that technology for less established and arguably morally problematic purposes, when they would not have used alternative, riskier technologies for such purposes. Thus increased safety can generate ethical problems as well as ethical benefits. Moreover, the existence of these ethical issues suggests that the implementation of cffDNA technology should take account of broader social values, especially since the clinical implementation of cffDNA technology may also be regarded as reflecting a more general shift towards non-invasive prenatal testing.

2.3 Hype, hope and trust in new technology

The technology is still being actively researched and developed, and serious practical difficulties in developing robust and reliable tests remain. It is important that from the outset, the tests are presented in a way that reflects both their potential and current limitations, in order to safeguard public trust in scientists and the medical profession.[9] In the context of policy deliberations and public communication it may be preferable to acknowledge that cffDNA is a technology with inherent weaknesses as well as strengths depending on the particular application. For example, speaking simply of 'free fetal DNA', with the boundless applications for NIPD this implies, could mislead broader audiences.[10] Similarly, researchers could be accused of a lack of transparency if the technology was justified in terms of its potential to detect serious medical diseases, if in fact it was also used for more ethically controversial purposes such as sex selection or paternity testing.

2.4 The scope of the technology

The range of current methods of detection and amplification of cffNA suggest that the technology will not have universal application. We focus upon methods which detect DNA sequences in cffDNA that have been inherited from the father (rather than more recently described shot-gun sequencing methodology, which is at an earlier stage of development but raises many similar issues), and on the clinical applications which are described in the main report from this project, namely the determination of fetal sex in pregnancies at risk of a sex-linked disease through the detection of male Y chromosome DNA; the selective detection of single gene disorders involving paternally inherited mutations; the detection of fetal aneuploidies by measuring the ratio between chromosomes; and the diagnosis of

9 See O'Neill, O. *Autonomy and trust in bioethics* (Cambridge University Press) (2002) for discussion of the nature and role of trust in medicine.

10 This language is adopted, for example, by Sequenom® in 'Corporate Presentation – December 2007', accessed at www.sequenom.com on 25 February 2007; subsequent 'Corporate Presentation – April 2008' refers to "cell-free fetal DNA", cf. http://www.sequenom.com/getdoc/f30a530e-2f97-4adb-be4c-867359ff8e89/APRIL_08, accessed 7 April 2007.

fetal blood group, such as the Rhesus factor D (RhD), through the detection of the paternal RhD gene, in RhD negative women. In addition, we consider the use of the technology for non-clinical applications, and we suggest that these cannot be set aside completely when considering the broader issues raised by cffDNA technology.

As the technology currently generally involves detecting differences between maternal and fetal DNA, it cannot yet be used for identifying certain types of single gene disorders, notably those caused by large mutations, deletions or translocations. The identification of fetuses which are homozygous for autosomal recessive diseases (such as cystic fibrosis or some haemoglobinopathies) is currently limited to compound heterozygotes in which the paternal mutation differs from the maternal one, and to date much of the research has concentrated upon X-linked disorders where the identification of fetal sex is a marker for predicting specific disorders. Despite these technical limitations, a broad range of single gene disorders can be diagnosed and managed with the help of cffDNA technology, and one would expect that judgements of whether to implement cffDNA testing will depend in part on the particulars of the condition in question. In other applications such as congenital adrenal hyperplasia, the pathology of the condition is related to fetal sex, and that knowledge can be used to improve pregnancy management. This raises qualitatively different issues as does testing to determine RhD status.

Given that cffDNA technology might in time prove to be significantly cheaper than alternative diagnostic methods,[11] one could imagine pressures on clinical genetics services to adopt cheaper testing methods and to prioritise testing for certain categories of genetic conditions over others. For autosomal dominant single gene conditions one might expect changes to existing care pathways and it is plausible to predict early marketing of direct-to-consumer testing). In turn, the availability of cffDNA for NIPD might affect how decisions are made to resource treatment and support services, etc. In the early stages of implementation, management on a condition-by-condition basis, the capital costs associated with testing (such as mass spectrometers, licence fees, providing appropriate staff training) together with economies of scale might cause the cffDNA technology to be confined to a few specialist laboratories, which could potentially threaten equity of access.

2.5 Earlier testing

The use of cffDNA technology allows certain characteristics of the fetus to be identified earlier in the pregnancy than would have previously been the case using existing testing methods. This has major clinical advantages in certain cases, for example in guiding appropriate treatment during pregnancy, whilst being 'non-invasive'.[12] Whilst the gatekeepers for this technology are at present researchers and expert medical services (such as clinical genetics services for single gene disorders, and antenatal services for RhD), existing law does not prevent the tests being accessed privately for non-medical purposes (such as sex determination and subsequent termination of pregnancy). The issue of private access to tests for the purpose of sex determination is complex, and discussed separately in Section 7 below.

11 Norbury, G & Norbury C.J. (2008) estimate the cost of cffDNA testing being around £250 per sample. Anecdotal evidence from the genetics community suggests that rationing of more expensive diagnostic prenatal tests sometimes occurs.

12 Such as congenital adrenal hyperplasia.

The prospect of earlier diagnosis of a fetus affected by a condition for which abortion is commonly sought is undoubtedly attractive, and the earlier diagnosis made possible by use of cffDNA technologies may offer significant benefits. For example, the choice to abort might be less physically and psychologically traumatic earlier in pregnancy,[13] and parents will have longer to consider what action to take. Furthermore, anxieties about the possible need to abort, which might prevent mothers bonding with their fetus, would be minimised if prenatal diagnosis were carried out earlier in pregnancy.[14] Finally, the availability of non-invasive diagnostic tests may be valued by prospective parents of babies with a genetic condition, even if the test result has no bearing on the parents' decision to continue with a pregnancy since they might influence the clinical management of the pregnancy.[15]

However, earlier testing could also make proceeding with an affected pregnancy a more difficult choice for parents for two reasons. First, because the risks associated with diagnosis are less, parents may feel that they "should" seek a diagnosis even though proceeding with that choice might lead them to make decisions they would have preferred to avoid. In recent years, many bioethicists have suggested that, as a result of developments in medical technologies, children are increasingly seen not as "gifts" to be cherished come what may, but as "commodities", with characteristics to be chosen.[16] They suggest that this is a problematic development insofar as it changes the nature of a basic human relationship.

Of course, whether such changes are bad, and whether cffDNA technologies might really affect such changes, are contested questions. However, it is clear that some parents who might want to view their children as "a gift" might feel pressurised into adopting a different attitude towards the fetus due to the availability and ease of cffDNA testing. Second, given the lower risks associated with earlier testing, society may come to be less supportive of those who choose to have disabled children. In turn, worries over social disapprobation may leave some parents feeling pressurised into terminating a fetus, although this runs contrary to what they would otherwise have chosen.[17] It is, then, not difficult to imagine a "loopback effect" developing whereby earlier detection of fetal abnormalities may hinder, rather than promote, parental choice by increasing the pressure both to test and to terminate.

13 A recent review of mental health and abortion concluded that among adult women who have an unplanned pregnancy, electing a single first-trimester abortion over delivery does not increase the relative risk of developing mental health problems. Limited evidence also suggests that women who terminate a wanted pregnancy on grounds of fetal abnormality experience an equivalent negative psychological burden to those who have a stillbirth or miscarriage but less than those who deliver a child with life-threatening abnormalities. American Psychological Association *Report of the APA Task Force on Mental Health and Abortion*. Table 4 (2008). There is an absence of methodologically sound research that compares women who terminate wanted pregnancies on the grounds of fetal abnormality at different states in pregnancy.

14 Newson, A. J. Ethical aspects arising from non-invasive fetal diagnosis. *Seminars in Fetal and Neonatal Medicine Non-Invasive Prenatal Diagnosis: Implications for Antenatal Diagnosis and the Management of High-Risk Pregnancies* 13(2): 103-108 (2008).

15 Polnay, J. C., Davidge, A. *et al*. Parental attitudes: antenatal diagnosis of cystic fibrosis. *Arch. Dis. Child*. 87: 284-286 (2002); Seror, V. What understanding of decision-making in prenatal screening could decision analysis provide? *Ultrasound Obstet Gynecol* 30: 921-923 (2007).

16 See, for example, Michael Sandel *The case against perfection: ethics in an age of genetic engineering* (Belknap Press) (2007). Although Sandel's focus is on technologies of genetic enhancement, his concerns seem applicable here.

17 Newson, A. J. Ethical aspects arising from non-invasive fetal diagnosis. *Seminars in Fetal and Neonatal Medicine Non-Invasive Prenatal Diagnosis: Implications for Antenatal Diagnosis and the Management of High-Risk Pregnancies* 13(2): 103-108 (2008).

2.6 Specification creep

Existing standards of clinical practice are likely to be used as a benchmark for determining whether cffDNA technology should be used for a particular application (for example, its use for Down screening would be assessed with respect to the current regime for Down screening). Existing standards might also provide a precedent for ethically acceptable uses if the technology is introduced in circumstances where the medical justifications for the application are well developed.[18] In addition to current clinical practice, guidance covering preimplantation genetic diagnosis, and implantation of embryos unaffected by serious genetic conditions in the context of artificial reproductive treatment, could be relevant, although currently this area is technologically intensive, limited to a small range of genetic conditions and highly regulated.

Although initially existing clinical precedents will probably guide uptake of the technology, ultimately cffDNA technologies may be applicable to a wider range of conditions. It is conceivable that, as analyses of cffDNA become more routinely accessible, applications will be considered for which there is no clear clinical precedent. The use of cffDNA technologies could facilitate a more general move towards prenatal genetic diagnosis precisely because the inconvenience, trauma, or risk associated with current invasive diagnosis (and any subsequent termination) is lowered. As a consequence, the technology could 'creep' into more generalized prenatal diagnostic use, such that conditions for which invasive diagnostic testing is not currently offered may be diagnosed using the technology.

For example, 22% of prenatal tests performed as part of a recent UK audit of fetal sex determination using cffDNA were for haemophilia, for which invasive prenatal diagnosis is not usually requested.[19] The technology could also be used on non-medical grounds, such as sex determination and sex selection. Interventions for applications that are currently unavailable or likely to be illegal in the regime of pre-implantation genetic diagnosis may come to be possible in the realm of non-invasive prenatal diagnosis. This may happen without adequate scrutiny from legislators, policy makers and the public. This also relates to the issue of private access to tests based on cffDNA technology.

2.7 Distinguishing between screening and diagnostic tests: informed choice

Some argue that in the context of screening, (including prenatal screening) that the traditional model of informed consent should be reformulated to place more emphasis upon the pre-existing values of the decision maker and less emphasis upon other elements such as the competence of the decision maker. The model that has emerged is that of 'informed choice'.[20] In the context of prenatal screening interventions, the extent of test uptake has

18 This might include selection for sex or other characteristics of an embryo (for example, as a tissue donor for a diseased sibling) in the context of pre-implantation genetic diagnosis.

19 Chitty, L. *et al*. Prospective Register of Outcomes of Free-fetal DNA testing (PROOF) results of a first years audit *Newsletter of the British Society for Human Genetics* **37**, 8-9 (2007). See also Bustamante-Aragones A. *et al*. Foetal sex determination in maternal blood from the seventh week of gestation and its role in diagnosing haemophilia in the foetuses of female carriers. *Haemophilia* **14**, 593-598 (2008).

20 Thus O'Connor and O'Brien have described informed choice as follows: 'An informed choice is one that is based on relevant knowledge, consistent with the decision-maker's values and behaviourally implemented'. O'Connor, A, O'Brien-Pallas, L.. Decisional conflict. In *Nursing Diagnosis and Intervention: Planning for Patient Care*, McFarlane, G., McFarlane, E. (Eds) Mosby: St Louis, MO 486-9 (1996).

been used as a measure of the extent to which women are effectively informed about the screening test taking account of their pre-existing values and beliefs. Such assessments have been facilitated by the development of research tools such as the Multidimensional Measure of Informed Choice, which have been used in a variety of settings.[21] Informed choice models place less emphasis upon establishing competence and lack of coercion on the part of the decision-maker, and tend to assume that the decision maker is an autonomous rational agent.[22] If the distinctive feature of informed choice, as opposed to informed consent, is the extent to which account is taken of pre-existing values, then this has implications for the type and nature of the information provided in the context of cffDNA testing.

CffDNA technology underlines the importance of informed choice because it could replace a multi-step screening process that may ultimately lead to an invasive diagnostic test (such as testing for Down's syndrome) with a single blood test providing a highly-predictive result. Existing screening regimes typically utilise initial screening tests (such as maternal age, blood tests and nuchal fold measurement in Down's syndrome) to identify a group at high risk of having an affected fetus who may be offered optional diagnostic testing.

It is a long-standing concern that at least some women who participate in Down screening do so without making an 'informed choice' to do so, and parents may participate in the process without understanding the significance and possible consequences of providing blood or undergoing an ultrasound scan for screening (especially if abnormalities are identified).[23] In the current Down screening regime, a high risk result also provides parents with a chance to reflect upon whether they want to investigate any further. CffDNA technology has the potential to yield a highly reliable result immediately following analysis of a maternal blood sample. Arguably, since the significance of the test is elevated, there is an increased need to ensure informed participation, especially as the diagnostic test is essentially non-invasive and thus clinically less conspicuous.

More generally, in considering changes to services based on cffDNA technology, one may wish to consider the effect such changes have on uptake and how they relate to the aims of the service.[24] Although it seems plausible to suggest that many parents would consent to prenatal testing, others may be less willing to consent given the perception that such testing might also lead to pressure to terminate. Therefore, it is important not to assume that (from the viewpoint of the autonomous parental decision-maker) "more information" is always "better", especially if the function of the screening process itself seems to be characterised by a shift from a public health intervention designed to reduce the prevalence of genetic conditions to a service designed to better inform parents.[25] For the reasons given above,

21 Marteau, T., Dormandy, E., and Michie, S. A measure of informed choice. *Health Expect* **4**:99-108 (2001); Michie, S,, Dormandy, E., and Marteau, T. The multidimensional measure of informed choice: a validation study. *Patient Educ Couns* **48**: 87-91(2002); Jaques, A.. *et al*. Informed choice in women attending private clinics to undergo first-trimester screening for Down syndrome *Prenatal Diagnosis* **25**:656-664 (2005).

22 Osterlie, W. *et al*. Challenges of informed choice in organised screening *J. Med Ethics*;34;e5 (2008).

23 Dormandy, E., Michie, S. *et al*. Informed choice in antenatal Down syndrome screening: A cluster-randomised trial of combined versus separate visit testing. *Patient Education and Counseling* 61(1): 56-64 (2006); Marteau, T. M. & Dormandy, E. Facilitating informed choice in prenatal testing: How well are we doing? *American Journal of Medical Genetics* 106(3): 185-190 (2001).

24 *E.g*. Dormandy, E., Michie, S. *et al*. Informed choice in antenatal Down syndrome screening: A cluster-randomised trial of combined versus separate visit testing. *Patient Education and Counseling* 61(1): 56-64 (2006).

25 Marteau, T. M. & Dormandy, E. Facilitating informed choice in prenatal testing: How well are we doing? *American Journal of Medical Genetics* 106(3): 185-190 (2001).

the introduction of cffDNA technology in this context may warrant reconsideration of the purpose of screening and how it should be evaluated, both with respect to parental choice and NHS policy more generally.[26]

2.8 Framing communications

The extent to which an intervention is identified as a screening or diagnostic tool, together with distinctive conceptions of how parental autonomy and privacy should be managed, might dictate the development of systems for consent and counselling. Where the test is intended as a screening tool, it might be enough to provide relevant information (coherent with the value system of the recipient) rather than ensure competence and lack of coercion on the part of the recipient.[27] The ease of prenatal diagnosis with cffDNA should not detract from the significance of the decision-making process associated with use of the technology. If cffDNA (or cffRNA) tests are to replace existing antenatal screening programmes, for example for Down's syndrome, then substantial issues are raised about the communication and the design of these programmes.[28]

Research has already demonstrated that communication about disabilities varies widely in different countries: for example, written information for people undergoing carrier testing for cystic fibrosis (CF) was more positive about the condition in the US than in the UK.[29] Providing "neutral" information on the basis of which parents can make their "own" choices is problematic. Even in clinical genetics, where professional norms of non-directiveness and shared decision making provide the context for genetic diagnosis, these ideals might be set aside if doing so is (believed to be) justified in the best interests of the fetus or mother. Where there is conflict between the best interests of the mother and the fetus, particular care is needed in framing communications appropriately.[30]

Any changes to existing practice in screening or clinical genetics need to be justified by more than a perception that an intervention is in the mother and/or fetus's best interests. In this context it is perhaps not surprising that the use of cffDNA technology to establish fetal RhD status is the most developed of all the potential applications since the consequences of failing to detect a RhD positive fetus in a RhD mother are potentially life threatening, and genetic diagnosis of the fetus does not carry adverse implications for the future of life of the

26 Some literature that might be brought to bear on this question is: Hagard, S. & Carter, F. Preventing the birth of infants with Down syndrome: a cost benefit analysis. *British Medical Journal* 1: 753-756 (1976); Seror, V. & Costet, N. Down syndrome serum marker screening: decision criteria and implicit values. *Health Policy* 43(1): 83-96 (1998); Seror, V. Fitting observed and theoretical choices - women's choices about prenatal diagnosis of Down syndrome *Health Economics DOI*: 10.1002/hec.1276 (2007).

27 Newson, A.J. (2007) *op. cit*. at page 105; UK National Screening Committee (2003) Criteria for appraising the viability, effectiveness and appropriateness of a screening programme. http://www.nsc.nhs.uk/uk_nsc/uk_nsc_ind.htm.

28 Seror, V. What understanding of decision making in prenatal screening could decision analysis provide? *Ultrasound Obstet Gynecol* 30: 921-923 (2007).

29 Loeben, G., Marteau, T. & Wilford, B. Mixed Messages: Presentation of Information in Cystic Fibrosis- Screening Pamphlets. *Am J Hum Genet 63*, 1181-1189 (1998); Hall, S. Chitty, L., *et al*. Undergoing prenatal screening for Down syndrome: presentation of choice and information in Europe and Asia. *European Journal of Human Genetic*s 15(5): 563-569 (2007). See also the SAFE report.

30 Scott, R. Prenatal Testing, Reproductive Autonomy, and Disability Interests *Cambridge Quarterly of Healthcare Ethics* 14, 65-82 (2005).

child, provided that there are no complications arising during pregnancy and birth.[31] Research is needed to identify the formal mechanisms for the establishment cffDNA technology for RhD typing and to consider how these might apply to new applications of cffDNA tests. This might allow insights into how diagnosis and intervention options are framed, and facilitate the development of robust clinical guidelines which are soundly based on firm ethical and legal principles.

31 Duster (2003) distinguishes between newborn screening, prenatal diagnosis, and carrier screening for genetic risk factors and cautions against the "large, impersonal forces" (p. 54) that favour increasing uptake of such genetic technologies, despite the fact the nature of genetic conditions is widely misunderstood. We do not share his pessimism and think that some applications of cffDNA technology will yield clinical benefits. Nevertheless, we argue that such applications and benefits should be distinguished from claims for a general shift to non-invasive prenatal diagnosis. Duster, T. *Back to Eugenics*. Routledge, (2003).

3.0 Pregnancy and Termination of Pregnancy

3.1 Epistemic and moral risks in testing and abortion

Even if abortion were illegal, prenatal tests, such as those based on cffDNA, could be useful and important as a way of allowing parents to plan for the birth of a disabled child. However, we cannot avoid the fact that prenatal tests are often used in the UK for the purposes of allowing a woman to decide whether or not to terminate her pregnancy. The ethics of abortion is, in turn, a contested area, and the extent of these disputes has become apparent recently in debates concerning proposed revisions to existing UK legislation. Therefore, it is useful to locate the use of cffDNA within the broader ethical debate over abortion.

Although there is (in the UK at least) agreement that abortion is ethically permissible, there is disagreement over whether abortion is permissible in all circumstances, and how the permissibility of abortion relates to the stage of fetal development. Some think that a mother has an absolute right to control what happens to her own body, including an absolute right to abort for whatever reasons she sees fit, whereas others think that there ought to be limits on abortion (either in terms of timing or the justifications of abortion).[32] This second position is officially reflected in UK law, and despite the beneficial role that cffDNA technology could have in generating information about the fetus, the use of the test for deciding whether or not to abort could imply that certain uses of cffDNA testing might be legitimate in some contexts, for certain purposes, but not in others.

However the UK law is extremely difficult to apply in practice and debate over the use of cffDNA tests within the UK needs to recognise that such tests might be used to justify abortions in cases of minor abnormality for which there is no independent legal ground (discussed further below). Of course, it might be argued that possible "extensions" of abortion beyond those allowed in law (and/or those clearly agreed on as legitimate) are no concern of the NHS. However, it is again important to note that "creep" can occur within the NHS, namely that controversial uses of technology can become a routine part of practice without legal and ethical analysis, and that the NHS is also part of the broader social system. As such, it would be short-sighted to assume that the use of cffDNA technologies within the NHS will not raise any questions about abortion, or that questions about non-NHS uses of cffDNA technology and abortion are irrelevant to NHS decision makers.

Furthermore, the application of cffDNA technology, by virtue of being earlier and less risky, could increase both detection and termination rates. For example, the National Down syndrome Cytogenetic Register estimates that 94% of prenatally diagnosed Down's syndrome pregnancies were terminated in 2005.[33] Given that around 40% of Down's syndrome cases currently remain undiagnosed prenatally it might be reasonable to conclude that the introduction of diagnostic cffDNA based tests could increase the termination rate, both because of increased testing rates (justified by the minimally invasive nature of the test) and

32 See Sumner, W. *Abortion and moral theory* (Princeton University Press) (1981).

33 National Down Syndrome Cytogenetic Register, Annual Report 2005. *"The data we have on outcome show that after the prenatal diagnosis of Down syndrome 94% of affected pregnancies are legally terminated and 6% are continued, some miscarrying naturally and some ending as still births."* As the outcome of all prenatally diagnosed cases is not yet known, this is based on the assumption that the proportion of terminations has remained consistent. www.wolfson.qmul.ac.uk/ndscr/reports/NDCSRreport05sup.pdf.

because diagnosis at an earlier stage in pregnancy could provide a less physically traumatic option for termination of pregnancy. Moreover, a significant number of Down's syndrome fetuses miscarry naturally, therefore earlier testing is likely to result in more diagnoses (and terminations) of fetuses that would not have survived to term. Literature about informed choice could be brought to bear on this question. In particular, evidence is needed as to whether the form and content of advice given varies with the identity of the counsellor (and their professional status as midwife or GP for example)[34] as one could imagine that counselling will be provided at different points of the care pathway as cffDNA technology is adopted. The timing of the test might dictate the professional group giving the advice.

It is worth pointing out that increased termination rates of fetuses with a genetic or chromosomal disorder might be appealing to some as a way of "saving" the NHS money. Most ethicists agree that this would be a bad reason to roll out further testing, as such a rationale both seems to suggest that parental choice is not truly important and to display a problematic attitude towards those with disabilities. However money-saving concerns might (implicitly) shape the attitudes of some healthcare providers and others to the development of cffDNA technologies.[35] In turn, then, if we are concerned with ensuring parental autonomy, it is paramount that any concerns with cost-savings are kept as far as possible from the clinical setting. These issues should also be kept separate from the even more problematic question (to be discussed below) of the extent to which prenatal diagnosis programmes are or might be perceived to be "eugenic".

3.2 The legal basis for termination of pregnancy

Some of the ethical complexity arising from this technology flows from the extent to which it might be combined with choices to terminate pregnancy. Within the UK, access to termination of pregnancy is regulated by the Abortion Act 1967 (as amended in 1990). This legislation operates by providing a defence to what would otherwise be a criminal offence[36] in certain prescribed circumstances.[37] The scope of the Abortion Act was debated when the Human Fertilisation and Embryology Bill was considered by Parliament in 2008. Although there were moves to reduce the time limit for abortions under s1(1)(a) of the Abortion Act to less than 24 weeks, on the basis that more babies now achieve viability at earlier gestation due to improvements in neonatal care, governmental majorities supported the status quo.

34 Some research has suggested that outcomes are a product of shared decision making rather than evidence of social pressure and undesired influence. Van der Berg, M., Timmermans, D. *et al*. Are Counsellors' attitudes influencing pregnant women's attitudes and decisions on prenatal screening? *Prenat Diagn*; 27:518-524 (2007).

35 Certainly in past debates over the introduction of prenatal testing technologies, claims about possible cost savings have often been made in support of new technologies. For example, it was claimed that prenatal screening for fragile X would save the NHS £8m per year because of lower costs of caring for fragile X sufferers (see BMJ http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1140694.) While use of such figures to guide policy is controversial, it is conceivable that savings from prenatal testing programmes, such as that promised by cffDNA technology, might be an important incentive for some providers.

36 The offence of 'intending to procure a miscarriage' is established by ss58, 59 of the Offences Against the Person Act 1861.

37 The Act requires two bona fide registered medical practitioners to have formed the opinion:
(a) that the pregnancy has not exceeded its twenty-fourth week and that the continuance of the pregnancy would involve risk, greater than if the pregnancy were terminated, of injury to the physical or medical health of the pregnant woman or any existing children of her family; or (b) that the termination is necessary to prevent grave permanent injury to the physical or mental health of the pregnant woman; or (c) that the continuance of the pregnancy would involve risk to the life of the pregnant woman greater than if the pregnancy were terminated; or (d) that there is a substantial risk that if the child were born it would suffer from physical or mental abnormalities as to be seriously handicapped.

There were also debates on whether the abortion legislation should be amended to reflect developments in the process of termination of pregnancy since it now can be achieved by oral administration of medication such as mifepristone[38] up to 63 days (9 weeks) gestation rather than by undergoing a surgical abortion.[39] Due to time pressures these issues were not explored in detail and the Bill received Royal Assent in November 2008.[40]

4.0 Specific pregnancy-associated clinical indications for cffDNA technology

Selective use of cffDNA technology in at risk pregnancies has the capability to reduce maternal and fetal morbidity and mortality:

4.1 RhD blood antigen testing

In RhD, the technology allows the selective treatment of only those RhD-negative women who have been shown to bear a RhD-positive fetus. The RhD status of the fetus can be determined non-invasively and those women who have RhD-negative fetuses do not have to be exposed to anti-D and risk infection with concurrent blood borne diseases.[41] A reduction in anti-D administration also has economic implications,[42] though these are likely to be moderate relative to the clinical benefits and would have to be weighed against the costs of cffDNA testing for the fetal RhD genotype. One clinical team in Belgium, that achieved a near 100% prediction of RhD status in a pilot study,[43] concluded that "mass testing for the fetal RhD genotype with maternal plasma is highly desirable for ethical and economical reasons".[44]

With respect to broader possible concerns about the introduction of cffDNA technology (Sections 2.4 and 2.5), we note that, if this were to be the case, all RhD-negative mothers (which we estimate to be around 15% of all pregnancies) would routinely be screened for the RhD genotype of their fetus by means of cffDNA technology. Despite evidence of increasing reliability, issues of sensitivity and specificity should be considered carefully if this technology is applied to larger populations, i.e. the population of all RhD-negative mothers

38 These issues were examined in the report by the House of Lords Science and Technology Committee (2007) Scientific Developments Relating to the Abortion Act 1967. Regulations allow mifepristone to be prescribed by GP's up to 63 days gestation but at present the drug is only licensed for use in hospitals rather than more widely. Kennedy, I. & Grubb, A. *Medical Law* (3rd Edition) page 1420-22 (2000). Even if the thresholds for obtaining these medications were to be changed to allow nurses rather than doctors to prescribe them, this does not necessarily mean that they would become easier to obtain.

39 Surgical abortion includes dilatation and curettage or suction aspiration of the foetus carried out between 8-12 weeks of gestation.

40 Changes to the legislation are summarised in House of Commons Library (2008) Human Fertilisation and Embryology Bill [HL]:Committee Stage Report 08/62 published 9 July 2008. See http://services.parliament.uk/bills/2007-08/humanfertilisationandembryology.html The Act can be accessed from: http://www.opsi.gov.uk/acts/acts2008/pdf/ukpga_20080022_en.pdf

41 Around 40% of Rh –ve women carry a Rh –ve fetus and obtain anti-D unnecessarily. Ellen van der Schoot, C. *et al*. Non-invasive prenatal diagnosis and determination of fetal Rh status, *Seminars in Fetal and Neonatal Medicine* **13**, (63-68) (2008).

42 The economic costs of anti-D administration are estimated to be around £2 million per annum.

43 There was near 100% concordance between fetal RhD status in maternal plasma and newborn RhD status at delivery (545 high-risk pregnancies; one false-positive owing to a previous liver transplant to the mother from a RhD+ donor, but amniocentesis indicated a RhD- fetus). Minon, J.-M., Gerard C. *et al*. Routine fetal RhD genotyping with maternal plasma: a four-year experience in Belgium.*Transfusion* 48(2): 373-381(2008).

44 Minon, J-M. *et al*. (2008) *op.cit*.

as opposed to only those RhD-negative women who have been sensitised at any point during pregnancy by a feto-maternal haemorrhage from a RhD-positive fetus.[45] Here the burdens associated with unnecessary administration of anti-D are minimal compared with the failure to treat a RhD-positive fetus born to a RhD-negative mother which, untreated, goes on to develop haemolytic disease of the newborn.[46] NICE has recently published updated guidance concerning the routine administration of Anti-D to RhD-negative women, which, whilst acknowledging the small risk of viral infection, notes the absence of an effective alternative treatment to Anti-D administration.[47] Use of cffDNA technology for this application may be particularly appropriate where patients have previously refused the administration of blood products such as anti-D on religious or philosophical grounds.

4.2 Congenital adrenal hyperplasia

CffDNA technology has been used to identify babies at risk of congenital adrenal hyperplasia by identifying fetal sex at the requisite stage in pregnancy (6-7 weeks).[48] In pregnancies in which the fetus is at risk of congenital adrenal hyperplasia, the identification of a female fetus guides options for treatment, namely high dose administration of dexamethasone to the mother to suppress virilisation of the genitalia. It is currently recommended to start treatment as soon as pregnancy is confirmed because masculinisation of the external genitalia begins by 8 weeks of gestation.[49] Invasive diagnostic testing is then undertaken as soon as possible, normally at 9-10 weeks, and dexamethasone is discontinued if the fetus is male or unaffected. As one review notes "Prenatal treatment is controversial, since the risk of having an affected female fetus is only one in eight when both parents are known carriers. Therefore, seven of eight fetuses will receive dexamethasone treatment unnecessarily."[50] CffDNA technology allows earlier, safer, determination of the sex of the fetus without risk from 7 weeks; if the fetus is found to be male, discontinuation of dexamethasone treatment is beneficial to both the fetus and the mother, since the side-effects of cortisone administration include weight gain, oedema and striae. It may also influence parental choices to terminate pregnancies affected by CAH, which are currently reported to be rare.[51] Earlier testing may also increase the acceptability of dexamethasone treatment, as unnecessary exposure of the mother to steroid treatment can be minimised if fetuses that will not benefit from this

45 There is a paucity of evidence concerning the efficacy of administering Rh immune globulin to Rh negative women who experience vaginal bleeding, spontaneous abortion or termination during the first trimester of pregnancy. Hannafin, B. *et al*. Do Rh-negative women with first trimester spontaneous abortions need Rh immune globulin? *Am J Emerg Med* 24(4):487-9 (2006). Despite this, the practice in many jurisdictions is for small doses of anti-D to be prescribed. Fung-Kee Fung, K. *et al*. Prevention of Rh Alloimmunisation. *J Obstet Gynaecol Can* Sep; 25(9):765-73 (2003).

46 Finning, K. *et al*. Effect of high throughput RHD tying of fetal DNA in maternal plasma on use of anti-RhD immunoglobulin in RhD negative pregnant women: prospective feasibility study *BMJ* doi:10.1136/bmj.39518.463206.25 (2008).

47 NICE (2008) TA 156 Routine antenatal anti-D prophylaxis for women who are rhesus D negative, http://www.nice.org.uk/nicemedia/pdf/TA156Guidance.pdf. However the long term effects of viral infection have been documented in a cohort of women who received anti D infected with Hepatitis C.

48 Rijnders, R.J.P. *et al*. Fetal Sex Determination from Maternal Plasma in Pregnancies at Risk for Congenital Adrenal Hyperplasia. *Obstet Gynecol* **98**, 374-378 (2001); Bartha, J.L. *et al*. Fetal sex determination from maternal blood at 6 weeks of gestation when at risk for 21-hydroxylase deficiency. *Obstet Gynecol* 101, 1135-1136 (2003).

49 Merke, D. P. & Bornstein S.R. Congenital adrenal hyperplasia. *The Lancet* 365(9477); 2125-2136 (2005); Nimkarn, S. Prenatal Diagnosis and Treatment of Congenital Adrenal Hyperplasia. *Hormone Research* 67: 53-60 (2007).

50 Merke, D. P. & Bornstein S.R. *op.cit*.

51 Cf. http://www.emedicine.com/PED/topic48.htm

treatment are identified earlier.[52] A comprehensive discussion of the merits of dexamethasone administration is outside the scope of this paper.

4.3 Early identification of problem pregnancies

The use of cffDNA technology in the context of pregnancy disorders is likely to be significant given that placental dysfunction is a major cause of perinatal morbidity and mortality. Implementation of cffDNA technology could be justified by a likely reduction in potential harms to mother and fetus as long as the technology is sufficiently reliable. However, although cffDNA levels are related to abnormal placentation and pre-eclampsia in some cases, individual variability in levels of cffDNA (linked with factors such as ethnicity and maternal weight) may reduce its diagnostic utility. Additional research in populations of different ethnic origin may be necessary in some applications to determine appropriate parameters for sensitivity and specificity, particularly if cffNA technology is to be used as a predictor of placental insufficiency or abnormality.

52 However, this raises the further and very difficult question of whether it should be assumed that dexamethasone treatment should be the default treatment of female cases of CAH. Studies of long-term effects of dexamethasone treatment are reviewed in Nimkarn, S. Prenatal Diagnosis and Treatment of Congenital Adrenal Hyperplasia. *Hormone Research* 67: 53-60 (2007).

5.0 Regulatory and legal issues

5.1 Legal and regulatory principles applying to cffDNA technology: autonomy, consent, and transparency

The trend in both common and statutory law within the UK has been to acknowledge that the patient is an autonomous agent who is competent to consent to medical care offered to her. Whilst this encourages greater transparency and openness,[53] the common law does not recognise that the fetus has an identity independent of the mother: the law regards fetal tissue as maternal in origin.[54]

Informed consent is regarded by many as a touchstone for ensuring respect for autonomy, but there is lack of agreement about the form and nature of the consent required to analyse genetic fetal material.[55] Practices for obtaining consent for diagnostic genetic tests vary considerably.[56] Through cffDNA analysis, a maternal blood sample has the potential to yield information about the fetus, the mother and the father of the fetus. Since some types of cffDNA analysis involves identifying DNA which is present in the fetus and absent from maternal DNA, it may follow that if a positive diagnosis is made in the fetus then the father is necessarily affected. There is also the potential for abnormalities in the maternal genome to be identified through this technology.[57] Current practice does not require that consent is sought from the parents of the person seeking genetic testing even if it is the case that confirming a diagnosis in a child will necessarily reveal the presence of the same condition in that family member. Neither can parents veto genetic testing in their child on the basis that it compromises their own privacy.[58]

However in some contexts, UK law confers a legal right for one person to veto the use of their tissue where the purpose is to obtain information that is relevant to another person. This right, conferred by the Human Tissue Act, only applies to cellular material where it is used for defined purposes other than treatment and diagnosis. Consent would therefore be required where cellular material is held for the purpose of DNA analysis and/or for the purpose of research. This might have implications for cffDNA technology used within a research programme, where consent from both parents could be routinely sought. More research is needed to address the form of consent currently obtained for prenatal diagnostic as opposed to prenatal screening tests. One might expect recent trends for increased transparency to

53 Moreover, the standards set for the provision of medical care are framed in terms of what the responsible medical practitioner considers to be reasonable rather than a more independent assessment. *Bolam v. Friern Hospital Management Committee* (1957) 1 BMLR 1, [1957] 1WLR 582; *Bolitho v. City and Hackney HA* (1993) 13 BMLR 111 (CA).

54 Fetal cellular material whether it is cells extracted for analysis, or the body of a stillborn fetus is deemed to be an extension of maternal tissue. Human Tissue Authority, *Code of Practice: The removal, storage and disposal for human organs and tissue*, Appendix B (2006).

55 Parker, M. & Lucassen, A. Genetic Information: a joint account? *British Medical Journal* 329, 165-167 (2004).

56 The Joint Committee on Medical Genetics used evidence from its membership to draft guidance on existing practice for post-natal genetic testing, culminating in its guidance 'Consent and Confidentiality in genetic practice: Guidance on genetic information and sharing genetic information' (2006).

57 Such as early onset primary dystonia 1 in Ashkenazi Jew populations (Norbury, G. & Norbury, C.J. (2008) *op. cit*).

58 Nevertheless, concerns about privacy pervade clinical genetics practice. For example, there is debate within the genetics community as to how proactive the service should be in notifying the family member who is at risk of developing disease.

influence practices in taking consent.[59]

5.2 Regulating termination of pregnancy and sex selection

Some have argued that existing legislation allows for medical practitioners acting in good faith to offer termination of pregnancy on the grounds that continuance of pregnancy would result in the birth of a child not of the "preferred" sex. This could be justified if the medical practitioners had sufficient evidence to reach a conclusion in good faith that '*continuation of the pregnancy would involve risks, greater than if the pregnancy were terminated, of injury to the physical or mental health of the pregnant woman or any existing children of her family*'.[60] Given the prohibition in the Human Tissue and Embryology Act which makes unlawful the sex selection of embryos for non-medical purposes in the context of assisted reproduction,[61] there have been similar calls to amend the Abortion Act to outlaw termination of pregnancy on grounds of fetal sex. Questions of sex determination and sex selection are discussed further in Section 7.

5.3 Discrimination: Implications for insurance and employment

There is potential for information derived from cffDNA technology to be used as a basis for discrimination by secondary users of information such as employers and insurers. Researchers and health care professionals involved in delivering the technology must be aware of the obligation to keep such information confidential. Where these techniques are used in a research context, increasingly there is an ethical imperative to ensure that appropriate counselling is available.[62]

5.4 The role of intellectual property

Most of the technologies associated with cffDNA testing are protected by patents. These restrict potential users and applications to those who have a licence. One of the main players is Sequenom®, which holds exclusive rights to European Patent No.0994963B1 for non-invasive prenatal genetic testing on fetal nucleic acids derived from material plasma or

59 Even in situations where there is no legal requirement to seek consent (such as the use of anonymised data and tissue) there is a trend in international and European law which seeks to ensure greater transparency, which has potential to conflict with national legislation. Declaration of Helsinki (2008) at http://www.wma.net/e/ethicsunit/helsinki.htm See Annex A for more details of the regulatory and statutory framework that applies to cffDNA technology.

60 Glanville Williams. *Textbook of Criminal Law* (2nd edition 1983), cited in Kennedy, I. & Grubb, A. *Medical Law* (3rd Edition) pages 1420-22 (2000).

61 Schedule 2 of the HFEA amends Schedule 2 of the Human Fertilisation and Embryology Act 1990 so to confine lawful gender testing of the embryo to cases where there is a particular risk that any resulting child will have or develop a gender related disability or serious illness.

62 See for example recommendations (not subsequently adopted) in the draft Amended Declaration of Helsinki which provided that 'potential research participants should be informed that secondary/chance findings or information on genetic disease dispositions may impact their personal or professional lives'.

serum.[63] These rights are framed very widely and extend to most types of cffDNA application (including sex determination) and include the development of mass spectrometric assay systems utilising panels of markers for multiple conditions including RhD and cystic fibrosis. Details of Sequenom®'s current and pending patent applications are available on their website and demonstrate the extent of their geographical scope and technical diversity of the applications. It seems likely that the scope, duration and financial burdens imposed by these intellectual property rights has potential to influence, if not dictate, the likely uptake of the technology as it is rolled out more widely. Experience suggests that the introduction of licence fees into a previously unrestricted market might centralise services. As discussed below, companies like Sequenom® arguably also drive the implementation of the technology by encouraging a general trend towards routine non-invasive prenatal diagnosis.

63 *'With the limited exception of Rhesus D testing performed in Europe on a real-time PCR platform, the exclusively licensed patent rights from Isis enable Sequenom's development and performance of tests, including gender determination tests for social and lifestyle purposes, on any relevant platform, including the Sequenom mass array® system'.* Sequenom® holds exclusive license rights to this patent throughout Europe. Sequenom® press release 2.11.06. See also *Cell-free fetal nucleic acids for non-invasive prenatal diagnosis* report, section 3.7.

6.0 Disability related issues

6.1 Choosing not to have an unhealthy child

The ethical permissibility of the development of prenatal tests for the purpose of reproductive choice is predicated upon the consensus that abortion is ethically permissible to prevent seriously disabled infants from being born. Clearly cffDNA testing, despite having limited diagnostic applications, may be used to detect the presence of genetic disease and give mothers the "power to make an informed decision about their unborn child", whether this choice be to terminate or to take steps to ensure appropriate care for the newborn. To the extent that womens' ability to make informed choices should be promoted,[64] one might think that development of such tests is extremely valuable (subject to questions of accuracy and reliability).

However, some claim that informed choice is only promoted if a woman can be assured that if she continues with her pregnancy the resulting (disabled) child will receive adequate state-funded support. It is claimed that, in the absence of sufficient state-funded provision of care for disabled infants, merely providing women with test results will leave them with no "real choice" but to abort. Prenatal tests, these writers conclude, only promote choice within a particular kind of institutional backdrop (and, as noted above, there might be worries that provision of this institutional backdrop could become politically more contentious as cffDNA technologies become more widespread).

Assessing these arguments is hard for three reasons. First, the assumption that choices can only be informed or real if other circumstances obtain may be intuitive, but very difficult to spell out; just how supportive must the social environment be for a woman to be said to have a real choice to carry a disabled fetus to term? Second, in the context of debate about how much should be spent on providing care to the seriously disabled, it would be strangely backward to claim that the budget should be set at such a level as to allow women to make real choices as to whether or not to have a disabled child. This would seem to ignore various resource constraint issues. On the other hand, it would be equally strange to claim that just because we cannot spend more on care for the disabled, we should not engage in prenatal testing, because so doing would leave women with no reasonable choice but to abort. This conclusion would seem to represent a poor option for those women who would want to know the disease status of their fetus since their need to know would seem stronger the fewer facilities there are to care for the disabled. Third, bioethicists are increasingly placing emphasis on issues of responsibility as well as choice. It could be argued that parents who choose to continue a pregnancy when they know that the fetus is disabled are responsible for caring for the resulting child, and the state's responsibility for the child is less than it would be were the birth of a disabled child to be unexpected. This kind of argument (understandably) worries many, and it is complicated by the fact that a social responsibility to look after a child arises regardless of parental choice, because the child him/herself is not responsible for his/her birth. However, it is clear that arguments which stress the importance of ensuring that choices are "real" might sit uncomfortably with those that emphasise responsibility.

64 A key theme in bioethical debate.

6.2 Protecting minority concerns

The philosophical tensions identified above may seem irrelevant if, regardless of the services in place for the disabled, the assumption is that most people would chose to abort a fetus that is likely to be born seriously disabled. Even if this is so, some argue that cffDNA technology enables a form of "passive eugenics",[65] such that over time we might find that, without any official or coercive state policies, the numbers with a particular disease will fall because parents will choose to terminate. Even assuming that the fall in the disability rate is not an intended outcome of state policy, members of the disability lobby claim that policies which would foreseeably reduce the rate of disability are inherently wrong. This is perhaps because they believe that people living with disabilities can lead perfectly decent lives (the choice to abort being more to do with the parents' wishes to avoid difficult and long-term demands being placed upon them or an image of what a "normal family" is like, than concerns about the welfare of the child). It may also result in increasing stigmatisation, or even lack of state-funded support, for those who continue to suffer from the relevant diseases.

More generally, it might be argued that even if the State's aim in promoting prenatal testing is not to reduce the disability rate, going ahead with a policy that has this effect might implicitly suggest undervaluation of the lives of those living with disabilities. These concerns are amplified when use of particular technologies for prenatal diagnosis is justified in terms of expected savings to the NHS: even if such an argument does not explicitly claim that the lives of the disabled are worthless, it does seem to treat disability as a burden on society. If use of, and arguments for, cffDNA technology do reflect (or are perceived as reflecting) a systematic undervaluing of the disabled, then we can expect its use to be controversial.

Although debates over the use of cffDNA should take note of these concerns, it is difficult to see how they should be reflected in policy making, particularly given the ethical and legal consensus that abortions are legitimate if a child is likely to be born with a "serious" disease or disability. It is important that the experiences of disabled people and their families are fairly reflected in framing policy and in consultative processes (to ensure a realistic view of disability and avoid stigmatisation), but it is difficult to see how worries over "passive eugenics" could dictate policy development given that the UK is committed to defending a woman's right to choose.[66] Of course, these comments are consistent with allowing that the "money saving" argument for prenatal technologies might be ethically suspect in the ways suggested by the disability lobby, and that other quasi-eugenic concerns *may* motivate some proponents of new technologies. If they are to be ethically legitimate, policies in this area should not only be framed in terms of, but genuinely motivated by, a concern for parental autonomy, rather than by any sense of reducing "social burdens".

Such concerns may seem far removed from the current main clinical application of cffDNA technology, that is determination of fetal sex to reduce the number of invasive diagnoses and associated risks. Here, cffDNA technology indeed allows for 'easier' (from the point of view of service providers) and 'safer' prenatal testing. However, since cffDNA is often discussed as a way of achieving non-invasive prenatal diagnosis (NIPD), it makes sense to also consider the broader issues raised by this prospect.

65 The phrase "passive eugenics" is associated with Philip Kitcher. Kitcher, P. *The lives to come* (Penguin) (1997).

66 See Mahowald, M.B. Prenatal testing for selection against disabilities. *Camb Q Healthc Ethics*;16:457e62 (2007).

7.0 Using the technology on 'non-medical' grounds

7.1 Background

It is common to distinguish between permissible practices, for example sex selection during IVF, depending on whether it serves a medical or a non-medical or 'trivial' purpose.[67] Related distinctions are those between clinical and non-clinical issues, or whether an intervention is warranted by the risk of a 'serious' medical condition. However, these distinctions are difficult to draw in practice,[68] and they often fail to delineate the permissible uses of a new technology. We have already touched on the absence of a ground in the law relating to termination of pregnancy for minor fetal anomaly (for which treatment or other interventions are available). Use of the technology to identify the susceptibility of the fetus to adult-onset diseases is not without difficulty, not least providing that the child is able to exercise their rights to decide for themselves whether they want a susceptibility test.[69] As discussed above, there may also be concerns about specification creep within medical settings (Section 2.5), which is of concern if cffDNA technology is regarded as part of a more general shift towards non-invasive prenatal diagnosis.

7.2 Use of cffDNA technology for purposes of sex determination and sex selection[70]

As the technical literature makes clear, cffDNA tests provide an extremely effective method of determining the sex of an unborn child at an early stage of pregnancy.[71] This may be valuable in identifying fetuses at risk of inherited sex-linked conditions,[72] such as Duchenne muscular dystrophy (DMD). In autosomal recessive conditions where the disease mutations are well characterised such as DMD, the effect of the technology is to change the risk assessment from 1/4 to 0 (for females) or 1/2 (for males). In other sex-linked conditions, the non-invasive nature of these tests may well encourage those who have not hitherto been offered an invasive test, to take a cffDNA test to determine the sex of their child (with the possibility that they could chose to terminate the pregnancy for 'social reasons'). Haemophilia is an example of a sex-linked condition for which invasive prenatal diagnosis is neither routinely offered nor

67 For example, Newson, in her review of the ethical aspects of cffDNA technology, seems satisfied that existing clinical practice provides adequate ethical justification for the implementation of the technology and raises particular concern about applications of the technology that are "external to any clinical oversight". Newson, A. J. Ethical aspects arising from non-invasive fetal diagnosis. *Seminars in Fetal and Neonatal Medicine Non-Invasive Prenatal Diagnosis: Implications for Antenatal Diagnosis and the Management of High-Risk Pregnancies* 13(2): 103-108 (2008).

68 See the debates on what constitutes a 'serious' medical condition as the Human Fertilisation and Embryology Bill proceeded through the House of Lords during 2008.

69 Current professional guidance suggests waiting until the child is competent to make their own decisions. However, different criteria may apply where prenatal testing is contemplated, as exemplified by the fact that the HFEA sanctioned list of conditions includes some adult onset diseases.

70 It is useful in these debates to distinguish between "sex determination" (which we understand to be the identification of fetal sex) and sex selection (which we understand to be the abortion of a fetus on the grounds of its sex). Sex determination may be an important and valuable activity for identification of disease status, but its use is complicated by the worries many feel over its potential use for purposes of "sex selection".

71 However we note that some types of test are prone to false negative results (especially those involving the *SRY* region of the Y chromosome), see *Cell-free fetal nucleic acids for non-invasive prenatal diagnosis* report.

72 In these conditions, male offspring have a 50% chance of inheriting the condition, but female offspring have a 50% chance of being a carrier.

requested, partly because the condition is amenable to treatment.[73] The historical fact that haemophilia has not previously been used as a justification for requesting termination of pregnancy on medical grounds does not mean that individuals might not use the knowledge that they gain from cffDNA testing to decide to seek a termination of pregnancy.

The technology also allows sex determination and sex selection to be applied in situations where there is no apparent medical justification, but claims to a social justification (such as family balancing). Questions of sex selection have been extremely hotly contested in reproductive ethics. Given the controversy of existing arguments about sex selection which have focused on techniques such as sperm-sorting or implantation of IVF eggs, i.e. procedures which do not involve termination of a fetus but a choice between "potential" children, we can only expect it to be more controversial if the test results are likely to be used to actively abort a fetus because it is the "wrong" sex.[74] It is useful to cover some of these debates given that the most developed application of cffDNA technology is for sex determination at an early stage of pregnancy, and that sex determination is necessary for sex selection.

In debates over sex selection, it is useful to distinguish three positions: extreme liberalism (sex selection is unproblematic); extreme conservatism (sex selection is never ethically justifiable); and mixed positions (sex selection is acceptable for some reasons or in some circumstances, but not in other circumstances or for other reasons). All three of these positions have strengths and weaknesses.

The extreme liberal position can seem to be in line with more general liberal commitments not to interfere with individuals' choices, and, in particular, not to interfere with their reproductive choices (their reproductive autonomy). From this perspective, then, the use of cffDNA technology for the purpose of sex selection would be ethically unproblematic (although even the liberal might claim that resource allocation issues mean that abortions for such reasons should not be supplied by the NHS). On the other hand, however, many feel that the extreme liberal position fails to appreciate either the harms that might follow from allowing sex selection (such as skewed sex proportions in the population), or that allowing sex selection might be seen to endorse attitudes that may be considered to be morally repugnant, such as favouring male over female children, which, are (allegedly) often expressed in parents' decisions. The worry over appearing to condone such attitudes is particularly strong in contexts such as the UK, where access to abortions is typically through the NHS, and thus government funded. Finally, the liberal is accused of misunderstanding the nature of having children: children should be seen as gifts which we receive, and not as commodities which we can decide to keep or return depending on our preferences.

The extreme conservative position clearly has the converse advantages and disadvantages. It has the advantage of preventing any of the harms alleged to follow from allowing sex selection, of refusing to endorse morally problematic attitudes, and of respecting the nature of the parent-child relationship. The latter view seems dominant in medical circles, as evidenced by the claim in a statement from the Royal College of Obstetricians and Gynaecologists, "it is to be hoped that the birth of every baby will be a special moment for the parents, regardless

73 An audit of cffDNA technology by L. Chitty demonstrated that 23% of 160 women obtaining NIPD for haemophilia (cited in Newson A.J (2008) *op.cit*.).

74 For an overview of these debates see the articles by John Harris and Thomas Baldwin in *Journal of Medical Ethics* 31. See also Savulescu, J., Dahl, E. Sex selection and preimplantation diagnosis. A response to the Ethics Committee of the American Society of Reproductive Medicine. *Human Reproduction*.15: 1879-1880 (2000).

of whether it is a boy or a girl. Focus should remain firmly on the health and care of the mother and developing baby, rather than gender".[75] For the conservative, then, the use of cffDNA technology for sex determination should be allowed when such determination is for "medical" reasons, but not when it is for purposes of "sex selection". However, it might seem that the extreme conservative position threatens to go too far: the view of the child as a "gift" threatens to make abortion for medical reasons appear impermissible, and thus to challenge the use of cffDNA technologies for nearly any purpose. The conservative position seems, then, to need some distinction between those abortions which are permissible (perhaps because they reflect important concerns about the future well-being of the child or mother) and those which are problematic mere reflections of preference. Drawing such a distinction is, of course, difficult, and there is understandably strong opposition to the idea that a list of conditions for which abortion is considered permissible should, or could, be created.

Other attacks on extreme conservatism claim it is an overreaction to the liberal position arguing that the harms allegedly associated with sex selection will not occur, or that the attitudes expressed in sex selection are not necessarily problematic (for example the desire to have a "balanced" family might underlie sex selective abortion and that such a desire need not reflect a problematic valuing of males over females although this topic remains controversial. Furthermore, even if these harms and attitudes were problematic, it is not clear that the State should somehow concern itself with policing individuals' private choices, particularly in the arena of reproductive choice. It should also be noted that even if the conservative objection to sex selective abortion is cogent, it can be difficult to see how such a position might be reflected in practice.

Between the two extreme positions, the moderate position claims that the acceptability of sex selection depends upon the rationale for its use (such as when people claim that sex selection might be acceptable for purposes of "family-balancing", but not acceptable if selection is driven by a sexist attitude that women are inferior to men).[76] A moderate might also distinguish between the permissibility of sex selection in different contexts. For example, she might claim that there is a real danger of a skewed sex ratio in the developing world, but not in the developed world; therefore, reasons against sex selection in the developing world do not apply to the developed world. Alternatively, she might claim that abortions for sex selection should be allowed in private clinics, but not allowed within state clinics, because in the latter case the state might be seen to condone sexist attitudes, whereas in the private case it might seem merely to allow such attitudes to be expressed.

Although the moderate view is appealing precisely because it attempts to steer a middle path between the extremes, it also inherits not only the plausibility, but all of the problems associated with, the two extreme views. Furthermore, the moderate view is plagued by practical difficulties and theoretical difficulties. Practical difficulties include: how, in practice, we might ensure that technology available in the UK is not available in the developing world (given that cffDNA testing kits are sold on the internet), or how to find out what someone's intentions in seeking an abortion are (if a woman discovers through cffDNA testing that her fetus is not diseased, and is a girl, and then seeks abortion on some grounds other than fetal

75 http://www.rcog.org.uk/index.asp?PageID=1973.

76 As, for example, is now allowed in Israel, where a family with four children of the same sex may apply for sex selective abortion.

sex, determining her "true" intentions may be both practically and ethically difficult). The theoretical difficulties arise from a suspicion that distinctions between reasons women might seek an abortion do not map onto any real moral difference, but, rather, reflect our own world view: "we do not like the idea of aborting females because they are female but we do feel that a balanced family is good."

Of course, defenders of the moderate view can defend themselves against these charges, both at the practical and at the theoretical level. At a theoretical level, we might claim that our intuition that sexism is wrong and family balancing is not may be culturally shaped, but argue that this does not render it indefensible. With regard to practical issues, the defender of the moderate view might allow that her position would be difficult to translate into regulatory policy; ensuring that cffDNA technology is not used solely for purposes of sex determination, and that the results of cffDNA testing are not used for sex selective abortions may be too subtle a task for regulation to achieve. Whilst it might not be possible to guarantee that cffDNA technology is not used solely for the purposes of sex determination, disincentives to abuse might include putting onus upon the provider of cffDNA tests that consent was validly obtained and requiring providers of social terminations to obtain declarations from consumers that they had not sought sex determination.[77]

Even if implementation of a mixed strategy would be difficult in practice, there might nevertheless be symbolic or expressive value in claiming that a mixed strategy has been adopted. It may be that *any* regulatory scheme placing limits on abortions for sex selection is likely to be problematic and that, if we value allowing women a choice at all, we may have to live with *de facto* sex selection, regardless of the ethical arguments for and against such a practice. However, this does not mean that we must be sanguine about such an outcome: rather, attempts to avoid such an outcome, through the medium of regulation for example, might serve to limit this outcome, and to show that we disapprove of it. Such measures might, for example, include regulations governing the sale of cffDNA testing kits over the internet or official guidelines issued for GPs, even if, in one sense (related to outcomes), such regulations do little, in another sense (related to the attitudes we express), they may do a lot.

7.3 Preferential uptake of cffDNA technology for sex selection within the UK

Sex selection practices in other countries, in particular India and China, and the resulting skewing of sex birth ratios are often mentioned in connection with cffDNA technology. It is unlikely that such population skewing would result from the availability of cffDNA technology in the UK, either in the context of the NHS or as a consequence of private access to sex determination kits. Moreover, one should be careful not to simply assume that as prenatal sex selection is practised in, say, India or China that UK populations derived from these countries will exhibit the same preferences and behaviour. Such inferences run the danger of propagating ethnic or racial stereotypes when, as the discussion above shows, it is difficult to articulate a single coherent position with respect to allowable uses of the technology. However, it is conceivable that sections of the UK population may have different preferences for the sex of their offspring or may find family balancing attractive. One recent report has linked a change in the birth sex ratio in a UK sub-population (Indian born women) to the

77 Newson, A.J. (2008) at page 106.

availability of techniques for prenatal sex determination, albeit this conclusion was based on statistical methods rather than documenting sex selective abortions as taking place in the UK.[78] However the effect on birth sex ratio was insignificant at the level of the UK population (the report estimated a 'deficit' of 1480 female births since 1990) due to sex selective practices among Indian-born women and further scrutiny of the validity of such research is warranted. Nevertheless, strategies for managing such preferences, and accounting for differences between populations, may need to be developed as cffDNA technology becomes available (via medical and non-medical intermediaries).

As discussed further below, it is certainly inadvisable to only label questionable uses of cffDNA technology as 'social' issues associated with the implementation of the technology. Within the UK, the current legislative requirement for two medical practitioners to sanction termination of pregnancy for social reasons coupled with largely positive cultural perceptions of women in society suggests that the impact of the ability to determine fetal sex from 7 weeks compared to 14 weeks onwards may be limited. Moreover the fact that the Human Fertilisation and Embryology Act (2008) makes sex selection of embryos without medical justification unlawful is an indication that there is a predominant sense that sex selection will not be considered favourable by UK law and by the public mores, even if, as noted above, some sex determination and sex selection in medical contexts may be unavoidable.

7.4 Other applications including the explicit use of the technology to determine paternity

Other uses could include using cffDNA analysis to determine the identity of the father of the fetus, outside a medical context in which the identity of the father is sought for the purpose of identifying the risk status of the fetus to a known genetic condition.[79] Although rates of non-paternity are difficult to assess, it is estimated to be around 10%. Rates of non-paternity are likely to be even higher among the newly pregnant population, since a proportion of women elect to have a termination of pregnancy of a fetus that is likely to have been conceived outside an existing relationship. Women who are unsure of the paternity of the fetus might explicitly seek paternity testing to decide the outcome of the pregnancy.[80] This service is already being offered from 13 weeks on a commercial basis in the USA and combines a blood sample from the mother (from which whole fetal cells are extracted) with a sample (which can be a forensic sample from underwear, tissue or cigarette butt) from the alleged father.[81]

If a woman were to seek termination of pregnancy on the grounds that the fetus was conceived outside an existing social relationship within the UK, having accessed a cffDNA

78 Dubuc, S. & Coleman, D. An Increase in the Sex Ratio of Births to India-born Mothers in England and Wales: Evidence for Sex selective Abortion. *Population and Development Review* 33: 383-400 (2007).

79 Even within the context of clinical genetics, there is debate about the scope of legal duties owed to clients, including the circumstances in which test results revealing false paternity should be revealed to the putative father. Lucassen, A., Parker M. Revealing false paternity: some ethical considerations. *The Lancet* **357**; 1033-35 (2001). Ross, L.F.; Lucast, E.K. Informed consent and the misattributed paternity problem in genetic counselling *Bioethics* **21**; 41-50 (2007). Both narrow and broader conceptions of the clinical geneticists role present significant ethical difficulties. See Lucast, E.K. (2007) *op. cit*.

80 Newson, A.J. (2008) page 107.

81 http://www.dnaplus.com/fetal_cell_prenatal_paternity_test.htm This testing is illegal under the Human Tissue Act 2004 if performed within the UK, but similar restrictions are not enforceable in relation to samples sent abroad for analysis.

test confirming the identity of the father, then provided that she could establish that the risks of proceeding with the pregnancy outweigh that of terminating it, she could proceed with a legitimate termination of pregnancy under the Abortion Act.

Within the UK, the collection and testing of tissue samples for the purpose of DNA analysis is now illegal following the Human Tissue Act 2004 which requires consent from the putative father. The requirement for transparency is reinforced by a voluntary code of practice[82] which is currently being finalised. Significantly the code requires that advertising, marketing and customer information material from paternity testing suppliers within the UK should not actively promote prenatal paternity testing. It requires effective procedures for obtaining appropriate consent from those providing samples.

Some of these recommendations are difficult to apply. For example, it is not clear that suppliers who provide paternity tests in the knowledge that they might be used to determine whether or not to terminate the pregnancy can ever be said to be placing 'the best interests of the child' as a primary concern. Nevertheless, the draft Code does recommend that commercial providers direct pregnant women to their GP or midwife 'before proceeding with a prenatal paternity test' to reduce the risks associated with invasive testing and also 'so that independent counselling be made available'. This has implications for the education and training of GPs and midwives.

7.5 Access to sex determination testing within the UK

The extent to which genetic tests should be available direct to the public, that is whether they are to be confined to regulated biomedical practice or as part of consumer healthcare, is a hotly contested area. Although it might be attractive to determine the acceptability of cffDNA technology on the basis of whether it were to be used for medical or non-medical applications, internet access to cffDNA technology may well render such policy initiatives unenforceable. Furthermore, technological development of direct-to-consumer technologies might be stimulated by, or depend on, development of such technologies within the public sector. Again, it is unclear precisely what these possibilities imply for practice. However, it would be problematic to claim that these issues can simply be ignored in the development and use of such technologies in well regulated clinical contexts.

7.6 Global issues

As noted above, sex selection practices in other countries, in particular India and China, are often mentioned in connection with cell-free fetal DNA. For example, in India, the experience of regulating other prenatal techniques is a cause for concern. Here in some states such as Uttar Pradesh and Haryana, prenatal ultrasound is already used as a tool for sex selection and the live birth rate has skewed to such an extent that whole villages may lack women of marriageable age. Indeed the Third National Family Health Survey in India found the sex ratio in the 0-6 age group to be 918 girls to 1000 boys[83] a rate correlated with

82 http://www.dh.gov.uk/en/Consultations/Closedconsultations/DH_082626.

83 Third National Family Health Survey India http://www.nfhsindia.org/NFHS-3%20Data/NFHS-3%20NKF/Report.pdf.

increasing prosperity and accessibility of prenatal sex selection methods.[84] Of course, it is unclear how the development of technologies such as cffDNA might find their way onto foreign markets, what obligations NHS policy makers have for outcomes in foreign countries, and how the ethical permissibility of sex selection relates to local economic and cultural circumstances. However, it certainly does seem true that in an increasingly globalised world of medical technology, technologies developed in one country can routinely be accessed in other countries, for purposes that those in the first (and many in the second) would find deeply problematic. Again, then, stressing the advantages of cffDNA technology without paying attention to the global dimensions of sex selection might be ethically problematic, and likely to weaken public trust in professionals.

84 'Sex selection has clearly shown that prosperity enhances and deepens inherent prejudices and provides the resources to act upon them. It is no coincidence that the most prosperous districts have the lowest sex ratios' Sharma Kalpana World without Women *The Hindu* 18 November 2007 http://www.thehindu.com/thehindu/mag/2007/11/18/stories/2007111850070300.htm.

8.0 Incidental findings

8.1 Incidental or inadvertent findings of non-paternity

Although a proportion of women may seek to use cffNA technology explicitly to determine the identity of the father of the fetus[85] (section 7.4), others may infer non-paternity from a risk classification or diagnosis, given adequate pre-test information about the disease and its inheritance patterns.[86] The possibility of inadvertent disclosure of the fetal paternity should be considered when framing consent protocol in both high risk referrals and screening for conditions such as RhD.

8.2 Medical implications for the father of the fetus

Within a clinical genetics setting, a family history of genetic disease may prompt a request for non-invasive prenatal testing. In this situation, the father is likely to have a confirmed diagnosis before the fetus is tested, and if he does not, since a positive diagnosis in a fetus confirms the presence of the disease in a parent, genetics services will usually counsel the parent to accept testing prior to testing a fetus.

85 Section 7.4.

86 Lucast, E. K. *op.cit*. p. 47. Lucast argues against routinely raising the possibility of non-paternity in pre-test counselling but instead dealing with the problem if it arises by (whilst keeping the child in question central) seeking to give the father relevant genetic information whilst continuing any deception as to paternity of the child. If the child cannot be kept central without disclosure then the woman should be warned and information disclosed in a supportive and sensitive fashion. This approach is also endorsed by Cho. Cho, M.K. Understanding Incidental findings in the context of genetics and genomics. *Journal of Law, Medicine and Ethics* p. 280-285 (2008).

9.0 Equity

We have already touched upon some of the drivers which might result in a less than equitable uptake of this technology. Inequalities in resources, variability in expertise and disparities between ethnic and socioeconomic groups are well recognised in the NHS context. However a distinctive feature of the cffDNA technology is the extent to which IP rights are limited. Specific research on the likely demand for testing (such as population specific referral rates and test take up), test availability (limited by laboratory provision, and applicable quality assurance standards), and policy initiatives (such as the effect of using the technology for Down's syndrome within the fetal anomaly screening programme)[87] is urgently needed.

The range of possible applications of the technology suggests that it is likely to have an impact upon a diverse spread of populations if fully implemented. It seems that access will be dependent upon existing methods of referral, at least in early phases of implementation. So for example, RhD management is situated within general antenatal care, whilst access to clinical genetics services requires referral from primary health care providers. Experience with the uptake of other new technologies such as cancer genetics, has demonstrated differential uptake of services determined by socio-economic status and ethnicity. If cffDNA technology recognises its potential, a simple substitution of cffDNA technologies for existing interventions within existing care pathways might exacerbate these underlying inequalities. Careful evaluation of these issues is needed at this early stage since inequities in access may be compounded by existing communication practices.[88]

Possible topics for further research could include the extent to which variability in seeking referral could deny certain groups access; variability in test uptake in different socio-economic groups; variability in locations and intake of laboratories and the role of UK Genetic Testing Network accreditation and laboratory quality assurance standards; and the extent to which the test might be offered within a screening programme.

87 As such National Screening Criteria would apply.

88 Mehta, P. (Genetic Interest Group) Promoting equity of access to genetic healthcare (2005); Wonderling, D. *et al*. A descriptive study of UK cancer genetics services: an emerging clinical response to the new genetics *British Journal of Cancer* 85, 166-170. doi:10.1054/bjoc.2001.1893 (2001); Dormandy, E., and Michie, S., *et al*. Low uptake of prenatal screening for Down syndrome in minority ethnic groups and socially deprived groups: a reflection of women's attitudes or a failure to facilitate informed choices? *International Journal of Epidemiology* 34(2): 346-352 (2005).

10.0 Safety, validity, predictive power

Decisions in the course of a pregnancy can be very difficult when there is uncertainty over the accuracy of tests used. One attraction of cffDNA technology is that it is based on fetal nucleic acids rather than on other markers or risk factors that correlate imperfectly with the genetic status of the fetus. As a consequence one might assume that cffDNA will allow a move from screening regimes to non-invasive diagnostic tests. In practice, however, ensuring that tests are accurate is extremely difficult. Despite technical advances,[89] the sensitivity and specificity of nucleic acid tests falls short of 100% and test results may still lead to ambiguous results, and considerable uncertainties remain as to how exactly the technology will be implemented.[90] This also makes prenatal tests problematic in general: on the one hand, we feel that a mother should know as much as possible about the health of her future child when deciding whether or not to carry the fetus to term; on the other hand however, there is a worry that the risk of error in testing might complicate, rather than help, parental decision making.

A further feature of certain nucleic acid based tests is that they are often sensitive to ethnic differences. Although tests can be refined to accommodate ethnic differences (such as the development of SNP panels applicable to >90% of different ethnic populations for Down's syndrome screening),[91] this serves to illustrate that uncertainties and difficulties in implementation and interpretation also apply to nucleic acid based screening. This raises further difficult questions about whether analyses of cell-free fetal nucleic acids should be used to supplement current screening programmes or to replace them, a question that is taken up further in the main report.

In discussing issues of testing reliability, there might seem to be an asymmetry: very roughly, we might think that false negatives are likely to have costs (the birth of children having conditions whom the parents would otherwise have chosen to abort), which false positives do not. It cannot be stressed enough that, from an ethical point of view, both of these errors are important. False positives can lead to unnecessary invasive diagnosis, possibly resulting in miscarriage, or even termination of pregnancy. Therefore, the debate over use of cffDNA tests should recognise that what might seem to be a purely technical issue: the development of tests which simultaneously minimise both false positives and false negatives has a complex ethical dimension, which, in turn, cannot be separated from larger questions about how people do (and ought to) view the acceptability of abortion, and what relative weight they place on the detection of affected pregnancies.[92] Unfortunately, in these kinds of contexts, it is extremely difficult to set some kind of best performance standard.

89 A recent research study of non-invasive prenatal diagnosis of trisomy 21 (Down's syndrome), based on allele ratios of *PLAC4* mRNA, achieved a sensitivity of ~90% and a specificity of >95%, though it can be expected that both sensitivity and specificity will be further improved. Lo, Y. M. D., Tsui, N. B. Y. *et al*. Plasma placental RNA allelic ratio permits noninvasive prenatal chromosomal aneuploidy detection. *Nat Med* 13(2): 218-223 (2007).

90 For example, for Down's syndrome.

91 Lo, Y. M. D., Tsui, N. B. Y. et al. Plasma placental RNA allelic ratio permits noninvasive prenatal chromosomal aneuploidy detection. *Nat Med*. 13(2): 218-223 (2007); 'Sequenom Corporate Presentation – April 2008'. http://www.sequenom.com/getdoc/f30a530e-2f97-4adb-be4c-867359ff8e89/APRIL_08, accessed 7 April 2008.

92 Seror, V. & Costet, N. Down syndrome serum marker screening: decision criteria and implicit values. *Health Policy* 43(1): 83-96 (1998).

11.0 Economic issues

Full economics analyses are needed to identify the cost of implementing the cffDNA technology in various applications, particularly given that throughput and economies of scale might favour centralisation of laboratory services and be justified on other commercial grounds (purchase of licenses, capital costs, and software). Where invasive procedures are required to substantiate a cffDNA test finding, those costs should be included. Research is needed as to whether expansion of cffDNA technology might deprive other services of funding, or where other service delivery models might be affected by implementing cffDNA (for example whether ultrasound screening is offered earlier in pregnancy to allow proper assessment of cffDNA results).[93] Possible considerations might include the availability of laboratory services, appropriate training and education of health professionals and laboratory staff; support from services providing imaging and diagnostic radiography etc. It is possible that access to the technology might be restricted (at least initially) to particular settings and that inequalities of access might result.[94]

Concerns about the economics of the test technology should not obscure the broader cost considerations noted in Section 3.1.

93 Newson, A.J. *op. cit.* (2008) also cited a study from the USA in which one half of the women receiving cffDNA analysis nevertheless opted for confirmatory testing 'just to be sure'. Zameroski, S.T. *et al.* Favourable attitudes toward testing for chromosomal abnormalities via analysis of fetal cells in maternal blood. *Genet Med* **3**:301-9 (2001).

94 Norbury, G. & Norbury, C.J. suggest a combined processing cost of £250 for cffDNA and £500 for CVS or amniocentesis samples.

12.0 Direct-to-consumer issues

12.1 Regulating access to testing

Whilst initial access to cffDNA technology is likely to be mediated by health care professionals, some types of testing are already available over the internet.[95] Internet providers of commercial mail order fetal sexing using maternal blood from a finger prick test include *Baby Sex Mentor*™ and *Pink or Blue*® marketed by Acu-gen Biolab Inc. and Consumer Genetics Inc. respectively. The availability of these tests raises questions about the extent to which they should be regulated. Where the internet is used to access tests overseas, the UK has no regulatory mandate in respect of the internet material itself. Companies are able to offer these tests because they currently operate within a regulatory gap because they are classed neither as medical device manufacturers nor pathology laboratories. The Human Genetics Commission considered these issues in their report 'Genes Direct' and supplementary report 'More Genes Direct'[96] and this work has been supplemented by the reports from advisory committees across the world making recommendations about how regulation could be enhanced.

The delivery models for these tests offer a range of support for consumers by way of pre-test and post-test counselling. One feature which may be especially problematic is the extent to which blood from finger prick tests may yield unreliable results, given the low volume, the small copy number of cffDNA within maternal blood and the potential for contamination of samples.[97] The direct to consumer availability of cffDNA based tests could create stresses upon existing NHS providers, as well as raising issues with respect to governance and regulation of termination of pregnancy. These will need to be monitored and may require intervention from policy makers, for example in respect of whether test providers should be required to provide counselling or support to those seeking tests elsewhere. More generally, we have suggested that the clinical implementation of cffDNA technology can be regarded, and is often presented, as part of a more general shift to non-invasive prenatal diagnosis, although the main use of the technology currently is to reduce the number of invasive procedures required (for example by determining fetal sex in suspected cases of X-linked conditions).

95 *Cell-free fetal nucleic acids for non-invasive prenatal diagnosis* report, section 3.8.

96 Human Genetics Commission *More Genes Direct* (2007).

97 Sample collection instructions from Pink or Blue® advise that household towels should not be used for hand washing prior to sample collection because of the risk of contamination (http://www.tellmepinkorblue.com/PorBKitInstructionsEnglish.pdf), and email correspondence from company representatives confirms that males should not be in the room at the time of sample collection for the same reasons (http://culturematters.wordpress.com/2007/06/21/early-fetal-gender-detection-gender-contagion).

13.0 cffDNA in context

The discussion above has illustrated that in a range of ways the implementation of cffDNA technology inevitably ties into broader ethical, legal and social issues. For example, it has been mentioned that medical interventions such as screening rely on conventionalised representations of the conditions screened for, and these may vary from one context to another. Similarly, judgements about acceptable false positive and false negative rates and thresholds for referral to invasive diagnosis, also imply implicit conventionalised judgements about and trade-offs between the value to be placed on human life, parental choice, cost and relative emphasis placed on detecting affected pregnancies. Pre- or antenatal care also affects lived experiences such as "being a mother". Furthermore interactions between medical services and patients may involve broader values and identities being brought into play and sometimes into conflict. This means that it is problematic to regard the implementation of cffDNA technology only as a technical issue, or to only consider technical requirements during the design of new services, and to set aside a consideration of its drivers, the broader values of the community, and the broader changes that may ensue from implementation of the technology.

In this context, one might again mention that private companies may be significant drivers of this technology, and many companies also make test kits available directly to the public. Sequenom, sees "Non-invasive Prenatal Screening" as a "large potential market", citing the fact that there are 130 million births world-wide annually of which 9.4 million are in the US and Europe. In a corporate presentation, the company notes that of this large number of births "6% are born with birth defects" and that non-invasive prenatal diagnosis may allow for the detection of more than 1400 genetic "disorders", including Down's syndrome, which is described as "the most common chromosomal abnormality".[98] We have emphasised that the introduction of cffDNA into existing services has clinical benefits but also pointed out that this can be seen as part of a more general shift towards non-invasive prenatal diagnosis. On the one hand, one might take this as a reason to distinguish more clearly between different potential applications of the technology, and as we have seen, it has strengths as well as weaknesses depending on the application. On the other hand, even if the implementation of cffDNA technology is part of a general shift towards prenatal diagnosis, then this should not prevent us from taking advantage of the benefits offered by the technology. Instead, one might ask how applications of cffDNA technology can be accommodated in the medical services of a pluralistic society. As noted above, it would arguably be a mistake to consider only what medical service providers see as abuse of the technology as the 'social' issues associated with the technology. The challenge may be to conceptualise and implement cffDNA technology in a way that also takes account of broader social values, a question that has been explored for preimplantation genetic diagnosis (PGD).[99] Further research could examine not only how non-invasive prenatal diagnosis, as taken up via the internet and via medical services, will interact with PGD and assisted reproduction in terms of medical practice, but also the extent to which any similarities in how the technologies relate to broader social values (such as the acceptability of sex selection) could help to frame the development of appropriate policy measures and regulation.

98 'Sequenom® Corporate Presentation – December 2007', accessed at www.sequenom.com on 25 February 2007; subsequent 'Corporate Presentation – April 2008' makes similar claims. http://www.sequenom.com/getdoc/f30a530e-2f97-4adb-be4c-867359ff8e89/APRIL_08, accessed 7 April 2007.

99 Franklin, S. & Roberts, C. Born and Made. Princeton University Press (2007).

14.0 Conclusions and recommendations

The complex interface between test provision, autonomous choice and broader issues such as the regulatory framework around consent and termination of pregnancy suggests that consideration of pertinent ethical, legal and social issues should play an important role in any plans to implement this technology.

One outcome of this review is to suggest a number of avenues for further research which could assist in framing future policy initiatives. Possible areas of research interest include:

- the extent to which cffDNA testing represents a shift from screening to diagnostic testing;
- the implications, if any, this has for the implementation of the technology, for example whether informed choice or informed consent is more appropriate;
- the implications for consent taking generally in prenatal diagnosis;
- identifying those responsible for framing best practice guidance;
- defining current existing care pathways and evaluating their effectiveness;
- clarifying how these might need to be altered to accommodate best practice changes;
- identifying which stakeholders are involved (including future users of the technology) and clarifying the point at which each should participate in this process;
- analysing how and to what extent the form and content of advice given varies with the identity of the counsellor as the cffDNA technology is rolled out;
- establishing the degree to which the implementation of cffDNA technology into clinical care represents part of a more general shift towards non-invasive prenatal diagnosis and describing the broader issues raised;
- to the extent that the development of cffDNA technology may be justified by current medical practice, evaluating how debates about the legitimacy of artificial reproductive technologies (including preimplantation genetic diagnosis) might be applied here and describing the extent to which broader issues are raised;
- communication practices, particularly those likely to be implemented within large-scale screening programmes (for example, for Down's syndrome). In addition, more research is needed into the design and purpose of existing screening programmes and their evaluation;
- the consequences and regulation of cffDNA tests that are made available on a direct to consumer basis (already available for sex determination and foreseeable for Down's syndrome testing);
- similar research questions raised where internet kits are used with the intention of sex determination. Here the question of sex selective abortion may need consideration from national as well as NHS policy makers. For example, providers might be asked for evidence that they have sought legal assurances from those seeking testing that they will not seek to use the information gained from the test for terminating pregnancy on the grounds of fetal sex. Pilot studies could be undertaken to assess the necessity for, and feasibility of such an approach.

Our analysis suggests that it is vital that health care professionals understand the potential benefits and limitations of the technology and that public expectations are managed appropriately. This requires education and resources to be made available for this purpose.

Our review of the literature also indicates that knowledge of the use of existing NIPD technologies is incomplete. This suggests a need to set up formal audit and monitoring systems, and to track uses of non-invasive prenatal diagnoses using cffNA technology over time. The results could be used to inform the current and future systems for obtaining consent and informed choice and also to clarify the extent to which the technology is and will be used outside current clinical boundaries (to monitor specification creep - a potential concern of implementing the technology).

The relative ease and safety of obtaining samples for NIPD using cffNA technology is likely to spawn a market for DTC services (for both medical and non-medical applications). The availability of such tests could result in pressure on publically funded health care providers to offer tests under the NHS and to provide ongoing support to those who have accessed testing privately. There are wider questions about the extent to which such tests should be publically accessible, the role of the state and extent of delegated authority in making and enforcing such decisions.[100]

Wider questions also arise about the interrelationship between the medical and social criteria for the termination of pregnancy: the interface between clinical care and the regulatory framework relating to abortion may continue to raise wider questions about how we balance conflicting private and public interests and rights, and how these form the basis for professional practice in future decades.

100 The main report also highlights the need for appropriate regulation of test performance.

Annex A Applicable Law

In addition to the governance and laws already described in detail, there are a number of other laws and regulations, which are likely to influence the uptake of the technology worldwide. In particular, within Europe, the Convention on Human Rights and Biomedicine 1997 is likely to have considerable impact as it frames some key ethical principles such as respect for human dignity, and the legal duties that flow from this such as the requirement for consent. It should be noted that the UK has neither signed nor ratified this Convention.

EU regulation

The EU is a 'multilevel system of governance'[101] which enables shared norms to be promulgated across a range of levels through sub-national to transnational institutions and players. Its influence is limited by the terms of the treaties which set up the EU institutions. Notwithstanding these limitations however, the EU has significant jurisdiction over public health matters even if it has limited direct control over health service delivery at national level. At one level the Council of Europe issues Conventions which may impact upon national health care systems.

EU Convention on Human Rights and Biomedicine 1997

An example is the Convention on Human Rights and Biomedicine which despite not being ratified by a number of EU Member States, including the UK, nevertheless constitutes an influential statement of human rights. An amended protocol to this Convention deals specifically with the genetic testing.[102]

The EU directives

Secondary legislation establishes a matrix of regulation which apply to cffDNA technology. These directives are implemented at national level by regulations which transpose the directives into national law. However member states may derogate or depart from the directives with justification.

EC Directive 98/79/EC on *in vitro* diagnostic medical devices

This directive forms the basis for the regulation of the diagnostic tests described in the project report since the cffDNA test technology is likely to qualify both as a medical device[103] and as an *in vitro* diagnostic medical device.[104] One essential requirement is that a regulated product will not compromise the clinical condition or safety of the user and it must be subjected to a rigorous assessment of risks as against benefits. This includes an assessment of the analytical and diagnostic sensitivity and specificity, accuracy and reproducibility. The directive establishes the principles for manufacture, marketing, labelling, etc. Significantly

101 Hervey, T.K. & McHale, J. Health Law and the European Union. Cambridge University Press (2004).

102 Steering Group on Bioethics (CDBI) Draft Additional Protocol to the Convention on Human Rights and Biomedicine concerning genetic testing for health purposes and draft explanatory report.

103 Article 1 section 2(a) defines medical device as 'any instrument, apparatus, appliance, material or other article…. used for the purpose of diagnosis, prevention, monitoring, treatment or alleviation of disease, other than by pharmacological, immunological or metabolic means'.

104 Defined in Article 1, section 2(b) as 'any medical device…. To be used in vitro for the examination of specimens, including blood and tissue donations, derived from the human body, solely or principally for the purpose of providing information [*including*]:
concerning a physiological or pathological state
concerning a congenital abnormality'

the directive does not require an assessment of the clinical utility and validity of the product.

Special rules apply to certain categories of devices, such as those tests used to determine ABO blood groups, RhD and HIV status.[105] Another set of regulations apply to reagent and reagent products for evaluating the risk of trisomy 21.[106] These apply a more onerous regime of inspection and product assurance devolving authority for inspection to notified bodies that are registered at national level. If cffDNA tests are used for RhD testing or for diagnosing trisomy 21 (but not other types of aneuploidy such as those involving chromosomes 13 or 18)[107] these regulations would apply.

The statutory authority responsible for implementation of the IVD directive in the UK is the Medicines and Healthcare products Regulatory Agency (MHRA)[108] which delegates its responsibilities for inspection and audit of devices to UK Notified Bodies. The MHRA has been urged to adopt more rigorous standards of assessment of clinical utility and efficacy for genetic tests before they enter the market to avoid harm to consumers who access tests directly.[109]

EC Directive 2000/70 as regards medical devices incorporating stable derivatives of human blood or human plasma

EC Directive 2001/83 on medicinal products

EC Directive 2003/63/ on medicinal products for human use

EC Directive 2004/23/EC on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells

Separate directives regulate human material intended for therapeutic human applications (such as donation or transplantation), medical devices incorporating blood or blood products and medicinal products. The interface between each regulatory regime is not always entirely clear. Guidance confirms that the principle purpose of the product should dictate which regime applies.[110] The main emphasis of these regimes is to ensure that human material can be transferred between member states without compromising patient safety. They may dictate the requirements for consent, traceability, labelling etc.

105 Directive 98/79/EC Annex II.

106 Directive 98/79/EC Annex II List B.

107 *Cell-free fetal nucleic acids for non-invasive prenatal diagnosis* report.

108 MHRA 'Medicine and Medical Devices Regulation: What you need to know' http://www.mhra.gov.uk/home/idcplg?IdcService=SS_GET_PAGE&useSecondary=true&ssDocName=CON2031686&ssTargetNodeId=362 (accessed 26 November 2007)

109 Consultation response to MHRA's consultation on 'Challenges and priorities for the next five years' by letter from Sir John Sulston (on behalf of the Human Genetics Commission) to Michael Darbyshire (MHRA) dated 13 October 2007.

110 For example, if the primary purpose of bone cement is to fix bone, the fact that it also contains some medicinal agents such as antibiotic does not mean that it is regulated under the medicinal uses directives. However if the primary purpose of the cement is the delivery of antibiotics then the medicinal uses directives apply. European Commission DG Enterprise (2001) Medical Devices Guidance Note.

EC Directive 2007/47

This directive which amends directives on active implantable medical devices and medical devices is to be implemented in the UK on 21 March 2010 by regulations which came into force in 2008.

National regulation

UK legislation comprises a mixture of statutory law and common law (judge made law which is refined case by case). The law relating to prenatal genetic testing is largely derived from the common law although various statutes may impinge on specific aspects of care. For example, different statutory regimes accord various weights to the paternal role in termination of pregnancy as against assisted fertility.[111]

The Medical Devices Regulations 2002

The *in vitro* diagnostic medical devices directive is implemented into UK law by the Medical Devices Regulations which came into force in June 2002. The regulations apply the definitions from the directive and establish systems for inspection and compliance. Products regulated by the directive must carry a CE mark which evidences that all relevant requirements have been satisfied and ensures that the manufacturer meets the claims that are made concerning the safety and performance of the device. The regulations also establish the fee structure for inspection and ratification.

The Human Tissue Act 2004

The Human Tissue Act regulates the analysis of DNA held in cellular material for certain purposes including where medical or scientific information from one person is to be used for the benefit of another. However the Act does not apply to sub-cellular material. It is a feature of cffDNA that it exists outside cells. The HT Act also does not apply to the retention, storage or use of material for the purpose of treatment and diagnosis. Nor does it codify the statutory framework for removal of cellular material from the living (which continues to be a function of the common law). One significant feature of the Act is that the infrastructure for licensing and guidance that it provides is sometimes applied to areas not strictly within the scope of the Act (such as extracted DNA). Another example is the best practice guidance for import and export of human tissue which seeks to establish a statutory framework that could be applied (but not enforced) outside the jurisdiction of the UK.

Codes of Practice to the Human Tissue Act 2004

The Human Tissue Act regulates the retention, storage and use of cellular material. There are 8 codes of practice ranging from codes on consent, to disposal of tissue and public display. An additional code of practice for researchers is under review. The codes relate only to cellular material but as a matter of best practice, some commentators are advising that these codes are adhered to even for material that falls outside the Act. For example, recent amendments to the draft Code of Practice on Consent suggest that it is best practice for consent to be obtained for the examination of fetal tissue for scheduled purposes, and that it is good practice to obtain consent for research on fetal and non-fetal tissue products of conception (including the placenta and amniotic fluid) even where the tissue has been anonymised and

111 Contrast the need for written consent from the paternal donor to proceed with implantation of embryos for fertility treatment and the absence of paternal consent to proceed with termination of pregnancy.

ethical approval has been obtained.[112] This may have implications for research methodology in this area. For example, the Medical Research Council have recently published a web-based learning tool which contains specific advice on the retention, storage and use of DNA and RNA, despite the fact that these extracellular materials are not regulated by the Act[113] and recent draft amendments to the Code of Practice on Consent indicates that guidance made under the Act applies equally to RNA. Guidance also urges researchers to 'respect the spirit of the Act' when considering the need for a separate consent for genetic analysis.

Congenital Disabilities (Civil Liability) Act 1976

This Act provides for a remedy for a child who has been negligently injured pre-conception or in utero. Section 1(2)(a) allows claims to be made where an occurrence has 'affected either parent of the child in his or her ability to have a normal, healthy child'. Some commentators suggest that this wording would include circumstances where the mother's opportunity to have a healthy child is compromised by negligent genetic counselling. In such circumstances the child would have a claim for wrongful life. This might be relevant where cffDNA tests yield false negative results resulting in the birth of a disabled child.[114]

Other Relevant Codes of Practice

There are a number of applicable codes of practice which tend to be jurisdiction, context and profession dependent. A detailed analysis of codes of practice is outside the scope of this review. There are specific codes which relate to prenatal testing for the purpose of serious genetic disease, the testing of children and the timing of presymptomatic diagnostic tests. Application based codes for research and clinical trials of medicinal products also apply.

112 See draft revisions to the Human Tissue Act (2004) Consent Code of Practice, available at http://www.hta.gov.uk/_db/_documents/2008-07-03_Revised_Codes_of_Practice.doc.

113 Medical Research Council (2007) Data and Tissues Toolkit .

114 Kennedy, I. & Grubb, A. Medical Law. London: Butterworths (3rd edition); p.1552. (2000).

This document is an appendix to the main report
Cell-free fetal nucleic acids for non-invasive prenatal diagnosis, *available from:*
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