

## POLICY

# Offering prenatal diagnostic tests: European guidelines for clinical practice

This article has been amended since online publication and a corrigendum appears in this issue.

Heather Skirton<sup>\*1</sup>, Lesley Goldsmith<sup>1</sup>, Leigh Jackson<sup>1</sup>, Celine Lewis<sup>2</sup> and Lyn Chitty<sup>3</sup>

For over four decades, it has been possible to offer prenatal diagnostic testing for fetal abnormalities. Prenatal testing is now available for a wide range of monogenic disorders as well as chromosomal abnormalities and should be provided within the ethical framework of informed consent and autonomous choice. However, there are no published guidelines for health professionals from varied disciplines who offer prenatal diagnosis (PND) in a range of possible settings including departments of maternity, obstetrics and clinical genetics. We used an Expert Group technique to develop a set of guidelines for provision of prenatal diagnostic services. Thirteen European health professionals, all experts in PND, participated in a workshop to develop the guidelines, which were then subjected to a wide consultation process. The objective of PND was defined as providing prenatal diagnostic testing services (for genetic conditions) that enable families to make informed choices consistent with their individual needs and values and which support them in dealing with the outcome of such testing. General principles, logistical considerations, clinical care and counselling topics are all described and are equally applicable to invasive and non-invasive testing. These guidelines provide a framework for ethical clinical care; however, they are flexible enough to enable practitioners to adapt them to their particular setting. Ideally, an individualised approach to each family is required to ensure autonomous choice and informed consent regarding prenatal diagnostic testing within the local ethical and legal framework.

*European Journal of Human Genetics* (2014) 22, 580–586; doi:10.1038/ejhg.2013.205; published online 11 September 2013

Prenatal diagnostic testing has been available to parents since the middle of the last century, when amniocentesis became available for the detection of fetal aneuploidy.<sup>1</sup> Initially, examination of the fetal chromosome number and microscopic structure could be offered; however, as understanding of the molecular basis of many genetic conditions has increased, so have the opportunities for prenatal diagnosis (PND) of a wide range of disorders.<sup>2</sup> PND using samples obtained via invasive tests (amniocentesis, chorionic villus sampling (CVS) or, very rarely, cordocentesis) is still generally used to detect monogenic and chromosomal disorders in the fetus.<sup>3</sup> In some clinical settings, amniocentesis or CVS for aneuploidy has been offered to all pregnant women of advanced maternal age.<sup>4–6</sup> In other circumstances or countries, discussion of invasive testing may be prompted by a high-risk screening result.<sup>7</sup> However, the opportunity to use non-invasive techniques for some conditions is now feasible<sup>8</sup> and these are increasingly available to women in some countries.<sup>9</sup>

Advances in technology increasingly facilitate parental choice with regard to PND; however, there are many ethical,<sup>10</sup> legal,<sup>11</sup> and social and psychological<sup>12</sup> issues related to the clinical offer of prenatal screening and testing that require consideration.<sup>13</sup> As with other medical procedures, enabling the parents to make an informed choice is integral to good clinical care; however, this can be challenging because of the understandable reluctance of parents to anticipate an abnormality in the fetus and the unpredictable nature of their reaction to the results.<sup>12</sup> Furthermore, there is evidence that parents may not be aware that such tests are optional. In a qualitative study of

38 mothers who had undergone prenatal testing, Potter *et al*<sup>14</sup> found that some women believed they had not given informed consent, mainly because of their beliefs that the testing was a routine part of antenatal care. Authors of the same study found that many women made their decisions based on moral judgements related to their own values, interpreting the factual information provided through their own moral lens. Therefore, whereas health professionals emphasise the importance of providing information, exploration of the individual views of the parents may be just as important in facilitating them to make a decision compatible with their beliefs.

Beliefs and values relate to cultural norms, and women from dissimilar cultural backgrounds may show varied responses towards information and prenatal counselling. For example, Tschudin *et al*<sup>15</sup> identified that Turkish women reacted differently while considering PND when compared with women of other European nationalities and found the counselling process itself more unsettling. Authors of other studies confirmed differences in the uptake of PND in women of Israeli Arab<sup>5</sup> and African American<sup>16</sup> ethnicity, while attitudes towards prenatal testing and subsequent pregnancy management varied depending on condition in a study comparing Pakistani and White women living in the United Kingdom.<sup>17</sup> It therefore appears that, although guidance on the best practice in counselling for prenatal testing can be devised, it must be sufficiently flexible to take cultural norms into account.

Non-invasive techniques to test the fetus, using cell-free fetal DNA in the maternal circulation, are increasingly available for fetal sex determination (for sex-linked conditions), aneuploidy detection<sup>18</sup>

<sup>1</sup>Faculty of Health, Education and Society, Plymouth University, Plymouth, UK; <sup>2</sup>Genetic Alliance UK, London, UK; <sup>3</sup>UCL Institute of Child Health, Great Ormond Street and UCLH NHS Foundation Trusts, London, UK

\*Correspondence: Professor H Skirton, Faculty of Health, Education and Society, Plymouth University, Drake Circus, Plymouth PL4 8AA, UK. E-mail: heather.skirton@plymouth.ac.uk

and diagnosis of single-gene disorders.<sup>19</sup> According to a recent systematic review on the factors influencing the use of NIPT,<sup>20</sup> users and potential users cite the advantages of the non-invasive test as including earlier diagnosis (allowing earlier reassurance or decisions about the future of the pregnancy) and removal of the risk of fetal loss owing to the test.<sup>21,22</sup> However, the ease with which the test can be performed has made some women, health professionals and members of the general public concerned that parents might consent to the test without sufficient consideration of the consequences.<sup>23,24</sup> A recent position statement on NIPT published by the National Society of Genetic Counsellors<sup>25</sup> cited the need for both appropriate counselling to accompany the test and the need for informed consent. This is particularly pertinent to the NIPT approach, as women and health professionals seem to vary in their attitudes towards this mode of testing<sup>26,27</sup> and ease of testing may increase use of direct-to-consumer testing.<sup>28</sup> It is essential therefore that pre- and post-test counselling and consent procedures should be rigorous, whether the sample was taken via an invasive or non-invasive route.

Despite the long history of PND, there have been no general guidelines issued to ensure that parents are equipped to make informed decisions about such testing. A search of the International Guidelines Library (<http://www.g-i-n.net/library/international-guidelines-library>) indicated that, although there were 10 guidelines related to antenatal care, none of these focussed on diagnostic testing. As part of the EuroGentest2 project, we were charged with producing a set of guidelines for those offering prenatal diagnostic tests in a clinical setting. According to local practice and the condition for which testing is offered, PND counselling may be provided by health professionals in the midwifery, obstetric or specialist genetics clinical teams, providing further challenges for ensuring good practice and equity of care. In view of the need for individual approaches to ensure that each woman or couple can make an informed choice, we developed a set of guidelines that can be adapted for use in a range of settings and according to the individual circumstances of the woman, couple or family involved.

The aim of this study was, therefore, to formulate a set of best practice guidelines for offering genetic testing in specific prenatal contexts, including NIPT.

## METHODS

We used an expert group to formulate the guidelines through a process of consensus and consultation. This approach has been utilised in other work to develop policy or recommendations in a genetic health-care context.<sup>29,30</sup> We aimed to invite a cohort of 13 experts with maximum variation in terms of European country of origin and clinical specialism and profession to participate in a workshop. We therefore invited specialists in the field of PND from Belgium, Czech Republic, Denmark, Finland, Greece, Italy, the Netherlands, Spain, Sweden and the United Kingdom. However, the participant from Greece was unable to attend, leaving representatives of nine European countries to contribute (see Supplementary File 1 for country, background and expertise of the participants). As the workshop was held in the United Kingdom, several additional people with relevant expertise working in the United Kingdom were also able to join the group. Prior to the workshop, the aims of the meeting and relevant peer-reviewed papers on the topic of PND were circulated (see online appendix for details) to enable the participants to become familiar with the latest existing work on the topic. Although all attendees were experts in their own areas, this established a foundation of knowledge across different disciplines.

The workshop began with an introduction and discussion to agree the aims and objectives. Representatives of clinical practice were then asked to make a

short presentation on the way in which PND was offered in their own country. This enabled the participants to gain an appreciation of the areas of commonality and variations in practice, national policies and legal regulation in those European countries. A presentation on service-user views and experiences of NIPT with a focus on the psychosocial aspects of the test was also given.

The participants decided to develop guidelines under four main headings: objectives of PND, general principles, logistical considerations (process) and principles related to the content of the counselling. We first agreed the objectives and determined the scope of the guidelines. After much discussion around the boundaries between prenatal screening and testing, we decided to address the issue by focussing on defining the three main groups of women who might present for prenatal testing in practice (Table 1). Another key issue covered in the initial discussion was whether the guidelines for non-invasive PND should be different in any way than those for invasive testing; the outcome was a decision to write the guidelines for invasive testing and then review them critically to see whether and how they might have to be altered for NIPT.

Work to further develop the guidelines under the three remaining headings (general principles, logistics and counselling content) was conducted in three multidisciplinary groups. The groups met at the end of each session for plenary discussions to raise specific matters that had arisen during small group discussion with the entire group. In the final plenary session, all guidelines were further discussed until a consensus was obtained. Returning to fitness of the guidelines for use with NIPT, it was agreed that they were equally applicable to invasive and non-invasive prenatal testing.

Following the workshop, the draft guidelines were sent to each participant for further consideration and suggestions. The document was then circulated broadly for consultation to the following:

1. Members of the European Society for Human Genetics (ESHG)
2. National professional societies for human genetics in all European countries
3. European societies for those practising obstetrics and gynaecology
4. Participants in the EuroGentest2 project.

The document was also posted onto the websites of the ESHG and EuroGentest2 project to enable open access by any interested person. This resulted in receipt of detailed comments from a further 14 experts from 12 countries and approval from members of the Executive Board of the ESHG and other national organisations (Supplementary File 2). Finally, the guidelines were reviewed and amended slightly where necessary, in the light of the comments received.

## Scope of the guidelines

These guidelines relate to PND for women whose fetus is at an increased risk of a specific condition. They, therefore, relate to testing offered with the intention of determining the presence or absence of a genetic or multifactorial condition in the fetus. Such testing may be performed using invasive or less invasive procedures (such as analysis of cfDNA or fetal imaging). Here, we suggest guidelines for the practical aspects of delivering PND to these high-risk women: discussion on more general ethical, legal, social and economic aspects is outwith the scope of this document. The guidelines do not refer to antenatal screening tests. Within the guidelines we used the terms women, parents, couples (women and their partners) or families, as appropriate; however, we did not make any assumptions about family composition when using those terms.

The guidelines are presented in three sections: general principles, logistical considerations (process) and principles related to the content of the counselling.

## RESULTS

### Objective and context

The objective of PND is to provide prenatal diagnostic testing services (for genetic conditions) that enable families to make informed

**Table 1** Specific considerations for each group of women

<i>Group 1</i>	<i>Group 2</i>	<i>Group 3</i>
<i>Women and/or their partners known to genetic services before pregnancy because of significant family history.</i>	<i>Women identified during pregnancy as having a fetus at risk of a genetic condition (for example, through disclosure of family history, potentially including genetic test results, during an antenatal consultation).</i>	<i>Women whose fetus is at risk because of abnormal ultrasound findings, particularly where the fetal karyotype is normal.</i>
<p>(1) During initial genetic counselling (before conception) by an appropriately trained health professional, the woman or her partner should have been advised that they are at risk and should contact the genetics team before pregnancy for a revision or update of relevant information. Before a pregnancy occurs, the genetic professional should:</p> <p>(a) Review the genetic diagnosis</p> <p>(b) Review treatment and outcome for the condition, involving other relevant health professionals if required</p> <p>(c) Review all prenatal diagnostic options, including genetic tests available</p> <p>(d) Ensure that any testing required is performed in a laboratory prepared to undertake PND if requested and that is accredited (eg ISO 15189) or can provide evidence of successful participation in External Quality Assessment (EQA) schemes where available.</p> <p>(e) Inform the woman that as soon as she is pregnant she should contact the genetics team, who will coordinate management.</p> <p>(2) Pre-test counselling should be given by an appropriately trained professional and should include the elements described under counselling topics (below).</p> <p>(3) If PND is requested, a scan should be undertaken to confirm the gestation as early in the pregnancy as possible to facilitate plans for testing.</p> <p>(4) Test results should only be conveyed by an appropriately trained professional. Post-test counselling should be offered and options for management of the current pregnancy discussed.</p> <p>(5) If the fetus is affected and the decision is made to terminate the pregnancy (ToP), then this should be performed in a unit offering appropriate and sensitive care. Where necessary, bereavement support should be offered.</p> <p>(6) If PND is declined (and the fetus is, therefore, still considered to be at risk) or the pregnancy continues with an affected fetus, there may be a need for referral for specialist ongoing pregnancy management and postnatal support.</p>	<p>(1) An urgent referral should be made to the appropriate team and then action as described above for Group 1, if PND is available.</p> <p>(2) In instances where it is too late for the option of ToP, the appropriate work up to identify the genetic cause of the condition should still be offered. Testing during pregnancy can be discussed, as this may guide management and delivery in the current pregnancy. Alternatively, testing after the pregnancy can be offered to guide management in future pregnancies and determine the consequences for other family members.</p> <p>(3) In the event of stillbirth or neonatal death, post-mortem examination by an expert in fetal and perinatal pathology should be offered. The reasons for this, including informing future reproductive options and consequences for other family members, should be clearly explained to parents so that they can make informed decisions regarding the post-mortem examination.</p> <p>(4) In the event that post-mortem investigations do not identify the underlying cause of the problems, where possible provisions should be made for further research to determine the exact cause of the genetic/multifactorial condition in the family.</p>	<p>(1) The woman should be referred urgently to the specialist team for expert PND. This may include the genetic and/or relevant paediatric team for counselling and discussion of prognosis and options for pregnancy management (see elements of counselling listed below).</p> <p>(2) The results should only be conveyed by an appropriately trained professional. Post-test counselling should be offered and options for management of the current pregnancy should be discussed.</p> <p>(3 and 4) As for Group 2.</p> <p>(5) Consent should be obtained for relevant DNA, tissue or other biological materials to be taken, stored and analysed.</p> <p>(6) The results of any testing during or after pregnancy should be discussed with the parents by an appropriate person and genetic counselling should be offered.</p>

Abbreviation: PND, prenatal diagnosis.

choices, consistent with their individual needs and values and to support them in dealing with the outcome of such testing. For the purpose of these guidelines, we are referring to prenatal diagnostic tests that may be offered to pregnant women in one of the three groups (Table 1).

### General principles underpinning PND

The general principles are presented in Figure 1. In order to provide a service that ensures appropriate standards of care for women and their families, all of the principles should be adhered to, although specific content addressed during counselling may vary according to the particular family situation and the condition (see Table 1).

### Logistical considerations (process)

The general considerations that apply to all the three groups of women are as follows:

1. There should be a designated professional who will act as the coordinator and facilitate communication between the multi-disciplinary team(s), the local doctor/midwife and the family.
2. Sensitive counselling by an appropriately trained professional should always be offered to support the couple in both making decisions and adjusting to the outcome, whatever their decision is.

The general principles are:

1. In each country, PND should be offered within the current national regulations, legal framework and standards of practice.
2. PND should be provided by multi-disciplinary teams of health professionals who are appropriately trained for the tasks involved in offering, discussing all implications of testing, providing and interpreting tests, discussing prognosis as well as managing the pregnancy and subsequent care.
3. Health professionals involved in offering PND must ensure they are informed and maintain their knowledge on all relevant aspects of PND. They must be aware of their own limitations and involve other professionals when required.
4. The test provided should be appropriate for the condition and level of risk involved. Targeted testing for the condition is to be preferred where possible to reduce the potential for results with unclear clinical significance and/or generation of incidental findings. Any changes in service should be driven by clinical utility rather than commercial interest or technological innovation.
5. PND is offered as a choice to prospective parents, there should be no element of pressure or coercion involved.
6. Professionals should ensure prospective parents are able to make an informed choice through provision of accurate, balanced information in a clearly understandable form. This should include the use of an independent interpreter when needed.

7. Provision of informed consent is a process based on a) access to and understanding of relevant information, b) understanding of the decision to be made, including possible consequences and c) communication of the decision to the health professional.
8. Parents should be made aware that they may change their decision after giving consent to testing if they wish. While the ultimate decision rests with the mother, where appropriate both parents should be involved in the process. The process should be documented in the medical record, including the use of a consent form where applicable.
9. Pre- and post-test counselling should be available and carried out by appropriately trained professionals (in many cases this will be a clinical geneticist or genetic counsellor) and should be based on the establishment of an empathic relationship. It should include exploration and acknowledgement of parents' values, beliefs and cultural norms. Post-test counselling may require involvement of teams who manage the condition in question and/or referral to relevant lay organisations, in order to allow fully informed parental consent regarding further management.
10. When the pregnancy continues after testing and the child is affected, suitable arrangements should be made for the ongoing management of the pregnancy and care of the child after birth in consultation with the relevant neonatal/paediatric teams.
11. In pregnancies where the fetus is unaffected, the pregnancy can be managed by the routine maternity care services.
12. To ensure clinical utility, views of clinical staff caring for patients and laboratory staff providing testing should be harmonised with regard to type and scope of testing offered.
13. Bereavement and social support should be available when required. This should be provided by appropriately trained professionals.
14. When a definitive diagnosis cannot be made in the course of the affected pregnancy, all efforts should be made to obtain a diagnosis after birth so that appropriate genetic counselling can be offered.

Figure 1 General principles underpinning PND.

3. To ensure effective communication with the woman and her partner, independent interpreting services should be used where necessary.
4. In every case, implications for other family members should be considered and appropriate family management should be discussed with the parents.
5. Where sharing of information is required, national practice should be followed, and consent sought to share the relevant case details with other professionals – for example, the referring doctor.
6. Where the diagnosis is uncertain and parents decide to terminate the pregnancy, they should be made aware that having a termination using medical methods could enable other investigations to take place, even if this means delaying termination following an early pregnancy diagnosis. This may facilitate diagnosis and identification of the underlying cause of fetal abnormality, which will be beneficial for risk assessment in future pregnancies and for other family members.
7. If informed consent is given for PND, the procedure should be undertaken by a trained professional with appropriate skills. The sample should be tested in an appropriate laboratory (see Table 1, section 1d).
8. Test results should only be conveyed by an appropriately trained professional. Post-test counselling should be offered and all options for management of the current pregnancy should be discussed within the local ethical and legal framework.
9. If PND is declined or not appropriate, as it is too late in pregnancy for intervention, (and the fetus is therefore still

Figure 1 (Continued)

- considered to be at risk) or the pregnancy continues with an affected fetus, there may be a need for referral for specialist ongoing pregnancy management and postnatal support.
10. Additional counselling should be offered after pregnancy to discuss future reproductive options and consequences, if they exist, for other family members.
  11. Consent should be obtained for relevant DNA, tissue or other biological materials to be taken, stored and analysed.

#### Counselling topics when offering a diagnostic test for a specific genetic condition

The key counselling topics should be discussed, and ideally a written summary of the discussion should be provided. Table 2 gives an

**Table 2 Topics to be covered during counselling for prenatal diagnostic tests**

<p><i>Issues about the condition:</i></p> <p>The couples' or family's experience and knowledge of the genetic condition</p> <p>Aspects of the condition, including: genetic cause, inheritance pattern, variance, expression, age of onset, phenotypic features, management and/or treatment, quality of life, life expectancy, social aspects including support available and relevant research developments</p> <p>The risk to the fetus in the current pregnancy</p> <p>Recurrence risk in each pregnancy</p> <p>Risk to other family members</p> <p>Future reproductive options.</p>
<p><i>Issues about the test</i></p> <p>Why the parents are being offered this particular test and for which conditions the fetus will be tested</p> <p>What the test entails and risks associated with the procedure</p> <p>Accuracy of test results</p> <p>Limitations of the test, whether these would render a result and the chance of unexpected (incidental) findings</p> <p>When the results will be available, how and by whom they will be communicated</p> <p>Whether results will have implications for other family members.</p>
<p><i>Practical aspects</i></p> <p>At what stage in pregnancy a test can be performed</p> <p>Time taken to get the results</p> <p>Accuracy of the results</p> <p>How the result will be communicated</p> <p>The options that will be available after the results are known, such as continuing with the pregnancy or ToP. This should include discussion of treatment options, such as intra-uterine or postnatal treatment or specialist management of the delivery</p> <p>Other professionals who need to be informed about the test results</p> <p>Confidentiality of test results</p> <p>Whether results could have implications for future insurance of individuals involved</p> <p>Referral to other expert health professionals, if appropriate</p> <p>Follow-up investigations – for example, wider family testing or counselling.</p>
<p><i>Psychosocial issues</i></p> <p>Taking time to think through the decision, including what they would do if the fetus is affected</p> <p>Thinking about the impact of the condition on the child and his or her quality of life</p> <p>Thinking about the impact of having a child with the condition in the context of their own lives and those of their family members</p> <p>Thinking about the impact of a ToP on their own lives, particularly in situations where there is a variable outcome associated with the condition in question.</p> <p>Signposting to support groups and good quality information sources, including the opportunity to access information about quality of life and living with a condition from people with first-hand knowledge (for example, disease specific lay support organisations)</p> <p>The possibility of further counselling if necessary, including psychosocial support.</p>

indication of the main topics; however, the discussion should be tailored to individual circumstances. Although many topics will be discussed prior to the test, appropriate post-test counselling to discuss the outcomes and support parental decision-making should always be available.

## DISCUSSION

Although new technologies may change the way in which samples for PND are obtained and tested, the underpinning principle of informed consent remains unchanged. These guidelines include the need for pre- and post-test counselling by an appropriate health professional to ensure that the woman (and her partner, if relevant) is able to access the information required to enable her to make an autonomous decision, and to use the results as she wishes, within the context of the local ethical and legal guidelines. However, despite a relatively long history of such testing, there is evidence that health professionals still find counselling in such situations challenging. Eldahdah *et al*,<sup>31</sup> for example, reported that some experienced obstetricians used a directive approach and reported discomfort with giving results of

prenatal testing for chromosomal abnormalities, whereas Williams *et al*<sup>32</sup> highlighted the challenges faced by both obstetricians and midwives in facilitating choice regarding prenatal testing. Adequate training for health professionals is essential to facilitate effective prenatal diagnostic counselling, and for that reason we have specified that the person providing counselling should be appropriately trained.

Information should be provided to women in both verbal and written forms. Kuppermann *et al*<sup>33</sup> undertook a study using a computerised decision tool to support information provision in a cohort of pregnant women and found that women preferred these to standard written information. However, other studies have shown that women value the opportunity to discuss their screening decisions in a personalised way with an appropriately trained health professional,<sup>34</sup> and there is no indication that this would be different in a diagnostic testing scenario.<sup>35,36</sup> In addition to this point, providing only written information assumes a level of literacy in the patient. We therefore recommend that individual discussion is undertaken to enable the woman to place the information into the context of her own life and that of her family. Of further relevance to

this point is the need to employ trained interpreters for discussion when indicated, as women who are not fluent in the language routinely used in the clinic are disadvantaged in terms of their ability to discuss and consider their options, make autonomous decisions and provide consent.<sup>37</sup>

In writing these guidelines, we have made an attempt to address not only current clinical issues but also those that may arise in the near future.<sup>38</sup> For example, the use of microarray testing in place of conventional karyotyping for fetal chromosomal analysis is increasing the potential for unexpected findings.<sup>39</sup> Although the empirical data available to inform the management of such findings are limited, albeit growing rapidly, it is claimed that the respect for patients' autonomy and the avoidance of paternalism necessitate disclosure.<sup>36</sup> We therefore suggest that the potential nature of unexpected findings, as well as whether and how they will be disclosed to the parents should be discussed before the sample is taken.

### Strengths and limitations

These guidelines have been based on in-depth discussions between acknowledged experts across the specialities involved in PND. In addition, they have been open for consultation among a much wider group of health professionals. Although the expert group took into account the current scientific evidence available through peer-reviewed literature, there are few empirical studies that involve a comparison of different models of care. This inevitably limits the objective scientific basis of this work.

### CONCLUSIONS

These guidelines are offered to health professionals working in a range of contexts. Owing to the need for an individualised approach that takes into account individual values and beliefs, cultural norms and ethnicity,<sup>38</sup> we have developed general guidelines that can be adapted to the individual setting and family. However, they will require modification for local, regional and national conditions. In the light of the rapidly changing situation in genetic healthcare, the guidelines should be reviewed every 3 years. This should be undertaken by relevant organisations working together to ensure that women and their partners are offered prenatal testing in a way that ensures that they have adequate information, are able to make an appropriate decision for their own family and are supported throughout the process.

### CONFLICT OF INTEREST

The authors declare no conflict of interest.

### ACKNOWLEDGEMENTS

This study was funded under the EuroGentest Coordination Action 2011 – EU Contract no.: HEALTH-F4-2010-2614692 project. The workshop participants who contributed greatly to the guidelines were: Katia Bilardo, Outi Kamarainen, Helena Kaariaianen, Susan Kelly, Faustina Lalatta Milan Macek, Olav Petersen, Thomy de Ravel, Martina Rodriguez de Alba, Maria Soller and Sally Taffinder. We acknowledge the support of Jan Preece in helping to organise the workshop. LSC is partially funded by the National Institute of Health Research Biomedical Research Centre at Great Ormond Street Hospital and the Great Ormond Street Hospital Children's Charity.

### DISCLAIMER

The views expressed in the article are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health.

- 1 Wolstenholme J, Rooney DE: Cytogenetics in the 1970s and 1980s. *Prenat Diagn* 2010; **30**: 605–607.
- 2 Raymond FL, Whittaker J, Jenkins L, Lench N, Chitty LS: Molecular prenatal diagnosis: the impact of modern technologies. *Prenat Diagn* 2010; **30**: 674–681.
- 3 Wieacker P, Steinhard J: The prenatal diagnosis of genetic diseases. *Dtsch Arztebl Int* 2010; **107**: 857–862.
- 4 Lo TK, Lai FK, Leung WC, Lau WL, Tang LC, Chin RK: A new policy for prenatal screening and diagnosis of Down syndrome for pregnant women with advanced maternal age in a public hospital. *J Matern Fetal Neonatal Med* 2010; **23**: 914–919.
- 5 Muhsen K, Na'amnah W, Lesser Y, Volovik I, Cohen D, Shohat T: Determinates of underutilization of amniocentesis among Israeli Arab women. *Prenat Diagn* 2010; **30**: 138–143.
- 6 Nakata N, Wang Y, Bhatt S: Trends in prenatal screening and diagnostic testing among women referred for advanced maternal age. *Prenat Diagn* 2010; **30**: 198–206.
- 7 UK National Screening Committee: Screening for Down's syndrome: UK NSC Policy recommendations 2011–2014 Model of Best Practice. 2011 (Online). Available at: <http://fetalanomaly.screening.nhs.uk/aboutus> (accessed 13 May 2013)
- 8 Hill M, Barrett AN, White H, Chitty LS: Uses of cell free fetal DNA in maternal circulation. *Best Pract Res Clin Obstet Gynaecol* 2012; **26**: 639–654.
- 9 Chitty L, Bianchi D: Noninvasive prenatal testing: the paradigm is shifting. *Prenat Diagn* 2013; **33**: 511–513.
- 10 Knoppers BM, Isasi RM: Regulatory approaches to reproductive genetic testing. *Hum Reprod* 2004; **19**: 2695–2701.
- 11 Klein RD, Mahoney MJ: Medical legal issues in prenatal diagnosis. *Clin Perinatol* 2007; **34**: 287.
- 12 Hunt LM, de Voogd KB, Castañeda H: The routine and the traumatic in prenatal genetic diagnosis: does clinical information inform patient decision-making? *Patient Educ Couns* 2005; **56**: 302–312.
- 13 Reid B, Sinclair M, Barr O, Dobbs F, Crealy G: A meta-synthesis of pregnant women's decision-making processes with regard to antenatal screening for Down syndrome. *Soc Sci Med* 2009; **69**: 1561–1573.
- 14 Potter BK, O'Reilly N, Etchegary H *et al*: Exploring informed choice in the context of prenatal testing: findings from a qualitative study. *Health Expect* 2008; **11**: 355–365.
- 15 Tschudin S, Huang D, Mor-Gültekin H, Alder J, Bitzer J, Tercanli S: Prenatal counselling—implications of the cultural background of pregnant women on information processing, emotional response and acceptance. *Ultraschall In Der Medizin* 2011; **32**(Suppl 2): E100–E107.
- 16 Kuppermann M, Learman LA, Gates E *et al*: Beyond race or ethnicity and socio-economic status: predictors of prenatal testing for Down syndrome. *Obstet Gynecol* 2006; **107**: 1087–1097.
- 17 Alsulaiman A, Hewison J, Abu-Amero KK, Ahmed S, Green J, Hirst J: Attitudes to prenatal diagnosis and termination of pregnancy for 30 conditions among women in Saudi Arabia and the UK. *Prenat Diagn* 2012; **32**: 1109–1113.
- 18 Boon E, Faas B: Benefits and limitations of whole genome versus targeted approaches for noninvasive prenatal testing for fetal aneuploidies. *Prenat Diagn* 2013; **33**: 563–568.
- 19 Lench NB, Fielding S, McKay F *et al*: The clinical implementation of non-invasive prenatal diagnosis for single gene disorders: challenges and progress made. *Prenat Diagn* 2013; **33**: 555–562.
- 20 Skirton H, Patch C: Factors affecting the clinical use of non-invasive prenatal testing: a mixed methods systematic review. *Prenat Diagn* 2013; **33**: 532–541.
- 21 Lewis C, Hill M, Skirton H, Chitty LS: Non-invasive prenatal diagnosis for fetal sex determination: benefits and disadvantages from the service users' perspective. *Eur J Hum Genet* 2012; **20**: 1127–1133.
- 22 Tischler R, Hudgins L, Blumenfeld YJ *et al*: Noninvasive prenatal diagnosis: pregnant women's interest and expected uptake. *Prenat Diagn* 2011; **31**: 1292–1299.
- 23 Kelly SE, Farrimond HR: Non-invasive prenatal genetic testing: a study of public attitudes. *Public Health Genomics* 2012; **15**: 73–81.
- 24 Hill M, Compton C, Lewis C, Skirton H, Chitty LS: Determination of foetal sex in pregnancies at risk of haemophilia: a qualitative study exploring the clinical practices and attitudes of health professionals in the United Kingdom. *Haemophilia* 2012; **18**: 575–583.
- 25 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 Counsel* 2013; **22**: 291–295.
- 26 van den Heuvel A, Chitty LS, 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.
- 27 Hill M, Fisher J, Chitty LS, Morris S: Women's and health professionals' preferences for prenatal tests for Down syndrome: a discrete choice experiment to contrast noninvasive prenatal diagnosis with current invasive tests. *Genet Med* 2012; **14**: 905–913.
- 28 Benn PA, Chapman AR: Ethical challenges in providing noninvasive prenatal diagnosis. *Curr Opin Obstet Gynecol* 2010; **22**: 128–134.
- 29 Holland A, Whittington J, Cohen O *et al*: The European Prader-Willi Syndrome Clinical Research Database: an aid in the investigation of a rare genetically determined neurodevelopmental disorder. *JIDR* 2009; **53**(Part 6): 538–547.
- 30 Thariani R, Wong W, Carlson JJ *et al*: Prioritization in comparative effectiveness research: the CANCERGEN Experience. *Med Care* 2012; **50**: 388–393.
- 31 Eldadah LT, Ormond KE, Nassar AH, Khalil T, Zahed LF: Outcome of chromosomally abnormal pregnancies in Lebanon: obstetricians' roles during and after prenatal diagnosis. *Prenat Diagn* 2007; **27**: 525–534.

- 32 Williams CP, Alderson P, Farsides B: Is nondirectiveness possible within the context of antenatal screening and testing? *Soc Sci Med* 2002; **54**: 339–347.
- 33 Kuppermann M, Learman LA, Gates E *et al*: Computerized prenatal genetic testing decision-assisting tool: a randomized controlled trial. *Obstet Gynecol* 2009; **113**: 53–63.
- 34 Barr O, Skirton H: Informed decision making regarding antenatal screening for fetal abnormality in the United Kingdom: a qualitative study of parents and professionals. *Nurs Health Sci* 2013; e-pub ahead of print 24 January 2013; doi10.1111/nhs.12034.
- 35 Lewis C, Hill M, Skirton H, Chitty LS: Fetal sex determination using cell-free fetal DNA: service users' experiences of and preferences for service delivery. *Prenat Diagn* 2012; **32**: 735–741.
- 36 Jackson L, Goldsmith L, O'Connor A, Skirton H: Incidental findings in genetic research and clinical diagnostic tests: a systematic review. *Am J Med Genet* 2012; **158A**: 3159–3167.
- 37 Hunt LM, de Voogd KB: Are good intentions good enough? Informed consent without trained interpreters. *J Gen Intern Med* 2007; **22**: 598–605.
- 38 Learman LA, Kuppermann M, Gates E, Nease RF, Gildengorin V, Washington AE: Social and familial context of prenatal genetic testing decisions: are there racial/ethnic differences? *Am J Med Genet* 2003; **119C**: 19–26.
- 39 Vetro A, Bouman K, Hastings R *et al*: The introduction of arrays in prenatal diagnosis: a special challenge. *Hum Mutat* 2012; **33**: 923–929.

Supplementary Information accompanies this paper on European Journal of Human Genetics website (<http://www.nature.com/ejhg>)