EJHG Open

European Journal of Human Genetics (2015), 1–13

www.nature.com/ejhg

POLICY

Non-invasive prenatal testing for aneuploidy and beyond: challenges of responsible innovation in prenatal screening

Wybo Dondorp*[,1], Guido de Wert[1], Yvonne Bombard[2], Diana W Bianchi[3], Carsten Bergmann[4,5], Pascal Borry[6], Lyn S Chitty[7], Florence Fellmann[8], Francesca Forzano[9], Alison Hall[10], Lidewij Henneman[11], Heidi C Howard[12], Anneke Lucassen[13], Kelly Ormond[14], Borut Peterlin[15], Dragica Radojkovic[16], Wolf Rogowski[17], Maria Soller[18], Aad Tibben[19], Lisbeth Tranebjærg[20,21,22], Carla G van El[11] and Martina C Cornel[11] on behalf of the European Society of Human Genetics (ESHG) and the American Society of Human Genetics (ASHG)

This paper contains a joint ESHG/ASHG position document with recommendations regarding responsible innovation in prenatal screening with non-invasive prenatal testing (NIPT). By virtue of its greater accuracy and safety with respect to prenatal screening for common autosomal aneuploidies, NIPT has the potential of helping the practice better achieve its aim of facilitating autonomous reproductive choices, provided that balanced pretest information and non-directive counseling are available as part of the screening offer. Depending on the health-care setting, different scenarios for NIPT-based screening for common autosomal aneuploidies are possible. The trade-offs involved in these scenarios should be assessed in light of the aim of screening, the balance of benefits and burdens for pregnant women and their partners and considerations of cost-effectiveness and justice. With improving screening technologies and decreasing costs of sequencing and analysis, it will become possible in the near future to significantly expand the scope of prenatal screening beyond common autosomal aneuploidies. Commercial providers have already begun expanding their tests to include sex-chromosomal abnormalities and microdeletions. However, multiple false positives may undermine the main achievement of NIPT in the context of prenatal screening: the significant reduction of the invasive testing rate. This document argues for a cautious expansion of the scope of prenatal screening to serious congenital and childhood disorders, only following sound validation studies and a comprehensive evaluation of all relevant aspects. A further core message of this document is that in countries where prenatal screening is offered as a public health programme, governments and public health authorities should adopt an active role to ensure the responsible innovation of prenatal screening on the basis of ethical principles. Crucial elements are the quality of the screening process as a whole (including non-laboratory aspects such as information and counseling), education of professionals, systematic evaluation of all aspects of prenatal screening, development of better evaluation tools in the light of the aim of the practice, accountability to all stakeholders including children born from screened pregnancies and persons living with the conditions targeted in prenatal screening and promotion of equity of access.
European Journal of Human Genetics advance online publication, 18 March 2015; doi:10.1038/ejhg.2015.57

INTRODUCTION

In the past few years, several professional societies have issued position statements on non-invasive testing (NIPT) for Down syndrome (trisomy 21) and other common autosomal aneuploidies (trisomy 18 and 13), based on sequencing of cell-free DNA (cfDNA) in maternal plasma.[1–5] The focus of these position statements was on NIPT as a promising novel approach to fetal aneuploidy screening, the level of evidence for the clinical validity of NIPT-based testing for these conditions in different populations, the inherent limitations of NIPT-based testing for these conditions, the risk of a premature

[1]Department of Health, Ethics & Society, Research Schools CAPHRI and GROW, Maastricht University, Maastricht, The Netherlands; [2]Li Ka Shing Knowledge Institute of St Michael's Hospital & Institute of Health Policy, Management and Evaluation, Faculty of Medicine, University of Toronto, Toronto, ON, Canada; [3]Department of Pediatrics, Obstetrics and Gynecology, Tufts University School of Medicine, Boston, MA, USA; [4]Center for Human Genetics Bioscientia, Ingelheim, Germany; [5]Department of Medicine, University Freiburg Medical Center, Freiburg, Germany; [6]Department of Public Health and Primary Care, Centre for Biomedical Ethics and Law, Leuven University, Belgium; [7]Clinical and Molecular Genetics Unit, UCL Institute of Child Health, Great Ormond Street Hospital and UCLH NHS Foundations Trusts, London, UK; [8]Service of Medical Genetics, University Hospital of Lausanne, Lausanne, Switzerland; [9]Medical Genetics Unit, Ospedali Galliera, Genova, Italy; [10]PHG Foundation, Cambridge, UK; [11]Section Community Genetics, Department of Clinical Genetics and EMGO Institute for Health and Care Research, VU University Medical Center, Amsterdam, The Netherlands; [12]Centre for Research Ethics and Bioethics, Uppsala University, Uppsala, Sweden; [13]Department of Clinical Ethics and Law (CELS), University of Southampton and Wessex Clinical Genetic Service, Southampton, UK; [14]Department of Genetics and Stanford Center for Biomedical Ethics, Stanford University School of Medicine, Stanford, CA, USA; [15]Clinical Institute of Medical Genetics, Ljubljana University Medical Centre, Ljubljana, Slovenia; [16]Laboratory for Molecular Biology, Institute of Molecular Genetics and Genetic Engineering (IMGGE), University of Belgrade, Belgrade, Serbia; [17]Deutsches Forschungszentrum für Gesundheit und Umwelt, Helmholtz Zentrum, München, Germany; [18]Division Clinical Genetics, University and Regional Laboratories Region Skåne, Lund University Hospital, Lund, Sweden; [19]Department of Clinical Genetics, Leiden University Medical Center, Leiden, The Netherlands; [20]Department of Audiology, Bispebjerg Hospital/Rigshospitalet, Copenhagen, Denmark; [21]Department of Clinical Genetics, The Kennedy Center, University of Copenhagen, Copenhagen, Denmark; [22]Institute of Cellular and Molecular Medicine, ICMM, University of Copenhagen, Copenhagen, Denmark
*Correspondence: Dr W Dondorp, Department of Health, Ethics & Society, Research Schools CAPHRI and GROW, Maastricht University, PO Box 616, 6200 MD Maastricht, The Netherlands. Tel: +31 43 3881712; Fax: +31 43 3670932; E-mail: w.dondorp@maastrichtuniversity.nl
Received 23 December 2014; revised 15 February 2015; accepted 19 February 2015

introduction and the need for further research including cost-effectiveness studies. These earlier statements made the point that NIPT should not be presented as a diagnostic test for fetal aneuploidy; many statements also insisted that there is insufficient evidence for NIPT to be used as a screening test in a general obstetrical population, although recently there have been several studies that demonstrate good performance in women at average risk (see below). Several specialty expert groups have also issued documents addressing specific concerns or points of attention, such as counseling issues arising with NIPT,[6] or the impact of NIPT on prenatal ultrasound practice.[7]

This document discusses the emerging and future scenarios for NIPT-based prenatal screening from an ethical perspective. Ethical aspects have been discussed in the literature,[8–12] in reports by National Ethics Committees and other public health bodies or institutions,[13–15] but have not yet been the main focus of professional position statements. This document is the result of a unique collaboration between the Public and Professional Policy Committee of the European Society of Human Genetics (ESHG) and the Social Issues Committee of the American Society of Human Genetics (ASHG). The first draft was written by the first author and discussed by members of both committees and external experts. After adaptation, the text was emailed and posted on the ESHG website for membership consultation on 10 October 2014 inviting comments til 15 November 2014, and sent to the ASHG and ESHG Boards to elicit further comments. The final version was approved by the ESHG Board on 15 December 2014 and by the ASHG Board on 23 December 2014, and also endorsed by the Human Genetics Society of Australasia, the Australasian Association of Clinical Geneticists, the British Society for Genetic Medicine, the Czech Medical Genetics Society and the PHG Foundation (Cambridge, UK).

In this document, we use 'NIPT' as a general term for non-invasive prenatal testing based on quantitative or qualitative analysis of cfDNA in maternal blood, used in the context of prenatal screening. By prenatal screening we understand the routine offer of medical tests to pregnant women without a known individual higher risk of having a child with a specific disorder or a compromised outcome of the pregnancy. This is usually a two-tier procedure, consisting of a screening test *stricto sensu* with diagnostic follow-up testing in case of a positive result. In many Western countries, prenatal screening is offered in a public health setting. This entails a systematic approach with quality controlled uniform provision procedures, and (different levels of) public funding. In other countries or states, such as in the USA, prenatal screening is made available to (self-paying or insured) patients through individual practitioners or practices, ideally in accordance with professional guidelines. Finally, NIPT for sex selection and paternity testing is commercially offered by laboratories as direct-to-consumer (DTC) tests.

When, in this document, we refer to 'women and their partners', or 'women or couples', this is to acknowledge that decisions about prenatal screening or its outcomes will often be shared by pregnant women with their partners and that these partners (mostly the biological father-to-be) do have an interest in knowing a diagnosis in their future child. Moreover, depending on the conditions tested, some outcomes may also have implications for the father himself.[16] However, professionals should ascertain that consent for prenatal testing and other procedures is based on a free and voluntary decision of the woman herself, as it is her body and her pregnancy. Legally, prenatal screening is offered to the woman only, with her partner having no say in the relevant decisions.

BACKGROUND

After the presence of cell-free fetal DNA in maternal blood was described in 1997,[17] early applications of NIPT included the determination of Rhesus D blood-group status and fetal sex as well as the diagnosis of autosomal dominant disorders of paternal inheritance.[18,19] The use of NIPT to screen for the presence of fetal aneuploidy became feasible with the development of massive parallel sequencing (MPS) and counting of cfDNA fragments.[20,21] Most current tests for this purpose use whole genome MPS in order to quantitatively compare the amount of, for example, chromosome 21 DNA molecules in a maternal sample with that of an euploid reference sample. Other tests use targeted sequencing, mapping only the chromosome regions of interest, or use a qualitative SNP-based approach.[22]

NIPT for common autosomal aneuploidies: test performance

In a recent meta-analysis in which the results of a large number of studies were pooled, NIPT was found to have a sensitivity of 99% for trisomy 21, and a specificity of 99.92%.[23] For trisomy 18, the reported figures were 96.8% (sensitivity) and 99.85% (specificity). For trisomy 13, they were 92.1 and 99.80% respectively.[23] It should be noted, however, that the performance of NIPT is better documented in trisomies 21 and 18 than for trisomy 13, which is a less frequent condition.[24]

Only a few of these studies have been conducted in lower risk populations. However, there is growing evidence that comparably good results can also be achieved in general obstetrical populations, making NIPT an alternative to current first-trimester screening protocols.[25–32] In the prospective multicenter Comparison of Aneuploidy Risk Evaluation (CARE) study (primary analysis cohort of 1914 cases), Bianchi *et al*[25] compared NIPT as a first-tier screening test with prenatal screening in the many different ways in which it is being performed in the United States. They found a sensitivity of 100% (for all three trisomies) (95% confidence interval (CI): 99.8–100), at a specificity of 99.7 and 99.8% for trisomies 21 and 18, respectively. A much larger prospective study, carried out in centers in the USA, Canada and Europe (the non-invasive examination of trisomy using cell-free DNA analysis (NEXT) study) is expected to confirm these observations.[30] In this study, NIPT was compared with a standard first-trimester screening in a general risk population of pregnant women.

A major reason why NIPT for common autosomal aneuploidies is less than fully accurate is because the DNA sequenced represents a combination of maternal and fetal cell-free DNA, with the latter actually deriving from the placenta.[33] A positive result (signaling a suspected aneuploidy) may be generated by factors other than an aneuploid fetal karyotype, including placental mosaicism, a vanishing twin or a maternal tumor; false alarms are inevitable.[34]

The actual impact of this becomes clear if the test is assessed in terms of its predictive value (rather than only its sensitivity and specificity), as this measure also takes the low prevalence of the relevant conditions in the target population into account. For instance, the positive predictive value (PPV) for trisomy 21 in the CARE-study was found to be 45.5% (95% CI: 16.7–76.6), meaning that in a general risk population more than half of positive NIPT results may generate false alarms.[25] Although 10 times better than the PPV of current first-trimester screening in a similar population (as reported in the same study), this is still far below the near 100% required for a diagnosis of trisomy 21.

If NIPT is offered to pregnant women with a higher *a priori* risk, the PPV increases. But even for those at a very-high *a priori* risk of 1:5, the

PPV does not exceed 99%.[35] This is why those who would consider a termination of pregnancy in case of a fetus with aneuploidy, should always be counselled to have follow-up testing (preferably amniocentesis) to confirm a positive NIPT result. Whereas trisomy 21 is a relatively frequent condition (1:500), the lower prevalences of trisomy 18 (2.3 in 10 000) and trisomy 13 (1.4 in 10 000)[36] will affect the PPV of NIPT for these conditions if tested in a general population.[37] For any of these conditions, by contrast, the predictive value of a negative NIPT result increases with lower a priori risks and is very close to 100% in a general risk population. This means that except for women at a very-high pretest risk of carrying a child with Down syndrome (or trisomy 18 or 13) a negative NIPT result is highly reliable.[35] However, false negatives cannot be excluded. One possible cause is that triploidies will not be picked up with present NIPT-technology (a deficiency that is expected to be overcome with technological improvements[38]). More generally, it is important that women or couples are made aware that screening for common aneuploidies will not pick up all chromosome abnormalities.

Cell-free DNA in the blood of pregnant women is for the most part of maternal origin. Only a small proportion (~10%) derives from the fetus (more precisely from the placenta). NIPT requires this 'fetal fraction' of cell-free DNA in maternal blood to be above a minimum level for adequate analysis, for which most laboratories set a limit at, for example, 4%.[39] Although cell-free fetal DNA can be found in maternal blood as early as 4 weeks of pregnancy, the fraction may not yet be large enough if testing is done prior to nine or ten weeks. Earlier testing may therefore lead to an inaccurate or failed result. However, in later testing, the fetal fraction may still be too low, due to maternal factors that are in need of further investigation. One clearly established risk factor for a failed result is a higher maternal body weight due to a dilution effect and most probably increased adipocyte turnover in obese women.[40,41] Reported failure rates vary considerably between laboratories, ranging from 0 to 5%.[42] After a failed result, NIPT can be repeated, or alternative testing can be considered, but this adds additional time to the screening and diagnostic process that may put pressure on further choices and may impact on whether the woman could still have a non-surgical termination. More evidence about failure rates and risk factors for failed NIPT is necessary. There is also still limited evidence about the performance of NIPT as a test for fetal aneuploidy in twin or triplet pregnancies.[43]

ETHICAL FRAMEWORK FOR PRENATAL SCREENING FOR FETAL ABNORMALITIES

Because of its connection with (selective) abortion, prenatal screening for fetal abnormalities is a morally sensitive practice. The relevant normative framework consists of a context-specific articulation of the more general set of principles for population screening, as initially formulated by Wilson and Jungner and further developed in the past decades.[44–46]

Aim of prenatal screening for fetal abnormalities

A core component of this framework concerns the precise aim of prenatal screening for fetal abnormalities such as Down syndrome. This is especially important when screening is provided as a public health programme rather than made available on the initiative of individual practitioners. Although population screening programmes are aimed at reducing the morbidity and mortality associated with disease or disorders in the population, there are two ethical problems with this aim when prenatal screening is concerned.[47] Firstly, if the success of the programme is thought to depend on the termination rate of fetuses with abnormalities such as Down syndrome, this may invite subtle pressure upon women to ask for an abortion if the fetus is found to be affected. Abortion decisions would thus be turned into a public health instrument. Secondly, the aim makes the practice vulnerable to what is known as the 'disability rights' or 'expressivist critique', according to which prenatal screening sends a discriminatory message about the worth of the lives of people living with the relevant conditions.[48] In order to avoid these ethical pitfalls, relevant policy documents stress that prenatal screening for fetal abnormalities is aimed, not at preventing the birth of children with specific abnormalities, but at enabling autonomous reproductive choices by pregnant women and their partners.[13,49–51] This may need to be qualified as referring to meaningful choices related to serious health problems, as maximizing reproductive autonomy as such cannot possibly be a justified public health aim.[49,52]

This account of the aim of the practice (and thus of its 'clinical utility') should be reflected in how prenatal screening for fetal abnormalities is presented, offered, carried out and evaluated.[47] Ideally, the 'effectiveness' of the practice should be assessed in terms of a measure of informed choice rather than only in terms of technical performance results such as the detection–miscarriage ratio. On the basis of earlier work, these instruments still need to be further developed and validated,[53,54] together with systematic interventions (information and counseling approaches) aimed at helping health-care professionals to facilitate informed choices in prenatal screening.[55]

Balance of benefits and harms

A further general requirement is that screening practices must be proportional. This is primarily a matter of the balance of benefits and harms for those being tested.[44–46] In the context of prenatal screening for fetal abnormalities, the possible benefits for pregnant women or couples are twofold: reassurance if shown to be at a low risk, or being helped to make an informed reproductive decision, more specifically with regard to continuing (and prepare for the birth of a child with special needs) or terminating the pregnancy, if the fetus is diagnosed with a fetal abnormality. Potential harms of prenatal screening include a false reassurance, decision stress, anxiety especially as a result of false-positive outcomes, and the risk of losing the pregnancy as a complication of invasive follow-up testing. As the balance of benefits and harms is directly affected by aspects such as the accuracy of the tests, access to follow-up, the quality of laboratory procedures, balanced information and counseling and so on, these quality aspects should all be taken into account when evaluating prenatal screening practices or considering adaptations to existing practices or novel forms of screening.

Societal and justice aspects

The above elements of the normative framework (aim, balance of benefits and harms for those tested) also apply when prenatal screening takes the form of a (commercial) testing offer made available to patients through individual practitioners or practices.[46] However, when screening is offered as a public health programme, societal and justice aspects need to be taken into account. This includes possible consequences for other individuals and groups (including those living with the relevant conditions), as well as cost-effectiveness of publicly funded services. As health budgets are inevitably limited (and increasingly under strain), opportunity costs will have to be taken into account as well.

NIPT FOR COMMON AUTOSOMAL ANEUPLOIDIES: CHANGING THE FIELD

The introduction of NIPT is currently changing the way in which prenatal screening for Down syndrome (and other common autosomal aneuploidies) is offered to pregnant women. In several countries, individual practices have started offering commercially available NIPT as a further option next to the existing prenatal screening tests, initially only to women at a known higher risk (as an alternative for direct access to invasive testing), but more recently as an alternative for first-tier screening to women at a low or general risk, even though professional societies do not yet recommend the latter approach. The availability of NIPT is already leading to a considerable reduction of invasive procedures in the USA, both as a result of women choosing NIPT over direct access to invasive procedures and of the lower false positive rate of NIPT as compared with other first-tier tests.[56]

In countries with a formal prenatal screening programme, the approach used in the past consists of a two-tiered procedure starting with a risk-assessment screen (combined first-trimester screening: cFTS), to be followed, in case of a positive result, by an offer of invasive testing (amniocentesis, chorion villus sampling; CVS) to allow a final diagnosis through cytogenetic (karyotyping) or molecular analysis (rapid aneuploidy test, chromosomal microarray). cFTS is based on two biochemical markers in maternal blood (PAPP-A and free β-hCG), combined with an ultrasound measuring fetal nuchal translucency thickness (NT-measurement). A cut-off (typically set at 1:150 or 1:200) is used to determine what outcomes count as positive. Depending on the maternal age distribution and choice of cut-off, cFTS has a sensitivity of 85–90% and a specificity of ~95% for trisomy 21. Both methods used for invasive follow-up testing (amniocentesis and CVS) have a procedure-related miscarriage risk of an estimated 0.5–1%.[57] With the low PPV of cFTS-based screening (~5%), an important drawback of the current approach is that the overwhelming majority of women undergoing invasive follow-up and exposing themselves to the risk of those procedures do so without actually carrying an affected fetus.

Scenarios of NIPT-based screening for common autosomal aneuploidies

With the advent of NIPT, different scenarios for improving prenatal screening for common autosomal aneuploidies emerge, each with its own pros and cons. The following three represent the main options for using NIPT in practice.

NIPT as a second test after cFTS using current risk cut-offs. In the past few years, professional bodies and policy authorities have recommended offering NIPT only to women who belong to a higher risk group, either based on maternal age or a positive cFTS. This limitation was motivated by the still pending status of the validity of NIPT-based screening in a general risk population. Inserting NIPT as a second test dramatically reduces the need for invasive follow-up testing, thus making the whole prenatal screening trajectory considerably safer. Because of the reduced need for costly invasive testing, adding NIPT as a second test may be cost-neutral or even cost-saving, bringing this approach within easy reach of publicly (or collectively) funded screening programmes for fetal aneuploidy.[58] A drawback is that with this approach the detection rate will not improve beyond that of cFTS, as cases that are initially screen negative will also not be found with the second screening step. As a result of additional false negatives, detection will, for a fixed uptake, actually be a bit lower than if all women who had a positive cFTs underwent invasive testing. Moreover, for a small percentage of women, the screening will consist of three steps, which will make the whole trajectory longer and more burdensome (and depending on the health-care context: more costly) for them, while possibly also impacting upon the choices available to them.

NIPT as a replacement for cFTS. With recent publications suggesting equally good test performance in lower risk populations, the further scenario of using NIPT instead of cFTS will be increasingly considered. As compared with the previous scenario, this approach would have the advantage of detecting more pregnancies with aneuploidy and practically eliminating false reassurance.[59] Secondly, using NIPT as a first-tier test significantly reduces the number of women who will receive an initial false alarm. Moreover, since NIPT can be done earlier in pregnancy than cFTS (at 9–10 weeks), this approach also means that for those receiving a negative result, testing can be completed earlier. Should NIPT be introduced as a first-tier test, it has been suggested as a further benefit that pretest information can be more straightforward as conceptually NIPT would be a more easy to understand type of test.[60] On the other hand, because of the lower *a priori* risk in the general population, the PPV of a positive NIPT result is significantly lower in this scenario than with NIPT as a second test, which will lead to more invasive procedures. As a further drawback, it has been pointed out that with falling use of cFTS, any extra information that this test may yield about clinically relevant conditions other than the targeted aneuploidies (see below) would also be lost.[61,62] Finally, as long as NIPT is still significantly more expensive than cFTS, costs are an important barrier to introducing NIPT as a first test in publicly (or collectively) funded screening programmes for fetal aneuploidy. Only with a considerable reduction in the costs of NIPT may this approach become sufficiently cost-effective.[63,64]

NIPT as a second test after adapted cFTS. Using NIPT as a second test while lowering the cFTS cut-off can be a way to keep costs down while still improving the detection rate in addition to reducing the need for invasive follow-up testing (Chitty *et al*, 2012). With a cut-off of 1:1000, this approach will now be evaluated in the UK, looking at implications for prenatal screening under the NHS.[62] Above this cut-off, women will be offered NIPT as a second test, while those with a risk above the old UK cut-off of 1:150 will be given the choice between NIPT and direct access to invasive testing. By adding further markers to the cFTS step, the researchers hope to be able to further enhance the detection of aneuploidies in this 'contingent' model.[61,62] The study will incorporate a health economic evaluation aimed at determining the budget impact of the proposed approach in comparison to the current screening pathway, while allowing adaptations.

Uptake

An unknown variable is the uptake of NIPT-based prenatal screening. This is especially important when prenatal screening is fully funded from public money, as uptake affects the projected overall costs of such programmes. At present, uptake of the screening offer varies greatly in different countries with public health-based prenatal screening programmes (from ~30 to more than 80%).[65] The way in which screening is embedded in health care (eg offered by midwives or gynaecologists), including different funding regimes, may have a role, together with information and counseling practices and professional attitudes towards prenatal screening.[65] Given that women's perception of the poor quality of cFTS-based screening in terms of accuracy and safety (given high chances of being offered invasive follow-up) seems an important reason why part of the target group at present declines

the test offer, making prenatal screening more robust in these respects may lead to render it a more acceptable proposition for more women[66,67] It is also possible that some women who would not consider abortion of an affected fetus may find a positive NIPT-result sufficiently informative even without confirmatory testing in that it enables emotional preparation for the possible birth of a child with extra needs. This can be considered a moral gain as it would mean that, compared with cFTS-based screening, more women can be helped to make what for them would be a meaningful reproductive decision.[15]

Balancing benefits and harms in different scenarios

If NIPT is implemented as a second-tier test, the benefits to harms ratio of prenatal screening for common autosomal aneuploidies will considerably improve with the greatly reduced invasive testing rate, as compared with the current cFTS-based approach. Also in studies among pregnant women as potential users of NIPT this was seen as an important benefit.[67] Assuming that any remaining uncertainties about the value of NIPT in a general pregnant population will be removed, the further debate is about how additional improvements can best be achieved by moving this better test either partly or completely toward the front of the screening trajectory. The trade-offs involved may lead to different choices in different settings and will require further analysis and stakeholder-research.

For instance, in different scenarios with NIPT as a second-tier test, the proposal to lower the cut-off in order to allow more women to profit from NIPT's higher detection rate, will inevitably lead to a somewhat higher chance of losing a healthy pregnancy and also to burdening many more women with a false-positive initial result, turning them for some amount of time into 'candidates for invasive testing'.[68] It is important to note that individual women may weigh these aspects differently, and that even if most would agree with the choices made by the experts on the basis of a careful balancing of different perspectives, not all will.[68] Also in light of the aim of prenatal screening for fetal abnormalities (see above), the question arises to what extent individual women or couples can and should be allowed to make their own choices with regard to some of those trade-offs. Clearly, the scope for this will be more limited in the context of a publicly funded screening programme, where costs are a constraining factor, than in settings where women or couples have to fully pay themselves.

Concerns about 'routinisation'

Concerns have been raised that, precisely as a result of NIPT's better performance, it may paradoxically become more difficult to achieve the aim of enabling autonomous reproductive choices.[10,11,14,66,69] These concerns were first formulated prior to the actual development of NIPT, on the assumption that the technology would be accurate enough to enable the traditional two-step screening for Down syndrome to be replaced by one simple non-invasive test. It was feared that this would lead to prenatal screening being presented by professionals and regarded by pregnant women as a routine procedure, rather than an option that well-informed women may either accept or decline. However, the screening would still have the same consequences in case of a positive final diagnosis. Preparing women for this would require giving all relevant information to all of them already at the pre-screening stage, whereas the present two-step approach (ideally) allows for further moments of (additional) information and reflection for those with a positive initial screen[11,70] By removing the risk to pregnancy, one-step screening might also deprive women of a possible reason for declining the screening offer.[10,68]

Although in any presently realistic scenario, the introduction of NIPT will not lead to abandoning two-step screening, these concerns about 'routinization of prenatal testing'[71] should nevertheless be taken seriously. They are also raised by pregnant women asked to reflect on the pros and cons of introducing NIPT for those conditions.[66,67] The much lower invasive testing rate and related a greater safety of NIPT-based prenatal screening for common autosomal aneuploidies (in any of the above scenarios) may lead to normalizing prenatal screening as just one further test pregnant women are expected to take. As almost all results will be reassuring, professionals may also find it less important to inform women about the choices they may be faced with down the line of a further screening trajectory.[72] Against the background of a continuing history of reports pointing at the discrepancy between the aim of the screening offer and the extent to which pregnant women are actually making informed choices,[73–76] avoiding these routinisation-effects may well be the greatest ethical challenge of NIPT-based prenatal screening.

Loss of additional findings with NIPT for common autosomal aneuploidies

As long as NIPT is used to only look for Down syndrome and trisomies 18 and 13, introducing this new test will *de facto* lead to narrowing the range of clinically relevant conditions that the screening may bring to light.[77] This is because, firstly, in each of the above scenarios, the follow-up rate and therefore also the rate of chromosomal abnormalities other than the targeted trisomies that may be detected at follow-up, will be (up to around 20%) lower than with the traditional approach.[77,78] Some of these additional findings are serious conditions, not all of which will come to light with the second trimester fetal anomaly scan.

Although the risk of thus missing a clinically relevant chromosomal abnormality is actually quite low (estimated range between 1:1600 and 1:4000),[59] some commentators have suggested that the benefits of NIPT may not outweigh the loss of these extra findings at the stage of invasive follow-up.[78] However, the problem with forgoing those benefits for this reason is that it puts women at a higher miscarriage risk in order to maximize the detection of conditions outside the scope of the screening to which they have consented. There is also an equal access problem here: maximizing detection of additional findings at follow-up does not equally benefit all those initially at the same risk for the relevant conditions.[79] A recent proposal is to make better use of cFTS markers (including NT-measurement) in order to define higher risk groups to whom invasive testing would still have to be offered.[77] Clearly, this would require redefining the scope of the screening (also in the pretest information and consent procedures) as targeting a wider range of chromosomal abnormalities than Down syndrome and other common autosomal aneuploidies.

Secondly, in the scenario with NIPT as a first-tier test a further loss of clinically relevant information is to be expected.[62,80] This refers to extra findings from the ultrasound part of cFTS: cases of a greatly increased nuchal translucency ($NT \geq 3.5$ mm) are considered to require further testing for a range of possible abnormalities including congenital cardiovascular defects and genetic syndromes such as Noonan syndrome.[81] Additionally, the biochemical markers used in cFTS may indicate risks of pregnancy complications such as pre-eclampsia and intra-uterine growth retardation.[82] Whether this loss of information from cFTS should be seen as a (further) reason for not moving toward using NIPT as a first-tier test, is a matter for debate. An alternative approach is to keep NT-measurement as a separate screening, for instance as part of a routine ultrasound at 13 weeks.

With regard to additional screening for risk of pregnancy complications, there are ethical reasons for keeping this apart (see below).

Additional findings of NIPT for common autosomal aneuploidies

Depending on targeted or non-targeted analysis and on the level of resolution, NIPT for common autosomal aneuploidies may lead to findings of abnormalities in other chromosomes, including submicroscopic abnormalities.[83] Ideally, there should be a fit between the range of abnormalities for which the screening is offered and accepted and the scope of the test used to find those conditions. Women or couples may otherwise be confronted with outcomes requiring them to make decisions that they were not sufficiently prepared for. These decisions can be especially difficult when conditions are mild or highly variable or when health implications are otherwise uncertain. This is not a new problem: such findings also emerge at follow-up testing after a positive cFTS (see previous section). However, at the NIPT stage, they precede decision making about invasive testing, which may entail putting the pregnancy at risk for confirming findings that not only have a low PPV (because of their low frequency), but that, if confirmed, may still have highly uncertain implications for the health of the future child. To the extent that findings beyond the scope of the screening offer can reasonably be avoided by technical means, doing so is ethically preferable. The argument that this would lead to missing findings that may be important, should be discussed in terms of whether broadening the screening offer to include those further findings would be justified or not.

To the extent that additional findings cannot (reasonably) be avoided, women or couples should be informed (as part of pretest information) about the possibility of such findings and also in general terms about the range of possible implications that these findings may have. As much as reasonably possible, it should also be discussed with them whether they would or would not want to be informed about clinically relevant findings beyond the scope of the screening offer.[83] Although there is no such thing as an absolute 'right not to know', it follows from international legal documents such as the European Convention on Human Rights and Biomedicine that health professionals involved in the provision of genetic tests should in principle respect people's wishes with regard to controlling the information they may receive as a result of being tested. This holds *a fortiori* for prenatal screening, given the above account of the aim of the practice.

Sex selection for non-medical reasons

A specific ethical issue related with NIPT is sex selection for non-medical reasons. Depending on how the test is carried out, the scenario with NIPT as a first screening test will lead to information about fetal sex being available at an early stage in all screened pregnancies. Commercial companies offering NIPT currently provide this information on an optional basis. There is a concern that some pregnant women and their partners may use this to have an abortion if the sex of the fetus does not match their preference.

The culturally and socially determined practice of selecting for males has led to a marked disturbance of the sex ratio in some Asian countries, with serious social effects.[84] Although research has shown that people in Western countries do not generally have a strong preference for sons,[85] there are reports suggesting sex-selective abortion for this reason is being practiced in certain cultural minorities.[86]

The outcry about the sexist character of this practice has led to legislation forbidding sex selection for non-medical reasons, which in most countries is limited to the context of medically assisted reproduction.[87] In 2011, the Parliamentary Assembly of the Council of Europe has called upon member states to also take legal measures to counteract sex selection in the context of legal abortion.[88] The scope for this, however, is limited, as the freedom of abortion and the right of access to information about test results would be at stake. Whereas in Germany legislation forbids informing pregnant women about the sex of the fetus in the first 12 weeks, the Health Council of the Netherlands has argued that such measures are disproportionate.[15] The best way to counteract improper use of information about fetal sex is to avoid its generation. As long as NIPT is not also directed at sex-chromosomal aneuploidies (see below), one could consider ways to filter out this information from the test result.

SCOPE OF NIPT-BASED PRENATAL SCREENING

It is expected that in the coming years, it will become possible to use NIPT to screen for the same range of conditions that are currently tested for using karyotyping or microarray technologies at the follow-up stage, including sex-chromosomal and submicroscopic abnormalities.[89] Commercial providers have already begun expanding their tests with conditions in this range.[90,91]

NIPT-based screening for sex-chromosomal aneuploidies

Sex chromosomal aneuploidies (SCA) include full-blown and mosaic numerical abnormalities leading to syndromes interfering with normal sexual development. These include Turner syndrome (45, X) and sex-chromosomal trisomies, such as Klinefelter (XXY) and triple X-syndrome (XXX). The impact on general health including psychosocial development is highly variable. Many individuals with SCA remain undiagnosed, with fertility problems often provoking the diagnosis.[92] Over the past decades, SCA have been detected mainly as additional findings of invasive testing. Because of the generally mild phenotype, those findings lead to difficult counseling and decision making, and even more so in case of mosaic SCA.[93] Based on EUROCAT data, a termination rate of 36% for sex-chromosomal trisomies was reported, as compared to 80–96% for Down syndrome.[94,95] Internationally, a decreasing trend of abortions for SCA is observed, which is attributed to a generally less bleak prognosis than assumed in the past.[94] Incidental prenatal diagnoses of SCA are reported to lead to milder phenotypes than found in individuals diagnosed on clinical grounds. Factors associated with decisions to terminate are parental fear of abnormal development of the child and directive counseling.[96]

NIPT makes it possible in principle to screen for SCA. Some commentators regard this as a 'logical next step' after the introduction of the technology in prenatal screening.[89] The recent statement of the Israeli Society of Medical Genetics includes sex-chromosomal abnormalities in its recommendation that NIPT may be offered to women at an *a priori* high risk for fetal chromosomal abnormalities.[97] Although commercial companies have already moved to report SCAs in certain countries, taking this step requires a careful assessment of the benefits and harms of doing so. Relevant aspects include test accuracy, counseling challenges, women's preferences, the interests of the future child and misuse of information about fetal sex.

The limited available data indicate that NIPT has a lower accuracy for SCA than for trisomies 21 and 18.[18,89,98,99] This is attributed to several factors including confined placental, placental or true fetal mosaiscism.[42,100] Moreover, a recent study found that in 8.5% of cases, discordance between NIPT findings and fetal karyotype could be directly attributed by an altered (X-chromosome loss) or mosaic maternal karyotype.[100] The authors recommend maternal karyotyping in case of NIPT results suggesting SCA, in order to improve the interpretation of such findings. Thus routine implementation of

screening for sex chromosome abnormalities could reverse the reduction in invasive testing seen following the implementation of NIPT for aneuploidy in the private sector by increasing the false positive rate through the identification of maternal sex chromosome abnormalities.

Specific counseling challenges and psychological impacts of NIPT for SCA have not yet been researched. However, the fact that with NIPT, SCAs are found at the screening step rather than as an additional finding of invasive follow-up testing seems a relevant difference, as it invites women not only to think about whether they would want to continue the pregnancy after a confirmed SCA diagnosis but also whether they would want to take the risk of invasive testing to rule out the probably more than 50% chance of a false alarm. The specifics of different SCAs, for instance the fact that 99% of 45,X fetuses miscarry, and that those who survive often also have abnormalities that are detected by ultrasound screening,[101] will have to be taken into account.

Little is yet known about women's preferences about prenatal screening for SCAs. Recent Chinese studies found that most women having NIPT for common autosomal aneuploidies also wanted information about NIPT results for SCA, but reported very different levels of interest in confirmatory invasive testing.[99,102]

As most prenatally found SCAs do not lead to pregnancy termination, a morally relevant question is also what active screening for these conditions means for the children subsequently born with a (suspected or confirmed) SCA diagnosis. On the one hand, prenatal detection will allow early treatment of health and behavioural problems (as well as, perhaps, timely fertility preservation) and may thus enhance the child's quality of life.[93] On the other hand, there are concerns about psychosocial harm (effect on self-esteem, parent-child interaction and stigmatization) as a consequence of being born with a diagnosis that otherwise might never have been made in many cases (or only much later as a result of fertility problems).[103] Clearly more research is needed to clarify this balance.[104]

Finally, a concern is that screening for SCAs by NIPT will make it impossible to avoid providing information about fetal sex to women or couples who might want to use this for aborting female fetuses (see above). Whether this would in itself amount to a prohibitive consideration depends on how large the misuse risk would be in the sociocultural context.

NIPT-based screening for chromosomal microdeletion syndromes

Several commercial companies have started offering expanded NIPT panels that also test for selected microdeletion syndromes (eg DiGeorge, Prader Willi/Angelman, Cri-du-chat, Wolf–Hirschhorn) with a phenotype including developmental delay, intellectual disability, dysmorphic features and other malformations.[90] Concerns have been raised that this expansion of the screening offer is based on proof of principle rather than validation studies, and that with the rarity of most of these microdeletion syndromes, the PPV is expected to be low.[91] Multiple false positives as a result of screening for microdeletions will undermine the main achievement of NIPT in the context of prenatal screening: the significant reduction of the invasive testing rate.

Depending on the resolution used for expanded NIPT, more of the recently identified smaller microdeletion (and duplication) syndromes may also be detected. Many of these are associated with generally milder phenotypes, whereas some may even be present in healthy individuals.[105] With higher resolutions, variants may also be found of which the clinical significance is still unknown. Screening for these conditions and subsequent follow-up testing (also of the parents) will lead to information and counseling challenges, as well as burdening pregnant women or couples with difficult decision making.[106]

This is not to deny that selected (well characterized and serious) microdeletion syndromes are candidate conditions for broader NIPT-screening scenarios that in the coming years may be considered also in settings where prenatal screening is a public health service. However, this requires more scientific evidence (validation studies), as well as a thorough assessment of the balance of benefits and harms for those to whom the screening is offered, taking account of the aim of the screening. In particular an evaluation of the false positive rate is required as in some studies it has been reported to be as high as 3%.[107] In addition, the limits of detection are unknown and small rearrangements may not be detected. Finally, the targeted approach may not be appropriate as the majority of pathogenic rearrangements arise *de novo* and are non-recurring.

Defining the scope of prenatal screening for fetal abnormalities

Given proof of principle regarding the analysis of the entire fetal genome in maternal plasma,[108,109] it is expected to eventually become technically possible to turn NIPT-based screening into a comprehensive fetal genome scan, looking beyond chromosomal abnormalities to Mendelian disorders and genetic risk profiles for multifactorial diseases. For the time being, costs remain prohibitive, but as sequencing and analysis get cheaper, this will become a realistic possibility for the future.

Inevitably, this raises the question of what the scope of prenatal screening for fetal abnormalities should be. Interestingly, the normative framework does not seem to contain a ready answer. Indeed, one might argue that by using genomic technologies in order to find as many fetal abnormalities as possible, is very much in line with the autonomy paradigm, as this would maximally expand the range of options for reproductive choice. However, there are some problems with this idea of 'looking for everything' that seem to call for a more cautious expansion of the practice.[9,52]

Firstly, unlimited choice may paradoxically undermine rather than serve or enhance reproductive autonomy.[110] Identifying traits with low or variable medical morbidity, as well as variants of uncertain clinical significance, may actually render it more difficult for pregnant women and their partners to make meaningful reproductive choices.[111] Expanding the scope of prenatal screening beyond a limited range of well-characterized conditions will also make it more difficult to provide adequate pretest information, help women to make an informed decision about whether or not to have the test, and to provide them with meaningful options for indicating which information they would or would not want to receive.[79] As a further complication, expanding the scope will increase the chance of findings that may have implications for the health prospects of the genetic parents themselves, as well as of their close relatives.

As a possible solution for the pretest information challenge, an alternative approach to informed consent for multi-disorder screening has been suggested that would avoid information-overload while still allowing well-informed decision making. This model of 'generic' consent involves presenting pretest information in general categories or types of outcomes, differentiated in view of their implications for the future child's health and well-being.[79,112] This would also enable women or couples to decide about which outcomes they do and do not want to be informed. However, the practical feasibility of this model has not yet been empirically tested in the prenatal context, and ethically, the question remains how 'informed' such generic consent would be, also in the light of the fact that the trade-offs involved will not be valued in the same way by all pregnant women.[68]

Secondly, given that expanded prenatal screening will reveal risk factors and abnormalities beyond serious childhood disorders, and that most of these will not lead to the woman asking for an abortion, the interests of the future child need to be taken into account. His or her interest in being protected against psychosocial and informational harm, and related autonomy rights, have not until now had a role in the ethics of prenatal screening. This will have to change with the possibility of a much wider range of findings, including gene-defects that predispose for serious later onset disorders. According to several current guidelines, testing children for such conditions is problematic unless there are effective treatments or opportunities for prevention that have to be started during childhood.[113–115] The concern is that this will do the child more harm than good, while also preempting his or her right to choose at a later age between knowing and not-knowing. Using a term coined by the American philosopher Feinberg, this has been referred to as a possible violation of the child's 'right to an open future'.[116] One need not only think here of serious late-onset disorders. A possible interest of the child in not-knowing may also be at stake when prenatal screening targets abnormalities so minor that most genotypically affected individuals have a normal health (as discussed above, this is also the case for some sex-chromosomal abnormalities). Which information would indeed be harmful and to what extent and what this should mean for the morality of offering prenatal screening and testing for specific conditions are matters for further research and debate.[9]

In the context of prenatal diagnosis of neurogenetic disorders (such as Huntington disease), a form of 'conditional access' to testing has been proposed as an ethically acceptable way out of the dilemma between respecting reproductive autonomy on the one hand and protecting the interests and autonomy rights of the future child on the other.[117,118] Following recent guidelines, the requesting couple should be told that 'if they intend to complete the pregnancy whether the fetus is a carrier of the gene expansion or not, there is no valid reason for performing the test'.[119] However, this approach seems ill suited to the different context of broad-scope prenatal screening which is not for one specific condition only, nor for conditions that those being tested can be expected to be already familiar with. This concern is also relevant in view of the realistic expectation that non-invasive screening will lead to an increased uptake 'just for information'. Curiosity on the part of the future parents needs to be balanced with the risk of exposing the future child to possibly harmful information.[120]

Pending further research and debate about the above concerns, there seems to be good reason for not moving beyond 'serious congenital and childhood onset disorders' when it comes to the scope of prenatal screening for fetal abnormalities. This can be justified in the light of the normative framework as providing women or couples with meaningful reproductive choices rather than with the (theoretical) option of receiving all information that genomic technologies can possibly reveal about the fetus. This is also in line with findings of attitudinal research among British and Dutch pregnant women. Concerns about wider testing included a slippery slope toward testing for minor abnormalities or cosmetic traits and a trivialization of abortion.[66,121] Dutch women said they wanted the possibility of testing 'for severe or fatal disorders that could lead to the early death of the child or a very low quality of life'.[66]

When prenatal screening for fetal abnormalities is publicly funded, considerations of distributive justice point in the same direction. Even when, with decreasing sequencing costs, it will become possible to chart the full genome of the fetus in one test, it will still be the case that a wider range of possible outcomes will require more information and more complex counseling. Inevitably, this requires defining 'meaningful reproductive choices' in a way that can be recognized by the tax payers whose solidarity is invoked to uphold the service, rather than leaving this to the private understanding of the pregnant woman and her partner.

Clearly, this demarcation of the scope of prenatal screening would require further specification. Moreover, practical solutions such as designing filters will be needed in order to as much as possible avoid generating extra information beyond the conditions for which the screening is offered.

PRENATAL SCREENING FOR DIFFERENT PURPOSES

Historically and ethically, prenatal screening for fetal abnormalities such as Down syndrome is to be distinguished from prenatal screening for conditions relevant to a healthy outcome of the pregnancy for mother and child. The latter practice includes screening for infectious diseases (such as hepatitis B, syphilis and HIV), rhesus factor and irregular erythrocyte antibodies. Unlike autonomy-aimed screening for fetal abnormalities such as Down syndrome, this other form of prenatal screening is aimed at prevention as a public health aim. For reasons already indicated (see above), this is an important distinction, with implications for how prenatal screening is to be presented and counseled and evaluated. As long as the two forms of prenatal screening are distinct practices, there need not be a problem with these different aims, but if they run together, there is a risk of moral messages getting mixed up.[122,123]

This is already a concern with the second trimester ultrasound examination, which is both a form of screening for fetal abnormalities that may lead to an abortion decision, and an instrument of pregnancy monitoring in the interest of a healthy outcome for mother and child. A similar confluence of screening with different purposes emerges when the biochemical markers used in cFTS as a test for common autosomal aneuploidies are simultaneously used to also test for pregnancy complication risks such as pre-eclampsia or intra-uterine growth retardation.[82] As previously indicated, the potential of cFTS to be used as a dual purpose test in this sense has a role in the debate about whether or not NIPT should (eventually) replace cFTS as a first-tier screen for fetal abnormalities.[61,62]

Further possibilities for multipurpose use may arise with NIPT. Already, NIPT is used for both types of prenatal testing: not just to screen for common autosomal aneuploidies, but also for determining the rhesus status of fetuses of RhD negative women.[124] These uses of NIPT were developed as separate tests to be conducted in different periods of the pregnancy, but they can in principle be combined into one test in early pregnancy. There are conflicting reports in the literature about the possibility of using altered levels of cell-free fetal DNA as a marker for placental complications such as pre-eclampsia, growth retardation and preterm birth.[33,125] If indeed possible, this might be a further instance of dual purpose NIPT. Moreover, it has been suggested that in the future, NIPT might be used to detect gene-expression patterns that would predict pregnancy complications and other problems with fetal development.[70]

What should be avoided here, with regard to these different types of prenatal screening, is confusing women and couples about what they are offered testing for, and what they can accept or decline, and on the basis of what considerations to decide about this. Whereas counseling for autonomy-aimed screening should be neutral and non-directive, there is no ethical problem with recommending prevention-aimed screening for maternal/fetal risk factors as something to be seriously considered by all pregnant women. As it will be difficult to keep these messages apart, it is ethically preferable to physically or temporarily keep autonomy- and prevention-aimed screening separated as much

as possible.[123] When this is impossible in practice (as also in the case of prenatal ultrasound), counselors should be aware of the need to avoid confusion by conceptually separating the two kinds of screening.

A recent review has sketched a future scenario in which broad-scope NIPT (using different types of 'omics'-information) will allow prenatal screening to turn into 'fetal personalized medicine'.[70] If this means that disorders that are now untreatable become treatable *in utero*, prenatal screening for those disorders will give the woman or the couple more options than only the choice between completion and termination of pregnancy, including treatments that may benefit the health prospects of the future child. The question arises what this should mean for the ethical framework. To what extent does the option of fetal therapy introduce considerations of parental and professional responsibility that require reconsidering the autonomy framework? A proactive ethical analysis of the implications of this development will be needed.[52]

PRENATAL SCREENING AS A PUBLIC HEALTH RESPONSIBILITY

In many countries, prenatal screening has in the past decades been offered to pregnant women in the form of national or regional population screening programmes. These programmes are run as public health services or are at least quality controlled by public health authorities. The idea behind these programmes and their funding from public money is that reproductive health is a collective responsibility and that this includes the ability to make meaningful reproductive choices related to the possibility of having a child with a serious disease or handicap.[45]

Whereas in the past, new screening technologies (such as cFTS replacing the second trimester triple test) have been readily introduced in these programmes, the introduction of NIPT into clinical practice has until now been largely left to commercial laboratories offering their version of the test through individual practitioners and practices, without governments or public health authorities assuming an active role in this process. Given the importance of offering NIPT in a setting in which all relevant aspects (including information and counseling) are quality controlled, it is time that these actors take a more active role. The recent UK initiative to study how NIPT can optimally be introduced within available budget constraints is a step in this direction.[62] Another example is the TRIDENT study (Trial by Dutch laboratories for Evaluation of Non-Invasive Prenatal Testing) of the Dutch National NIPT consortium, which consists of a comprehensive evaluation of the stepwise introduction of NIPT in prenatal screening for common aneuploidies in the Netherlands, for which the Ministry of Health has granted a license under the Dutch Population Screening Act.[126]

The notion that prenatal screening should be regarded a public health responsibility may, but does not necessarily entail that all costs are paid from public money without asking for any (co-)payment from those being tested. It is important to note that these are separate (though connected) issues. In light of the aim of providing options for reproductive choice, it might be argued that asking women to pay for prenatal screening increases the awareness that there is truly a choice to be made.[127] On the other hand, depending on the height of the financial barrier, this may limit access to prenatal screening to those who are better off, which raises an issue of justice.

Societal spending on prenatal screening is commonly justified by appeal to the importance of the reproductive autonomy interests of intended parents.[45] A more contentious argument is that prenatal screening leads to long-term societal savings by avoiding the high costs of lifetime care for people with conditions such as Down syndrome. There is nothing inherently problematic about this 'savings argument', as long as it is not turned into an alternative account of the aim of prenatal screening.[128] Although higher public spending on NIPT-based prenatal screening may well be outweighed by these long-term savings,[129,130] it is not obvious how the necessary calculations should be done, even apart from the reality of short-term budgetary constraints.[131] In the light of those constraints, implementing NIPT as a first-tier test in a fully funded prenatal screening programme may only become possible if the cost per unit can be brought down considerably.[130–132] In fact, the costs of NIPT are decreasing and companies have announced a low-cost NIPT by the end of 2014. But even if, at least for the time being, prenatal screening with NIPT as a first-tier test will require private (co-)payment, much will be gained if such screening is offered in a setting guaranteeing quality control of all relevant aspects, including information, counseling and follow-up. This requires an active engagement of governments and public health authorities.

Determining the parameters of what should be offered as part of an ethically robust prenatal screening programme in the public realm is important as it will set a clear standard for the use of NIPT. Our view is that any programme that is established should be in accordance with the aforementioned ethical principles. An active and coordinating role of public health authorities is also needed to address the challenges arising with emerging possibilities of combining autonomy- and prevention-aimed forms of prenatal screening, including prenatal screening opening up possibilities for prenatal therapy and to set up a governance structure for responsible innovation in this field.[133]

NIPT AS A COMMERCIAL DTC-TEST

Whereas cFTS screening (because of the ultrasound component) requires direct contact with a health professional, NIPT makes it possible in theory to offer prenatal testing for fetal abnormalities as a direct-to-consumer test.[134] Ethically, this would be a problematic development. In order to maintain minimum quality standards, prenatal testing for fetal abnormalities should always be offered through health professionals with the expertise and training to provide the necessary pre-and post-test information and counseling. This is also how NIPT is currently made available by the companies selling the test. However, direct advertising to the target group of pregnant women who then only need to ask for the right product, may serve to diminish the role of the professional as an independent advisor and is therefore also an issue of concern.

Currently, NIPT is available through the internet as a commercial DTC-test specifically for fetal sex determination and paternity testing. In light of the above discussion of NIPT results being potentially used to abort healthy female fetuses just because of being of the 'wrong' sex, it is clear that DTC-tests for early fetal sex determination should be regarded with concern, given that those who only want to know what color to paint the baby room will have ample opportunity to learn about the sex of the fetus later in pregnancy. Although paternity testing may lead to abortion of healthy fetuses as well, women may have legitimate reasons for wanting to know the identity of the father of the child they are carrying.[10] Paternity testing, however, also raises issues of consent and privacy.

RECOMMENDATIONS

1. NIPT offers improved accuracy when testing for common autosomal aneuploidies compared with existing tests such as cFTS. However, a positive NIPT result should not be regarded as a final diagnosis: false positives occur for a variety of reasons

(including that the DNA sequenced is both maternal and fetal in origin, and that the fetal fraction derives from the placenta as well as the developing fetus). Thus women should be advised to have a positive result confirmed through diagnostic testing, preferably by amniocentesis, if they are considering a possible termination of pregnancy.

2. The better test performance, including lower invasive testing rate of NIPT-based screening should not lead to lower standards for pretest information and counseling. This is especially important in the light of the aim of providing pregnant women with meaningful options for reproductive choice. There should be specific attention paid to the information needs of women from other linguistic and cultural backgrounds or who are less health literate.
3. If NIPT is offered for a specific set of conditions (eg trisomies 21, 18 and 13), it may not be reasonably possible to avoid additional findings, such as other chromosomal anomalies or large scale insertions or deletions. As part of pretest information, women and couples should be made aware of the possibility of such additional findings and the range of their implications. There should be a clear policy for dealing with such findings, as much as possible also taking account of pregnant women's wishes with regard to receiving or not receiving specific information.
4. Expanding NIPT-based prenatal screening to also report on sex-chromosomal abnormalities and microdeletions not only raises ethical concerns related to information and counseling challenges but also risks reversing the important reduction in invasive testing achieved with implementation of NIPT for aneuploidy, and is therefore currently not recommended.
5. Emerging opportunities for combining prenatal screening for fetal abnormalities with screening aimed at prevention may undermine adequate counseling by sending mixed messages. The objective of any prenatal screening activity should be made explicit and, as far as possible, forms of prenatal screening with different aims should be presented separately. If not physically possible, this separation should at least be made conceptually when providing the relevant information.
6. In countries where prenatal screening for fetal abnormalities is offered as a public health programme, governments and public health authorities should adopt an active role to ensure the responsible introduction of NIPT as a second or first-tier screening test for Down syndrome and other common autosomal aneuploidies. This entails ensuring quality control also extending to the non-laboratory aspects of NIPT-based prenatal screening (information, counseling), education of professionals, systematic evaluation of all aspects of the screening programme, as well as promoting equity of access for all pregnant women within the confines of the available budget, and setting up a governance structure for responsible further innovation in prenatal screening.
7. Different scenarios for NIPT-based screening for common autosomal aneuploidies are possible, including NIPT as an alternative first-tier option. The inevitable trade-offs underlying those scenarios should not just be regarded as a matter of screening technology and health economics; the question is also how these trade-offs enable or impede meaningful reproductive choices and how they affect both the balance of benefits and burdens for pregnant women and their partners, and the screening goals and values acceptable to society.
8. In order to adequately evaluate prenatal screening practices, there is a need to further develop and validate measures of informed choice as well as interventions aimed at enabling informed choices. The transition to NIPT-based prenatal screening presents an opportunity to fill this gap in knowledge.
9. In the light of sequencing technologies becoming better and cheaper, there is an acute need for a proactive professional and societal debate about what the future scope of prenatal screening for fetal abnormalities should be. As argued in this document, there are strong ethical reasons for not expanding the scope of prenatal screening beyond serious congenital and childhood disorders.
10. The scenario in which prenatal screening would open up possibilities for fetal therapy in addition to autonomous reproductive choice raises fundamental questions about the relation between reproductive autonomy and parental responsibility that require an in depth proactive ethical analysis.

CONFLICT OF INTEREST

Employers of WD, GdW, LH, CvE & MC received research grants for implementation and evaluation research on NIPT from The Netherlands Organisation for Health Research and Development (ZonMw) and The Netherlands Genomics Initiative. DB is a member of the Reproductive and Genetic Health Advisory Board for Illumina and receives an honorarium for this position. She also has a sponsored research grant from Illumina that is administered through Tufts Medical Center, Boston, USA. CB is an employee of Bioscientia/Sonic Healthcare, Ingelheim, while holding a part-time faculty appointment at the University of Freiburg, Germany. In addition, several of the authors work in health-care settings in which NIPT is being offered.

1 American College of Obstetricians and Gynecologists Committee on Genetics: Committee Opinion No. 545: Noninvasive prenatal testing for fetal aneuploidy. *Obstet Gynecol* 2012; **120**: 1532–1534.
2 Benn P, Borrell A, Cuckle H *et al*: Prenatal detection of Down Syndrome using massively parallel sequencing (MPS): a rapid response statement from a committee on behalf of the Board of the International Society for Prenatal Diagnosis, 24 October 2011. *Prenat Diagn* 2012; **32**: 1–2.
3 Gregg AR, Gross SJ, Best RG *et al*: ACMG statement on noninvasive prenatal screening for fetal aneuploidy. *Genet Med* 2013; **15**: 395–398.
4 Langlois S, Brock JA, Wilson RD *et al*: Current status in non-invasive prenatal detection of down syndrome, trisomy 18, and trisomy 13 using cell-free DNA in maternal plasma. *J Obstet Gynaecol Can* 2013; **35**: 177–181.
5 Royal College of Obstetricians & Gynaecologists. Non-invasive Prenatal Testing for Chromosomal Abnormality using Maternal Plasma DNA. Scientific Impact Paper No. 15. March 2014. Available at: https://www.rcog.org.uk/globalassets/documents/guidelines/sip_15_04032014.pdf (last accessed 22 December 2014).
6 Devers PL, Cronister A, Ormond KE, Facio F, Brasington CK, Flodman P: Noninvasive prenatal testing/noninvasive prenatal diagnosis: the position of the National Society of Genetic Counselors. *J Genet Couns* 2013; **22**: 291–295.
7 Salomon LJ, Alfirevic Z, Audibert F, Kagan KO, Yeo G, Raine-Fenning NISUOG Clinical Standards Committee: ISUOG consensus statement on the impact of non-invasive prenatal testing (NIPT) on prenatal ultrasound practice. *Ultrasound Obstet Gynecol* 2014; **44**: 122–123.
8 De Jong A, Dondorp WJ, de Die-Smulders CE, Frints SG, de Wert GM: Non-invasive prenatal testing: ethical issues explored. *Eur J Hum Genet* 2010; **18**: 272–277.
9 Donley G, Hull SC, Berkman BE: Prenatal whole genome sequencing: just because we can, should we? *Hastings Cent Rep* 2012; **42**: 28–40.
10 Newson AJ: Ethical aspects arising from non-invasive fetal diagnosis. *Semin Fetal Neonatal Med* 2008; **13**: 103–108.
11 Schmitz D, Netzer C, Henn W: An offer you can't refuse? Ethical implications of non-invasive prenatal diagnosis. *Nat Rev Genet* 2009; **10**: 515.
12 Vanstone M, King C, de Vrijer B, Nisker J: Non-invasive prenatal testing: ethics and policy considerations. *J Obstet Gynaecol Can* 2014; **36**: 515–526.
13 Comité Consultatif National d'éthique (CCNE). Questions ethiques associees au developpement des tests genetiques foetaux sur sang maternel. Paris, CCNE, 2013. Available at: http://www.ccne-ethique.fr/fr/publications/questions-ethiques-associees-au-developpement-des-tests-genetiques-foetaux-sur-sang#.VBE6h2NQR8w (last accessed 22 December 2014).
14 Hall A, Bostanci A, John S: *Ethical, legal and social issues arising from cell-free fetal DNA technologies. Appendix III to the report: Cell-free fetal nucleic acids for*

noninvasive prenatal diagnosis. Cambridge: PHG Foundation, 2009. Available at: http://www.phgfoundation.org/download/ffdna/ffDNA_appendix.pdf (last accessed 22 December 2014).
15 Health Council of the Netherlands. NIPT: dynamics and ethics of prenatal screening. The Hague, Health Council of the Netherlands, 2013 [Dutch; summary in English]. Available at: http://www.gezondheidsraad.nl/en/publications/preventie/nipt-dynamics-and-ethics-of-prenatal-screening (last accessed 22 December 2014).
16 Deans Z, Hill M, Chitty LS, Lewis C: Non-invasive prenatal testing for single gene disorders: exploring the ethics. *Eur J Hum Genet* 2013; **21**: 713–718.
17 Lo YM, Corbetta N, Chamberlain PF *et al*: Presence of fetal DNA in maternal plasma and serum. *Lancet* 1997; **350**: 485–487.
18 Bianchi DW, Platt LD, Goldberg JD, Abuhamad AZ, Sehnert AJ, Rava RP on behalf of the MatErnal BLood IS Source to Accurately diagnose fetal aneuploidy (MELISSA) Study Group: Genome-wide fetal aneuploidy detection by maternal plasma DNA sequencing. *Obstet Gynecol* 2012; **119**: 890–901.
19 Daley R, Hill M, Chitty LS: Non-invasive prenatal diagnosis: progress and potential. *Arch Dis Child Fetal Neonatal Ed* 2014; **99**: F426–F430.
20 Chiu RW, Chan KC, Gao Y *et al*: Noninvasive prenatal diagnosis of fetal chromosomal aneuploidy by massively parallel genomic sequencing of DNA in maternal plasma. *Proc Natl Acad Sci USA* 2008; **105**: 20458–20463.
21 Fan HC, Blumenfeld YJ, Chitkara U, Hudgins L, Quake SR: Noninvasive diagnosis of fetal aneuploidy by shotgun sequencing DNA from maternal blood. *Proc Natl Acad Sci USA* 2008; **105**: 16266–16271.
22 Mersy E, Smits LJ, van Winden LA *et al*: Noninvasive detection of fetal trisomy 21: systematic review and report of quality and outcomes of diagnostic accuracy studies performed between 1997 and 2012. *Hum Reprod Update* 2013; **19**: 318–329.
23 Gil MM, Akolekar R, Quezada MS, Bregant B, Nicolaides KH: Analysis of cell-free DNA in maternal blood in screening for aneuploidies: meta-analysis. *Fetal Diagn Ther* 2014; **35**: 156–173.
24 Gekas J, Langlois S, Ravitsky V *et al*: Identification of trisomy 18, trisomy 13, and Down syndrome from maternal plasma. *Appl Clin Genet* 2014; **7**: 127–131.
25 Bianchi DW, Parker RL, Wentworth J *et al*: CARE Study Group: DNA sequencing versus standard prenatal aneuploidy screening. *N Engl J Med* 2014; **370**: 799–808.
26 Dan S, Wang W, Ren J *et al*: Clinical application of massively parallel sequencing-based prenatal noninvasive fetal trisomy test for trisomies 21 and 18 in 11,105 pregnancies with mixed risk factors. *Prenat Diagn* 2012; **32**: 1225–1232.
27 Fairbrother G, Johnson S, Musci TJ, Song K: Clinical experience of noninvasive prenatal testing with cell-free DNA for fetal trisomies 21, 18, and 13, in a general screening population. *Prenat Diagn* 2013; **33**: 580–583.
28 Gil MM, Quezada MS, Bregant B, Ferraro M, Nicolaides KH: Implementation of maternal blood cell-free DNA testing in early screening for aneuploidies. *Ultrasound Obstet Gynecol* 2013; **42**: 34–40.
29 Nicolaides KH, Syngelaki A, Ashoor G, Birdir C, Touzet G: Noninvasive prenatal testing for fetal trisomies in a routinely screened first-trimester population. *Am J Obstet Gynecol* 2012; **207**: 374, e1-6.
30 Norton ME, Jacobsson B, Swamy GK *et al*: Non-invasive examination of trisomy using cell free DNA analysis: The NEXT Study. *N Engl J Med* 2015, in press.
31 Song Y, Liu C, Qi H, Zhang Y, Bian X, Liu J: Noninvasive prenatal testing of fetal aneuploidies by massively parallel sequencing in a prospective Chinese population. *Prenat Diagn* 2013; **33**: 700–706.
32 Quezada MS, Gil MM, Francisco C, Oròsz G, Nicolaides KH: Screening for trisomies 21, 18 and 13 by cell-free DNA analysis of maternal blood at 10-11 weeks' gestation and the combined test at 11-13 weeks. *Ultrasound Obstet Gynecol* 2014; **45**: 36–41.
33 Taglauer ES, Wilkins-Haug L, Bianchi DW: Review: cell-free fetal DNA in the maternal circulation as an indication of placental health and disease. *Placenta* 2014; **35**: S64–S68.
34 Bianchi DW, Wilkins-Haug L: Integration of noninvasive DNA testing for aneuploidy into prenatal care: what has happened since the rubber met the road? *Clin Chem* 2014; **60**: 78–87.
35 Morain S, Greene MF, Mello MM: A new era in noninvasive prenatal testing. *N Engl J Med* 2013; **369**: 499–501.
36 Savva GM, Walker K, Morris JK: The maternal age-specific live birth prevalence of trisomies 13 and 18 compared to trisomy 21 (Down syndrome). *Prenat Diagn* 2010; **30**: 57–64.
37 Verweij EJ, de Boer MA, Oepkes D: Non-invasive prenatal testing for trisomy 13: more harm than good? *Ultrasound Obstet Gynecol* 2014; **44**: 112–114.
38 Straver R, Sistermans EA, Reinders MJ: Introducing WISECONDOR for noninvasive prenatal diagnostics. *Expert Rev Mol Diagn* 2014; **14**: 513–515.
39 Canick JA, Palomaki GE, Kloza EM, Lambert-Messerlian GM, Haddow JE: The impact of maternal plasma DNA fetal fraction on next generation sequencing tests for common fetal aneuploidies. *Prenat Diagn* 2013; **33**: 667–674.
40 Ashoor G, Syngelaki A, Poon LC, Rezende JC, Nicolaides KH: Fetal fraction in maternal plasma cell-free DNA at 11-13 weeks' gestation: relation to maternal and fetal characteristics. *Ultrasound Obstet Gynecol* 2013; **41**: 26–32.
41 Wang E, Batey A, Struble C, Musci T, Song K, Oliphant A: Gestational age and maternal weight effects on fetal cell-free DNA in maternal plasma. *Prenat Diagn* 2013; **33**: 662–666.
42 Benn P, Cuckle H, Pergament E: Non-invasive prenatal testing for aneuploidy: current status and future prospects. *Ultrasound Obstet Gynecol*. 2013; **42**: 15–33.
43 Huang X, Zheng J, Chen M *et al*: Noninvasive prenatal testing of trisomies 21 and 18 by massively parallel sequencing of maternal plasma DNA in twin pregnancies. *Prenat Diagn* 2014; **34**: 335–340.
44 Haddow J, Palomaki G: ACCE: a model process for evaluating data on emerging genetic test; in Khoury M, Little J, Burke W (eds): *Human Genome Epidemiology. A Scientific Foundation for Using Genetic Information to Improve Health and Prevent Disease*. Oxford: Oxford University Press, 2004, pp 217–233.
45 Health Council of the Netherlands: *Screening: Between Hope and Hype*. The Hague: Health Council of the Netherlands, 2008. Available at: http://www.gezondheidsraad.nl/en/publications/preventie/screening-between-hope-and-hype (last accessed 22 December 2014).
46 Juth N, Munthe C: *The Ethics of Screening in Health Care and Medicine: Serving Society or Serving the Patient?*. Dordrecht, Heidelberg, London, New York: Springer Science+Business Media, 2012.
47 Clarke AJ: Prenatal screening. Paradigms and perspectives; In Harper DS, Clark AJ (eds): *Genetics, Society and Clinical Practice*. Oxford: Bios Scientific Publishers, 1997, pp 119–140.
48 Parens E, Asch A: Disability rights critique of prenatal genetic testing: reflections and recommendations. *Ment Retard Dev Disabil Res Rev* 2003; **9**: 40–47.
49 Health Council of the Netherlands: *Prenatal Screening. Down's syndrome, neural tube defects, routine-ultrasonography*. The Hague: Health Council of the Netherlands, 2001 [Dutch; summary in English]. Available at: http://www.gezondheidsraad.nl/en/publications/preventie/prenatal-screening-downs-syndrome-neural-tube-defects-routine-ultrasonography (last accessed 22 December 2014).
50 UK National Screening Committee. Criteria for Appraising the Viability, Effectiveness and Appropriateness of a Screening Programme. Available at: http://www.screening.nhs.uk/criteria (last accessed 22 December 2014).
51 Sundhedsstyrelsen: Retningslinjer for fosterdiagnostik. Prænatal Information, Risikovurdering, Rådgivning og Diagnostik. København, Sundhedsstyrelsen, 2004 [Danish]. Available at: https://www.sst.dk/publ/Publ2004/Informeret_valg.pd (last accessed 22 December 2014).
52 De Jong A, De Wert GM: Prenatal screening: an ethical agenda for the near future. *Bioethics* 2015; **29**: 46–55.
53 Michie S, Dormandy E, Marteau TM: The multi-dimensional measure of informed choice: a validation study. *Patient Educ Couns* 2002; **48**: 87–91.
54 Ames AG, Metcalfe SA, Archibald AD, Duncan RE, Emery J: Measuring informed choice in population-based reproductive genetic screening: a systematic review. *Eur J Hum Genet* 2015; **23**: 8–21.
55 Van Agt HM, Korfage IJ, Essink-Bot ML: Interventions to enhance informed choices among invitees of screening programmes–a systematic review. *Eur J Public Health* 2014; **24**: 789–801.
56 Larion S, Warsof SL, Romary L, Mlynarczyk M, Peleg D, Abuhamad AZ: Association of combined first-trimester screen and noninvasive prenatal testing on diagnostic procedures. *Obstet Gynecol* 2014; **123**: 1303–1310.
57 Tabor A, Alfirevic Z: Update on procedure-related risks for prenatal diagnosis techniques. *Fetal Diagn Ther* 2010; **27**: 1–7.
58 Morris S, Karlsen S, Chung N, Hill M, Chitty LS: Model-based analysis of costs and outcomes of non-invasive prenatal testing for Down's syndrome using cell free fetal DNA in the UK National Health Service. *PLoS One* 2014; **9**: e93559.
59 Verweij EJ, de Boer MA, Oepkes D: Non-invasive prenatal diagnosis for Down syndrome: no paradigm shift, just better testing... and it is already here!. *Ultrasound Obstet Gynecol* 2012; **40**: 484–485.
60 Verweij EJ, Oepkes D, de Boer MA: Changing attitudes towards termination of pregnancy for trisomy 21 with non-invasive prenatal trisomy testing: a population-based study in Dutch pregnant women. *Prenat Diagn* 2013; **33**: 397–399.
61 Nicolaides KH, Wright D, Poon LC, Syngelaki A, Gil MM: First-trimester contingent screening for trisomy 21 by biomarkers and maternal blood cell-free DNA testing. *Ultrasound Obstet Gynecol* 2013; **42**: 41–50.
62 Hill M, Wright D, Daley R *et al*: Evaluation of non-invasive prenatal testing (NIPT) for aneuploidy in an NHS setting: a reliable accurate prenatal non-invasive diagnosis (RAPID) protocol. *BMC Pregnancy Childbirth* 2014; **14**: 229.
63 Okun N, Teitelbaum M, Huang T, Dewa CS, Hoch JS: The price of performance: a cost and performance analysis of the implementation of cell-free fetal DNA testing for Down syndrome in Ontario, Canada. *Prenat Diagn* 2014; **34**: 350–356.
64 Ayres AC, Whitty JA, Ellwood DA: A cost-effectiveness analysis comparing different strategies to implement noninvasive prenatal testing into a Down syndrome screening program. *Aust NZ J Obstet Gynaecol* 2014; **54**: 412–417.
65 Crombag NM, Vellinga YE, Kluijfhout SA *et al*: Explaining variation in Down's syndrome screening uptake: comparing the Netherlands with England and Denmark using documentary analysis and expert stakeholder interviews. *BMC Health Serv Res* 2014; **14**: 437.
66 Lewis C, Silcock C, Chitty LS: Non-invasive prenatal testing for Down's syndrome: pregnant women's views and likely uptake. *Public Health Genomics* 2013; **16**: 223–232.
67 Van Schendel RV, Kleinveld JH, Dondorp WJ *et al*: Attitudes of pregnant women and male partners towards non-invasive prenatal testing and widening the scope of prenatal screening. *Eur J Hum Genet* 2014; **22**: 1345–1350.
68 Hewison J: Psychological aspects of individualized choice and reproductive autonomy in prenatal screening. *Bioethics* 2015; **29**: 9–18.
69 Deans Z, Newson AJ: Should non-invasiveness change informed consent procedures for prenatal diagnosis? *Health Care Anal* 2011; **19**: 122–132.

70 Bianchi DW: From prenatal genomic diagnosis to fetal personalized medicine: progress and challenges. *Nat Med* 2012; **18**: 1041–1051.
71 Van den Heuvel A, Chitty L, Dormandy E *et al*: Will the introduction of non-invasive prenatal diagnostic testing erode informed choices? An experimental study of health care professionals. *Patient Educ Couns* 2010; **78**: 24–28.
72 Allyse MA, Sayres LC, Havard M *et al*: Best ethical practices for clinicians and laboratories in the provision of noninvasive prenatal testing. *Prenat Diagn* 2013; **33**: 656–661.
73 Seror V, Costet N, Ayme S: Dépistage prénatal de la trisomie 21 par marquers sériques maternels: del'information à la prise de décision des femmes enceintes. *J Gynecol Obstet Biol Reprod (Paris)* 2000; **29**: 492–500.
74 Dahl K, Kesmodel U, Hvidman L, Olesen F: Informed consent: attitudes, knowledge and information concerning prenatal examinations. *Acta Obstet Gynecol Scand* 2006; **85**: 1414–1419.
75 Van den Berg M, Timmermans DR, ten Kate LP, van Vugt JM, van der Wal G: Informed decision making in the context of prenatal screening. *Patient Educ Couns* 2006; **63**: 110–117.
76 Tsouroufli M: Routinisation and constraints on informed choice in a one-stop clinic offering first trimester chromosomal antenatal screening for Down's syndrome. *Midwifery* 2011; **27**: 431–436.
77 Petersen OB, Vogel I, Ekelund C, Hyett J, Tabor A, Danish Fetal Medicine Study Group, Danish Clinical Genetics Study Group: Potential diagnostic consequences of applying non-invasive prenatal testing: population-based study from a country with existing first-trimester screening. *Ultrasound Obstet Gynecol* 2014; **43**: 265–271.
78 Susman MR, Amor DJ, Muggli E, Jaques AM, Halliday J: Using population-based data to predict the impact of introducing noninvasive prenatal diagnosis for Down syndrome. *Genet Med* 2010; **12**: 298–303.
79 De Jong A, Dondorp WJ, Frints SG, de Die-Smulders CE, de Wert GM: Advances in prenatal screening: the ethical dimension. *Nat Rev Genet* 2011; **12**: 657–663.
80 Chitty LS, Hill M, White H, Wright D, Morris S: Noninvasive prenatal testing for aneuploidy-ready for prime time? *Am J Obstet Gynecol* 2012; **206**: 269–275.
81 Bilardo CM, Timmerman E, Pajkrt E, van Maarle M: Increased nuchal translucency in euploid fetuses–what should we be telling the parents? *Prenat Diagn* 2010; **30**: 93–102.
82 Zhong Y, Tuuli M, Odibo AO: First-trimester assessment of placenta function and the prediction of pre-eclampsia and intrauterine growth restriction. *Prenat Diagn* 2010; **30**: 293–308.
83 Lau TK, Jiang FM, Stevenson RJ *et al*: Secondary findings from non-invasive prenatal testing for common fetal aneuploidies by whole genome sequencing as a clinical service. *Prenat Diagn* 2013; **33**: 602–608.
84 Madan K, Breuning MH: Impact of prenatal technologies on the sex ratio in India: an overview. *Genet Med* 2014; **16**: 425–432.
85 van Balen F: Attitudes towards sex selection in the Western world. *Prenat Diagn* 2006; **26**: 614–618.
86 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. *Pop Dev Rev* 2007; **33**: 383–400.
87 Dondorp W, De Wert G, Pennings G *et al*: ESHRE Task Force on ethics and Law 20: sex selection for non-medical reasons. *Hum Reprod* 2013; **28**: 1448–1454.
88 Council of Europe. Parliamentary Assembly. Prenatal sex selection. Resolution No. 1829. Available at: http://assembly.coe.int/Main.asp?link=/Documents/AdoptedText/ta11/ERES1829.htm (last accessed 22 December 2014).
89 Mazloom AR, Džakula Ž, Oeth P *et al*: Noninvasive prenatal detection of sex chromosomal aneuploidies by sequencing circulating cell-free DNA from maternal plasma. *Prenat Diagn* 2013; **33**: 591–597.
90 Hayden EC: Prenatal-screening companies expand scope of DNA tests. *Nature* 2014; **507**: 19.
91 Vora NL, O'Brien BM: Noninvasive prenatal testing for microdeletion syndromes and expanded trisomies: proceed with caution. *Obstet Gynecol* 2014; **123**: 1097–1099.
92 Bojesen A, Juul S, Gravholt CH: Prenatal and postnatal prevalence of Klinefelter syndrome: a national registry study. *J Clin Endocrinol Metab* 2003; **88**: 622–626.
93 Pieters JJ, Verhaak CM, Braat DD, van Leeuwen E, Smits AP: Experts' opinions on the benefit of an incidental prenatal diagnosis of sex chromosomal aneuploidy: a qualitative interview survey. *Prenat Diagn* 2012; **32**: 1151–1157.
94 Boyd PA, Loane M, Garne E, Khoshnood B, Dolk HEUROCAT working group: Sex chromosome trisomies in Europe: prevalence, prenatal detection and outcome of pregnancy. *Eur J Hum Genet* 2011; **19**: 231–234.
95 Loane M, Morris JK, Addor MC *et al*: Twenty-year trends in the prevalence of Down syndrome and other trisomies in Europe: impact of maternal age and prenatal screening. *Eur J Hum Genet* 2013; **21**: 27–33.
96 Jeon KC, Chen LS, Goodson P: Decision to abort after a prenatal diagnosis of sex chromosome abnormality: a systematic review of the literature. *Genet Med* 2012; **14**: 27–38.
97 Michaelson-Cohen R, Gershoni-Baruch R, Sharoni R, Shochat M, Yaron Y, Singer A: Israeli Society of Medical Genetics NIPT Committee: Opinion 072013: Non-invasive prenatal testing of cell-free DNA in maternal plasma for detection of fetal aneuploidy. *Fetal Diagn Ther* 2014; **36**: 242–244.
98 Samango-Sprouse C, Banjevic M, Ryan A, Sigurjonsson S *et al*: SNP-based non-invasive prenatal testing detects sex chromosome aneuploidies with high accuracy. *Prenat Diagn* 2013; **33**: 643–649.
99 Yao H, Jiang F, Hu H *et al*: Detection of fetal sex chromosome aneuploidy by massively parallel sequencing of maternal plasma DNA: initial experience in a Chinese hospital. *Ultrasound Obstet Gynecol* 2014; **44**: 17–24.
100 Wang Y, Chen Y, Tian F *et al*: Maternal mosaicism is a significant contributor to discordant sex chromosomal aneuploidies associated with noninvasive prenatal testing. *Clin Chem* 2014; **6**: 251–259.
101 Huang B, Thangavelu M, Bhatt S, J Sandlin C, Wang S: Prenatal diagnosis of 45,X and 45,X mosaicism: the need for thorough cytogenetic and clinical evaluations. *Prenat Diagn* 2002; **22**: 105–110.
102 Lau TK, Chan MK, Salome Lo PS *et al*: Non-invasive prenatal screening of fetal sex chromosomal abnormalities: perspective of pregnant women. *J Matern Fetal Neonatal Med* 2012; **25**: 2616–2619.
103 Clarke A: The genetic testing of children. Working Party of the Clinical Genetic Society (UK). *J Med Genet* 1994; **31**: 785–797.
104 Herlihy A, Halliday J, Mclachlan R, Cock M, Gillam L: Assessing the risks and benefits of diagnosing genetic conditions with variable phenotypes through population screening: Klinefelter syndrome as an example. *J Community Genet* 2010; **1**: 41–46.
105 Slavotinek A: Microdeletion Syndromes. *eLS* 2012.
106 Crawford G, Foulds N, Fenwick A, Hallowell N, Lucassen A: Genetic medicine and incidental findings: it is more complicated than deciding whether to disclose or not. *Genet Med* 2013; **15**: 896–869.
107 Lo K, Boustred C, McKay F, Fielding S, Plagnol V, Chitty L: Detection of "sub-chromosomal" pathogenic changes by sequencing cfDNA in maternal plasma: feasibility and implementation strategies. *Prenat Diag* 2014; **34**: 10.
108 Lo YM, Chan KC, Sun H *et al*: Maternal plasma DNA sequencing reveals the genome-wide genetic and mutational profile of the fetus. *Sci Transl Med* 2010; **2**: 61ra91.
109 Kitzman JO, Snyder MW, Ventura M *et al*: Noninvasive whole genome sequencing of a human fetus. *Sci Transl Med* 2012; **4**: 137ra76.
110 Schwartz B: *The Paradox of Choice. Why More is Less*. New York: HarperCollins Publishers, 2004.
111 Van El CG, Cornel MC, Borry P *et al*: ESHG Public and Professional Policy Committee. Whole-genome sequencing in health care. Recommendations of the European Society of Human Genetics. *Eur J Hum Genet* 2013; **21**: S1–S5.
112 Elias S, Annas GJ: Generic consent for genetic screening. *N Engl J Med* 1994; **330**: 1611–1613.
113 American Academy of Pediatrics (AAP). Committee on Bioethics, Committee on Genetics, and the American College of Medical Genetics and Genomics Social, Ethical, and Legal Issues Committee: Ethical and policy issues in genetic testing and screening of children. *Pediatrics* 2013; **131**: 620–622.
114 Borry P *et al*: Public and Professional Policy Committee of the European Society of Human Genetics: Genetic testing in asymptomatic minors: recommendations of the European Society of Human Genetics. *Eur J Hum Genet* 2009; **17**: 720–721.
115 British Society of Human Genetics (BSHG). Report on the Genetic Testing of Children. Birmingham, BSHG, 2010. Available at: http://www.bsgm.org.uk/information-education/websites-downloads/ (last accessed 22 December 2014).
116 Feinberg J.: The child's right to an open future; In Aiken W, LaFolette H (eds): *Whose Child? Children's Rights, Parental Authority and State Power*. Totowa NJ, Littlefield: Adams & Co, 1980, pp 124–153.
117 De Wert G: Ethical aspects of prenatal testing and preimplantation genetic diagnosis for late-onset neurogenetic disorders: the case of Huntington's disease; In Evers-Kiebooms G, Zoeteweij M, Harper P (eds): *Prenatal Testing for Late-onset Neurogenetic Diseases*. Oxford: BIOS Scientific Publishers Ltd, 2002, pp 129–157.
118 De Die-Smulders CE, de Wert GM, Liebaers I, Tibben AEvers-Kiebooms G: Reproductive options for prospective parents in families with Huntington'sdisease: clinical, psychological and ethical reflections. *Hum Reprod Update* 2013; **19**: 304–315.
119 MacLeod R, Tibben A, Frontali M *et al*: Editorial Committee and Working Group 'Genetic Testing Counselling' of the European Huntington Disease Network: Recommendations for the predictive genetic test in Huntington's disease. *Clin Genet* 2013; **83**: 221–231.
120 Deans Z, Clarke A, Newson A: For your interest? The ethical acceptability of using non-invasive prenatal testing to test 'purely for information'. *Bioethics* 2015; **29**: 19–25.
121 Farrimond HR, Kelly SE: Public viewpoints on new non-invasive prenatal genetic tests. *Public Underst Sci* 2013; **22**: 730–744.
122 Dondorp WJ, de Wert GM: The 'thousand-dollar genome': an ethical exploration. *Eur J Hum Genet* 2013; **21**: S6–S26.
123 Jørgensen JM, Hedley PL, Gjerris M, Christiansen M: Including ethical considerations in models for first-trimester screening for pre-eclampsia. *Reprod Biomed Online* 2014; **28**: 638–643.
124 Van der Schoot CE, Hahn S, Chitty LS: Non-invasive prenatal diagnosis and determination of fetal Rh status. *Semin Fetal Neonatal Med* 2008; **13**: 63–68.
125 Poon LC, Musci T, Song K, Syngelaki A, Nicolaides KH: Maternal plasma cell-free fetal and maternal DNA at 11-13 weeks' gestation: relation to fetal and maternal characteristics and pregnancy outcomes. *Fetal Diagn Ther* 2013; **33**: 215–223.
126 TRIDENT 2014. Trial by Dutch laboratories for Evaluation of Non-Invasive Prenatal Testing (NIPT). Available at: http://www.emgo.nl/research/quality-of-care/research-projects/1451/trident-study-trial-by-dutch-laboratories-for-evaluation-of-non-invasive-prenatal-testing-nipt/background/ (last accessed 22 December 2014).
127 Munthe C: A new ethical landscape of prenatal testing: individualizing choice to serve autonomy and promote public health: a radical proposal. *Bioethics* 2015; **29**: 36–45.

128 John S: Efficiency, responsibility and disability: philosophical lessons from the savings argument for prenatal diagnosis. *Polit Philos Econ* 2015; **14**: 3–22.
129 Walker BS, Jackson BR, LaGrave D, Ashwood ER, Schmidt RL: A cost-effectiveness analysis of cell free DNA as a replacement for serum screening for Down syndrome. *Prenat Diagn* 2014; **34**: 1–7.
130 Beulen L, Grutters JP, Faas BH, Feenstra I, van Vugt JM, Bekker MN: The consequences of implementing non-invasive prenatal testing in Dutch national health care: a cost-effectiveness analysis. *Eur J Obstet Gynecol Reprod Biol* 2014; **182C**: 53–61.
131 Neyt M, Hulstaert F, Gyselaers W: Introducing the non-invasive prenatal test for trisomy 21 in Belgium: a cost-consequences analysis. *BMJ Open* 2014; **4**: e005922.
132 Cuckle H, Benn P, Pergament E: Maternal cfDNA screening for Down syndrome—a cost sensitivity analysis. *Prenat Diagn* 2013; **33**: 636–642.
133 Cornel MC, van El CG, Dondorp WJ: The promises of genomic screening: building a governance infrastructure. Special issue: genetics and democracy. *J Community Genet* 2012; **3**: 73–77.
134 Skirton H, Jackson L, Goldsmith L, O'Connor A: Are health professionals ready for direct-to-consumer genetic and genomic testing? *Personalized Med* 2013; **10**: 673–682.