



## PSYCHOLOGICAL ASPECTS OF INDIVIDUALIZED CHOICE AND REPRODUCTIVE AUTONOMY IN PRENATAL SCREENING

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### Keywords

*Prenatal screening, women's perspectives, individualized choice*

### ABSTRACT

*Probably the main purpose of reproductive technologies is to enable people who choose to do so to avoid the birth of a baby with a disabling condition. However the conditions women want information about and the 'price' they are willing to pay for obtaining that information vary enormously. Individual women have to arrive at their own prenatal testing choices by 'trading off' means and ends in order to resolve the dilemmas facing them. We know very little about how individuals make these trade-offs, so it is difficult to predict how new technologies will affect their choices and preferences. Uptake decisions can be expected to change, especially in the group of women who now are put off by some aspect of the current screening approach, where the avoidance of miscarriage risk may have provided a kind of 'psychological shelter', protecting a lot of people from having to make other decisions. Technologies such as Pre-implantation Genetic Diagnosis may remove a second 'psychological shelter' because they offer the means of avoiding the birth of an affected child without terminating a pregnancy.*

*Even if new technologies will make some decisions easier in terms of their cognitive demands, they will also create new dilemmas and decision making will not necessarily become less stressful in emotional terms. Key challenges concern information and decision-making.*

Probably *the* main purpose of reproductive technologies is to enable people *who choose to do so* to avoid the birth of a baby with a disabling condition. In years gone by, people who knew or suspected that a disabling condition ran in their family had limited options if they wanted to avoid having children with the condition. In some cultural settings, pre-marital counselling might have been available – on a more or less scientific basis – but for the great majority of people, the only real option was not to have children at all. Reproductive technologies have greatly expanded the available options and changed the decisions women have to make, not only in affected families, but in pregnant populations around the world.

Although the title of this article refers to 'psychological aspects' of prenatal screening, only limited reference has been made to the academic psychological literature, which has focused on a few rather traditional psychologi-

cal topics, such as risk perception and anxiety, or taken an overly-theoretical approach to the very complex relationship that exists between attitudes and behaviour.<sup>1</sup> Many published studies could also be described as essentially adopting a service provider's perspective rather than an individual woman's. For example, it's a pervasive finding that women do not always think about risk the same way experts do, to which the response has been: we

<sup>1</sup> J.M. Green, J. Hewison, H.L. Bekker, L.D. Bryant & H.S. Cuckle. Psychosocial aspects of genetic screening of pregnant women and newborns: a systematic review. *Health Technol Assess* 2004; 8(33): 1–128; J.M. Harris, L. Franck & S. Michie. Assessing the psychological effects of prenatal screening tests for maternal and foetal conditions: a systematic review. *J Reprod Infant Psychol*. 2012; 30: 222–246; M. Van den Berg, D.R. Timmermans, D.L. Knol, J.T.M. van Eijk, D.J. de Smit, J.M. van Vugt, et al. Understanding pregnant women's decision making concerning prenatal screening. *Health Psychol* 2008; 27: 430–437.

must find ways of improving their risk perception.<sup>2</sup> And even work that is ostensibly about choice can turn out to be derived from an over-simplified analysis of the factors affecting people's choices, with a consequent over-hasty acceptance of the idea that the 'right' choice for an individual woman can be readily and reliably ascertained.<sup>3</sup>

A more understandable limitation to the psychological literature on prenatal testing is that it has struggled to keep up with technological changes as they are implemented 'on the ground', particularly in relation to the role of a test in a care pathway. There is, however, a substantial methodological literature on how to evaluate the 'clinical utility' of a test, which emphasizes that test properties such as accuracy, and hence acceptability, are properties of the test-in-context, not of a particular technology.<sup>4</sup> Insights from this literature are heavily drawn upon in what follows, since it is impossible to understand women's perspectives on say, non-invasive testing, without making clear distinctions between the different roles the technology can play in a specific care pathway, such as that delivered by the UK's Down's Syndrome Screening programme.

Individual women take many different routes through a prenatal testing programme, leading to many possible outcomes for mother and baby. A woman herself will choose parts of that route, but her understanding of what the future might hold will also change depending on the results of any tests she chooses to have. This article is about a complex process and how changes to the technology embedded within it will change the nature of individuals' experience 'on the ground', offering new choices but also creating new dilemmas.

## CHOICES, DILEMMAS, MEANS AND ENDS

In a publicly funded healthcare system such as the UK NHS, policymakers have to decide what should be offered, since they want to:

- offer women the choices reproductive technologies afford,
- while protecting people from foreseeable harm,
- and respecting the public interest.

Using the example of *tests for Down's syndrome*, what choices do women want to have, should they be allowed by law to exercise those choices, and if so, at public or private expense?

Different countries resolve their policy dilemmas in different ways, but all impose constraints of some kind on both the means and the ends of prenatal testing. Within those constraints, individual women have to arrive at their own prenatal testing choices, by 'trading off' means and ends in order to resolve the dilemmas facing them. The dilemmas and the trade-offs that underlie them take a variety of forms, but three have particularly far-reaching implications and are considered in more detail here.

1. Diagnostic quality information versus risk of miscarriage.
2. Information on different conditions versus risk of miscarriage.
3. Avoiding a birth versus ending a pregnancy.

### Trade-off 1

In an ideal world, definitive information as to whether a baby did or did not have, say, Down's syndrome, would be obtainable without any risk of harm arising from the testing procedure. Ultrasound scans and tests performed on the mother's blood are examples of such 'non-invasive' tests, suitable for use as *screening* tests offered to all pregnant women. Unfortunately, the information obtainable non-invasively has not in the past been definitive, and a woman who needed certainty, perhaps because she would consider ending the pregnancy if the baby had Down's syndrome, needed to subject herself to an invasive *diagnostic* test and had to accept the risk of a procedure-related miscarriage (0.5–1%).

This dilemma has faced many women over many decades and in its basic form it has been extensively studied by clinicians and social scientists alike. At first glance, a non-invasive test seems to be the obvious solution. Innovative technologies are seldom as straightforwardly beneficial as enthusiasts expect, however, and to explain why, it is necessary first to identify some of the less visible trade-offs involved whenever a medical test – here, a test for Down's syndrome – is evaluated and used to determine subsequent care.

In the UK Down's Syndrome Screening programme, non-invasive *screening* tests (blood tests and ultrasound scans) are offered to all pregnant women; if these tests are accepted, the likelihood that the baby has Down's syndrome is then calculated, and an invasive *diagnostic* test is

<sup>2</sup> M. Siegrist, P. Orlow & C. Keller. The effect of graphical and numerical presentation of hypothetical prenatal diagnosis results on risk perception. *Med Decis Making* 2008; 28: 567–574; A. Edwards, J. Gray, A. Clarke, J. Dundon, G. Elwyn, C. Gaff, et al. Interventions to improve risk communication in clinical genetics: systematic review. *Patient Educ Couns.* 2008; 71: 4–25.

<sup>3</sup> J. Hewison & L. Bryant. Informed consent: what should we be doing? In: Kehoe S., Chitty L., Homfray T., editors. *Reproductive Genetics* (Royal College of Obstetricians and Gynaecologists 57th Study Group). London: RCOG Press; 2009. p. 205–216.

<sup>4</sup> P.M. Bossuyt, L. Irwig, J. Craig & P. Glasziou. Comparative accuracy: assessing new tests against existing diagnostic pathways. *BMJ* 2006; 332(7549): 1089–1092; A. Hayen, P. Macaskill, L. Irwig & P. Bossuyt. Appropriate statistical methods are required to assess diagnostic tests for replacement, add-on, and triage. *J Clin Epidemiol.* 2010; 63: 883–891.

offered to every woman whose calculated risk of Down's syndrome exceeds a specified threshold. That threshold is determined by health policymakers, using data from large numbers of women on the performance of the screening programme. The lower the threshold is set, the greater the number of women who will be offered invasive testing, with its associated miscarriage risk. The majority of women undergoing an invasive test for Down's syndrome learn that the baby does not have the condition. However, for any specific test, raising the threshold in order to reduce the numbers of such 'false alarms' will have the effect of increasing the number of 'missed' cases of Down's syndrome. Judgements about the relative importance of these two kinds of unsought-for outcome are both entailed in setting the policy threshold.

The policymakers' intention is that the same risk cut-off, based on what might be described as a population-level trade-off, should be applied to all women. However, not all individuals attach the same value judgements to the various test outcomes that the policymakers do. Avoiding miscarriage is undoubtedly the overriding consideration for many women, but not for all. Data from non-NHS providers shows significant levels of demand for invasive testing amongst women who would not be offered an NHS diagnostic test because their screening test result suggested a relatively low likelihood that the baby had Down's syndrome.<sup>5</sup> For some women in some circumstances, a miscarriage would not be the worst outcome of the pregnancy; and they would rather accept the procedural risk and have an invasive test than continue the pregnancy with even a low likelihood of Down's syndrome. Women whose personal threshold is *higher* than that of the policymakers (i.e. women who would only consider invasive testing if there was a very high chance that the baby had Down's syndrome) can decline any offer of invasive testing at that point (though some may need support in doing so), i.e. their needs are, at least in principle, met by current NHS provision.

The Holy Grail of non-invasive prenatal diagnosis (NIPD) was to avoid Trade-off 1. Put into the scientific language of test evaluation studies, NIPD was intended to be a *substitute* for an Invasive Diagnostic (ID) test.<sup>6</sup> However, as far as Down's syndrome is concerned, it has now become clear that current non-invasive technology cannot produce diagnostic quality information, i.e. the best non-invasive test still picks out a lot of babies who turn out not to have Down's syndrome ('false positives', in test parlance) as well as ones that do. To understand how this can be true, it is necessary to revisit the test

evaluation literature<sup>7</sup> and understand the crucial distinction between the specificity of a test and its positive predictive value. In the present context, if a test is highly specific – as the test for Down's syndrome using currently available non-invasive technologies undoubtedly is – that means that only a small proportion of babies without Down's syndrome will 'test positive'. However, a general population sample will consist almost entirely of unaffected babies, so even a small proportion of this large fraction will generate a lot of 'test positive' results. Nearly all the babies *with* Down's syndrome will also 'test positive' using the same technology, but in a general population sample, there will not be many of them. It follows that, in these circumstances, the proportion of the 'test positive' babies who have Down's syndrome – the test's 'positive predictive value' (the PPV) – may actually be quite low. The PPV will be better in a high risk sample, because the proportion of babies with the condition will be higher, but an *a priori* risk of 1 in 200 still translates into a PPV of only around 60%, i.e. 4 in 10 of the test positives will not have Down's syndrome.

The UK National Screening Committee is enthusiastic about introducing non-invasive technologies into the Down's syndrome screening programme, but for the reasons given above, the anticipated role, and hence the name used for the new test, has had to change. Conditional on supportive findings from ongoing research, current UK NSC plans are for non-invasive prenatal testing (NIPT) to be an *add-on* to the existing *screening test*, i.e. a second line *screen*, offered only to women with a high risk result from the initial screening test, and with invasive diagnostic testing still being offered to those women who get a second high risk result.<sup>8</sup>

It may reasonably be asked at this point if it would not make more sense for NIPT to be considered as a likely substitute for the *initial* Down's Syndrome Screening test, but in the UK public sector this has been ruled out on cost grounds, at least for the foreseeable future. In the UK private sector, non-invasive testing for Down's syndrome (and for some other chromosomal abnormalities) is widely available. Concerns have been raised about the information that is provided to women in such circumstances,<sup>9</sup> particularly in relation to the need for high risk results to be confirmed by invasive testing, which may not be made sufficiently clear.

<sup>7</sup> Bossuyt et al. *op. cit.* note 4; Hayen et al. *op. cit.* note 4.

<sup>8</sup> J.M.E. Walsh & J.D. Goldberg. Fetal aneuploidy detection by maternal plasma DNA sequencing: a technology assessment. *Prenat Diagn.* 2013; 33: 514–520; UK National Screening Committee (UK NSC). 2013. *Public Information Briefing – Non-Invasive Prenatal Testing (for Down's syndrome)*. London: UK NSC. Available at: <http://fetalanomaly.screening.nhs.uk/programmestements> [Accessed 25 April 2014].

<sup>9</sup> R. Daley, M. Hill, C. Lewis & L. Chitty. Non-invasive prenatal testing for Down's syndrome – where are we now? *B J Midwifery* 2014; 22: 85–93.

<sup>5</sup> K.H. Nicolaides, F.A. Chervenak, L.B. McCullough, K. Avgidou & A. Papageorghiou. Evidence-based obstetric ethics and informed decision-making by pregnant women about invasive diagnosis after first-trimester assessment of risk for trisomy 21. *Am J Obstet Gynecol.* 2005; 193: 322–326.

<sup>6</sup> Hayen et al. *op. cit.* note 4.

As an add-on screening test, what impact might non-invasive testing have on the initial uptake of Down's syndrome screening in the NHS programme, and on 'flows through the system'? And what might the psychological consequences be? It must be remembered that changing a test pathway does not of course change the incidence of Down's syndrome in a given population; all a pathway change can do is alter the numbers of people in possession of different types of information at different times.

In test evaluation parlance, a new test can improve on what went before by one or both of the following mechanisms: it can reduce the number of 'missed' cases of the target condition, or it can reduce the number of 'false alarms'.<sup>10</sup> Big technological advances can sometimes do both, but the argument for introducing a new test into the NHS usually hinges on one or the other. Assuming for the present that the definition of a high risk case on the initial screening test is not changed (i.e. the risk cut off stays the same), then 'missed' cases can only be identified if women classified as low risk by the first test are tested again with the new test. In these circumstances, an add-on (or contingent) test, which is only offered to women identified as high risk by the first test, cannot find previously missed cases, but it can reduce the numbers of 'false alarms', i.e. reduce the numbers of women needing to be offered invasive tests, many of which will show that the baby does not have Down's syndrome.

Such a change would clearly be highly desirable: as well as fewer women experiencing a procedure-induced miscarriage with its attendant psychological harms (anxiety, distress and guilt), others – a larger number – could be spared worrying about having one. This latter group would still however experience some aspects of a 'false alarm', in that an initial non-reassuring result (from the first screening test) would be followed by a reassuring result from the add-on test. This apparent discrepancy can cause anxiety in some women that may not be readily resolved.<sup>11</sup> As described earlier, some women prioritize diagnostic reassurance over miscarriage risk, and those who do may not all be persuaded by the revised screening risk and hence might still press for an invasive test. It can also be argued that a small minority of women would actually be worse off under the new arrangements, in that a definitive result would not be obtained until they had undergone three tests rather than the present two, although any extra anxiety or distress might potentially be alleviated by the woman's knowledge that she had followed a testing pathway designed to minimize risk to the pregnancy.

In the above example, the identification of benefits achieved and harms avoided assumes that the same risk

threshold (calculated from the initial screening test) is used for offering the NIPT add-on screen as is currently used for offering an invasive diagnostic test. However, will – indeed, should – the new cut-off be the same as the old one? Since miscarriage risk is not a factor in deliberations, perhaps the opportunity of reducing the numbers of 'missed cases' should also be seized, by adopting a lower risk threshold for the add-on non-invasive test offer than is currently used for the invasive test offer? If so, how should the new threshold be decided?

The risk threshold currently in use in the UK NHS for offering an invasive diagnostic test is 1 in 150 (i.e. there is more than a 1 in 150 chance that the baby has Down's syndrome). Two research projects currently underway in the UK<sup>12</sup> are utilizing lower thresholds than this for offering the NIPT add-on screen, one project pragmatically opting for 1 in 1000 and the other for 1 in 3000. This broadening of the definition of 'high risk' is intended to reduce the numbers of 'missed cases' (because all the women with risk values between 1 in 150 and say, 1 in 1000, will now be offered further testing, whereas they would not have been before), but it must be remembered that this can only be achieved by increasing the proportion of the initially screened population treated as 'high risk'. There are, in other words, disadvantages as well as advantages to lowering the risk threshold, and the optimal value recommended for adoption by a service will depend on how – explicitly or implicitly – these different factors are weighted.

To recap then, the NHS role currently anticipated for non-invasive testing for Down's syndrome is as an add-on screening test, offered to women regarded as 'high risk' – on an expanded definition – based on their initial screening test result, and with invasive diagnostic testing being offered to women testing positive on the non-invasive add-on screen. The anticipated strategy is designed to achieve two substantial benefits: exposing fewer women to the risk of miscarriage, and reducing the number of 'missed cases'. In a comprehensive assessment of a testing pathway, potential harms as well as anticipated benefits do however need to be considered, so where might such harms lie?

Most women who have prenatal tests get reassuring results. It has been argued that seeking reassurance is the reason most women have tests,<sup>13</sup> and staff emphasise to

<sup>10</sup> Walsh, *op. cit.* note 8.

<sup>11</sup> Green et al., *op. cit.* note 1.

<sup>12</sup> UK Clinical Research Network (UK CRN). 2013. *NIPT for aneuploid evaluation study*. Leeds: UK CRN. Available at: [public.ukcrn.org.uk/search/StudyDetail.aspx?StudyID=13865](http://public.ukcrn.org.uk/search/StudyDetail.aspx?StudyID=13865) (accessed 25 April 2014); UK Clinical Research Network (UK CRN). 2013. *First-trimester cfDNA testing*. Leeds: UK CRN. Available at: [public.ukcrn.org.uk/Search/StudyDetail.aspx?StudyID=15084](http://public.ukcrn.org.uk/Search/StudyDetail.aspx?StudyID=15084) (accessed 25 April 2014).

<sup>13</sup> J.M. Green, C. Snowdon & H. Statham. Pregnant women's attitudes to abortion and prenatal screening. *J Reprod Infant Psychol*. 1993; 1: 31–39.

women being offered invasive testing that most of those tested will get a reassuring result. If the risk threshold for offering NIPT is lower than the one currently used for offering invasive testing, that will increase, compared with now, the overall numbers of women waiting for reassurance, and increase the amount of time they *spend as candidates* for invasive testing.

How best to offer tests to women as part of the new care pathway? As has been made clear, there are disadvantages as well as advantages to the changes being proposed and although the majority of women may ‘weight’ these in the same way the experts do, inevitably that will not be true for all. Women will therefore need to be given enough information to enable them to make up their own minds, and service providers will need to be alert to unintended harms as well as psychological benefits brought about by the new arrangements.

The net effect of all the changes in terms of women’s decision-making about testing will not be known for some time. However, before leaving the relatively familiar territory of Down’s syndrome screening and Trade-off 1, it is worth briefly speculating about the future and identifying subgroups of women whose decision-making is likely to be affected differently by the introduction of a non-invasive add-on screening test for Down’s syndrome. It must also be acknowledged that the relative size of these subgroups is at present unknown.

#### *Women whose screening decisions might be changed*

- People put off screening by some aspect of *current* pathway but not by the new one.
- People who accept the current pathway, but who would be deterred by the new one.

#### *And most likely to stay the same?*

- People not wishing to avoid the birth of a child with Down’s syndrome.
- People who would not consider a termination for Down’s syndrome.
- People who accept both test pathways.

#### Trade-off 2: same process, but more information

Down’s syndrome screening has always identified conditions other than Down’s syndrome. Historically this has happened following invasive diagnostic testing, but screening tests for Down’s syndrome are increasingly providing information about the likelihood that the baby

has some other condition.<sup>14</sup> These developments are driven by technological advance, not by a desire to respond to what women want, and in fact surprisingly little is known about the information that people do want regarding conditions other than Down’s syndrome. A very important distinction must be made before developing this point further. Families at high risk of inherited genetic disorders will understandably want information related to the condition that runs in their family. Here we are considering the more general question of information desired by women in the general population being offered screening during their pregnancy.

The ability to test for multiple conditions (e.g. using Next Generation Sequencing) is often presented as a positive NIPT feature<sup>15</sup> – perhaps because scientists are excited by the possibilities. Samples obtained from *invasive* diagnostic testing could in principle have been tested for multiple conditions for many years, but this was never offered routinely. Interestingly, the scope for identifying additional conditions was presented as a *disadvantage* by some protagonists in the long running debate about whether a specific PCR (polymerase chain reaction) based test for Down’s syndrome should replace karyotype analysis, on the grounds that such identification might lead to ‘unnecessary’ terminations.<sup>16</sup> The realization that early ultrasound scans also contain information indicating the likelihood of different conditions<sup>17</sup> raised the possibility of offering additional information at the *screening* (i.e. general population) stage rather than further down the pathway. The arrival of NIPT technologies has greatly increased the scope for offering tests for multiple conditions, further widening the gap between the original purpose of, say, a programme set up to offer screening for Down’s syndrome, and the many different screening purposes tests can be used for today.

If it is agreed that more conditions should be screened for, which conditions should they be? Developments in technology make it easy to extend the tested-for list in specific ways, e.g. by offering screening tests for trisomy 18 (Edwards’ syndrome) and trisomy 13 (Patau’s syndrome) alongside the test for trisomy 21 (Down’s syndrome), and this is likely to be recommended by the UK National Screening Committee. However the similarity between Down’s syndrome and the other two trisomies ends there (babies with Edwards’ or Patau’s syndrome

<sup>14</sup> K. Spencer, A.W.J. Liao, H. Skentou, S. Cicero & K.H. Nicolaidis. Screening for triploidy by fetal nuchal translucency and maternal serum free  $\beta$ -hCG and PAPP-A at 10–14 weeks of gestation. *Prenat Diagn.* 2000; 20: 495–499.

<sup>15</sup> Y.M.D. Lo, K.C.A. Chan, H. Sun, E.Z. Chen, P. Jiang, F.M.F. Lun, et al. Maternal plasma DNA sequencing reveals the genome-wide genetic and mutational profile of the fetus. *Sci. Transl. Med.* 2010; 2: 61ra91.

<sup>16</sup> W.C. Leung & T.T. Lao. Rapid aneuploidy testing, traditional karyotyping, or both? *Lancet* 2005; 366(9480): 97–98.

<sup>17</sup> Spencer et al. *op. cit.* note 14.

can seldom stand, walk or talk, and few survive childhood) so a single 'trisomy screening test' has been ruled out. Instead, it is anticipated that women who want testing for only some of these conditions will be able to choose to be screened only for the two very severe conditions, or only for Down's syndrome, if that is their preference.

Technology continues to advance, and for some conditions, diagnostic quality information can already be obtained by non-invasive means.<sup>18</sup> In high risk families, such techniques can provide much-needed explanations of known problems (although they can also produce 'incidental findings', the significance of which may be unclear), but that does not mean benefits would necessarily outweigh harms if such techniques were introduced in a population screening context.

Focussing on technology tells us what's possible, not what's desirable or indeed what's desired. The difference between the trisomies highlights the more fundamental question: which conditions are considered sufficiently serious to justify prenatal testing? And by whom? Official bodies tend to avoid being too specific here, perhaps influenced by the desire to avoid adverse publicity from pressure groups opposed to abortion. One UK body has however been obliged to create an official list of conditions deemed to be serious, namely the Human Fertilisation and Embryology Authority (HFEA), which licenses clinics wishing to use a reproductive technology known as Pre-implantation Genetic Diagnosis (PGD):

Before PGD clinics are permitted to test for a condition or combination of conditions, the HFEA must first agree that the condition they want to test for is sufficiently serious. This list of conditions are those that HFEA has so far agreed that it is acceptable for clinics to use PGD to test for.<sup>19</sup>

Although over 270 conditions are included on the 2013 list, and new conditions continue to be added, the *grounds* on which HFEA makes its inclusion or exclusion decisions remain unclear.

And what about the recipients of test offers? Do we know what conditions women in the general population would like to be tested for? Test uptake rates – and termination rates – are known to differ between conditions

*for which testing is currently available and permitted,*<sup>20</sup> but since real tests for specific conditions are only offered in specific – and highly variable – circumstances, like-with-like comparisons of actual uptake figures cannot be interpreted with any confidence.

Surveys asking people what they think they would do are useful in these circumstances, always remembering their fundamental limitation: what people say they want to do, and what they actually do, may differ. On the other hand, many influences are involved in both, and the temptation to over-interpret behavioural measures at the expense of information about what women say they want must also be resisted. As explained above, a woman may decline current prenatal tests for Down's syndrome for a variety of reasons, each with different implications for predicting choices and behaviour in the future. What clinicians assume people will do is not a good guide to behaviour either – there is no 'gold standard' here, and women's views about what they think they would do form an important part of the overall picture.

More than a decade ago, the UK's Economic and Social Research Council (ESRC) funded colleagues and myself to study women's views about prenatal testing and termination for different conditions. There was already recognition that new technologies were rapidly extending the number of conditions which could be tested for, and an emerging concern about the implications for offering women choice. One way of addressing the problem would be to offer initial screening tests for combinations, or categories, of conditions,<sup>21</sup> but that immediately raises the question of how the categories should be formed. More fundamentally, is it actually possible to form meaningful categories? They would only be helpful if individuals want information about the same conditions – but do they?

The ESRC Innovative Health Technologies (IHT) Project surveyed the views of over 400 women about prenatal testing and termination of pregnancy for 30 conditions, reflecting a range of physical, mental and sensory disabilities.<sup>22</sup> Importantly, although the test technology described was very hypothetical at the time – non-invasive, providing definite answers – it corresponds

<sup>18</sup> N. Lench, A. Barrett, S. Fielding, F. McKay, M. Hill, L. Jenkins, et al. The clinical implementation of non-invasive prenatal diagnosis for single gene disorders: challenges and progress made. *Prenat Diagn.* 2013; 33: 555–562; A. Srinivasan, D.W. Bianchi, H. Huang, A.J. Sehner & R.P. Rava. Noninvasive detection of fetal subchromosome abnormalities via deep sequencing of maternal plasma. *Am J Hum Genet.* 2013; 92: 167–176.

<sup>19</sup> Human Fertilisation and Embryology Authority (HFEA). 2013. *PGD conditions licensed by the HFEA*. London: HFEA. Available at: <http://www.hfea.gov.uk/cps/hfea/gen/pgd-screening.htm> [Accessed 25 April 2014].

<sup>20</sup> C. Mansfield, S. Hopper & T.M. Marteau. Termination rates after prenatal diagnosis of Down syndrome, spina bifida, anencephaly and Turner and Klinefelter syndromes: a systematic literature review. *Prenat Diagn.* 1999; 19: 808–812; B.L. Shaffer, A.B. Caughey & M.E. Norton. Variation in the decision to terminate pregnancy in the setting of fetal aneuploidy. *Prenat Diagn.* 2006; 26: 667–671.

<sup>21</sup> A. de Jong, W.J. Dondorp, C.E. de Die-Smulders, S.G. Frints & G.M. de Wert. Non-invasive prenatal testing: ethical issues explored. *Eur J Hum Genet.* 2009; 18: 272–277.

<sup>22</sup> J. Hewison, J. Green, S. Ahmed, H. Cuckle, J. Hirst, C. Hucknall & J. Thornton. Attitudes to prenatal testing and termination of pregnancy for 30 different conditions: a comparison of white and Pakistani women in the UK. *Prenat Diagn.* 2007; 27: 419–430.

closely to today's specification for actual Non-invasive Prenatal *Diagnosis*.

When individual women's views were aggregated, there were clear differences between conditions in views about testing and termination. Ranking conditions from lowest to highest interest in testing, and in termination, created an empirical dimension of seriousness or severity, as women perceived it in the prenatal testing context. While very informative in many respects, such an analysis does not address the 'Can conditions be grouped?' question, because it throws no light on the constellation of views held by individual women. Analysed this way, the study found only very limited support for grouping conditions together. At the 'more severe' end of the spectrum, attitudes to testing for anencephaly, trisomy 13/18, quadriplegia, Duchenne muscular dystrophy, and to a lesser extent, severe learning difficulties, did tend to cluster, but more generally, views were not predictable enough *across conditions* to form the basis of a classification system, even for initial screening choice purposes.

The above conclusions about aggregate and individual views may appear contradictory on initial reading, but the distinction may be readily illustrated using study data from just two conditions: Duchenne muscular dystrophy (DMD) and Huntington's disease. These showed that:

- Attitudes towards the two conditions were strongly associated: 68% of the sample wanted testing for both conditions.
- However, another 15% (63 women) only wanted testing for one of the two conditions (7 for Huntington's and 56 for DMD).
- So although more people overall wanted testing for DMD than Huntington's, a small minority took a different view.

The challenge of providing enough information to enable all pregnant women to make informed, individualized test choices for all conditions is clearly formidable. However, a classification system would undoubtedly bring its own problems. In qualitative interviews, participants in the IHT study – who were thinking about tests that would provide definitive information – expressed strong opposition to being offered indivisible clusters of tests, and felt it was their right to decide for themselves which tests they did and did not want.

Paradoxically, the fact that NIPT is not diagnostic for a condition such as Down's syndrome may give prenatal screening programmes an opportunity to develop some kind of practicable, staged approach to information giving, on the assumption that additional and more specific information will always be provided at a subsequent stage of the test pathway. While an informed decision to embark on the initial stage of a pathway clearly does require awareness of what the future might hold, i.e. awareness of the kinds of conditions being tested for, that

initial decision does not require a full understanding of each and every one of those possibilities. Finding an acceptable compromise between the paediatric textbook and the old fashioned 'we'll tell you when there's something you need to know' approach has had to be tackled in connection with fetal anomaly ultrasound scanning,<sup>23</sup> a procedure which can also provide information on numerous different conditions, sometimes only in terms of probabilities, but sometimes to a diagnostic standard (e.g. some of the major structural abnormalities). It may be that a similar approach will need to be adopted for NIPT.

We can now imagine what some of the psychological effects of non-invasive testing might be, starting with people who accept currently available prenatal screening technology.

- Anxieties – some of them enduring – associated with a two (or three) stage process (probabilities not diagnoses, miscarriage risk, being a 'false positive') would remain when using non-invasive tests that were *non-diagnostic*.
- If available for a specified condition, non-invasive *diagnosis* could reduce all of these anxieties in people who would have had a test for that condition anyway.
- Non-invasive *diagnosis* could also reduce the cognitive demands (e.g. understanding probabilities) made by two-stage testing but could increase the decision-making burden overall if more than one condition was involved.

As and when non-invasive diagnosis becomes a reality for some conditions, what of the 'new recruits' to prenatal testing, previously deterred by miscarriage risk?

Although for any one condition, test uptake decisions should become easier in terms of their cognitive demands, they would *not necessarily be less stressful in emotional terms*. This is because the avoidance of miscarriage risk may have provided a kind of 'psychological shelter', protecting a lot of people from having to make other decisions. For a proportion of women, accepting an offered test will require them to confront some long-held attitudes to disability and to ending a pregnancy, and that can be a real shock.

Turning to the even more stressful decision to continue or end a pregnancy, at present nearly all the people facing that decision wanted diagnostic information strongly enough to undergo an invasive test. Termination rates are high<sup>24</sup> in this group – perhaps unsurprisingly – but 'new recruits' would not be so self-selected, and consequently may find decision-making more stressful.

<sup>23</sup> NHS Fetal Anomaly Screening Programme (NHS FASP). Revised 2010. *Having a mid pregnancy ultrasound scan?* London: NHS FASP. Available at: <http://fetalanomaly.screening.nhs.uk/leafletsforparents> [Accessed 25 April 2014].

<sup>24</sup> Mansfield et al., *op. cit.* note 20; Shaffer et al., *op. cit.* note 20.

Tests carried out ‘only for information’ might also increase. Although it cannot be assumed that all women who learn this way that their baby has a problem will regret having – or indeed acting upon – such knowledge, it is likely that many of the ‘new recruits’ will need support in facing such unanticipated and very stressful decisions.

Summing up the likely impact of NIPT, we can say that:

- As well as reducing the Down’s syndrome ‘false alarm’ rate, NIP *Testing* could change the size and composition of the group offered invasive diagnosis, particularly if testing was also offered for more conditions.
- A woman accepting invasive testing for any one condition may also want information on others, as the miscarriage risk stays the same.
- The conditions on which women *would like* information vary enormously.
- The effect of the availability of extra information on current screening test uptake is unpredictable.
- NIP *Diagnosis* brings new challenges as well as new benefits.

However, it must be remembered that miscarriage risk is not the only ‘price’ women have to pay . . .

### Trade-off 3: Does avoiding a birth mean ending a pregnancy?

To return to a point made earlier, most women face a dilemma when they are offered a prenatal test, because to make a decision either way, they have to ‘trade off’ their *attitudes* to the current test pathway *and its limitations* against their attitudes to avoiding the birth of a child with a disability. *Test uptake*, in other words, is the result of trading off the (available) means against the (desired) ends.

We all need to understand Trade-off 3 better, because technological development is changing the nature of the dilemma in quite a fundamental way. Ends and means (avoiding a birth, by terminating a pregnancy) used to be inseparable, but now testing technology can *in principle* break that connection.

Pre-implantation genetic diagnosis (PGD) is already in widespread use for some conditions that run in families.<sup>25</sup> In-vitro fertilization (IVF) techniques are used to create embryos which are then tested for the condition in question. Only embryos without the disease-causing genes are selected for implantation.

Because of the need for IVF, PGD is clinically very demanding and quite unsuitable for screening purposes,

but it is nonetheless illuminating to consider the impact a similar technology might have on test uptake, e.g. for Down’s syndrome.

#### *Whose testing decisions might be changed?*

- People wishing to avoid the birth of a child with Down’s syndrome but who would not consider a termination for that condition.

#### *And whose most likely to stay the same?*

- People not wishing to avoid the birth of a child with Down’s syndrome.
- People who accept the limitations of current reproductive technology.

As in the case of Trade-off 1, we simply do not know the relative size of these subgroups. They probably vary over time and place and reflect other changes, e.g. moving testing to earlier in pregnancy will have made a difference to women who would consider an early but not a later termination.

Changes in uptake figures over time do not in themselves provide the necessary information, because they are amenable to more than one explanation. In the UK, for example, the proportion of people not wishing to avoid the birth of a child with Down’s syndrome has probably declined over time, but understanding and awareness of the drawbacks associated with current technologies – even the newer, better tests – has also probably increased. These and other factors change the ‘trade off’ for women.

#### *‘Seriousness’ and reproductive technologies*

PGD offers the means of *avoiding the birth* of an affected child without *terminating a pregnancy*. From the perspective of service commissioners, the advantage of PGD is clear: ‘For many people, a termination is either unacceptable or less preferable on humanitarian or religious grounds.’<sup>26</sup> The Genetic Alliance, a service user support and advocacy charity, expresses a very similar view in its information for parents: termination ‘is a difficult and often traumatic decision. However, PGD is performed before pregnancy begins, thus eliminating these difficult

<sup>25</sup> HFEA, *op. cit.* note 19.

<sup>26</sup> Welsh Health Specialised Services Committee (WHSSC). 2013. *Pre-implantation Diagnosis*. Cardiff: WHSSC. Available at: <http://www.wales.nhs.uk/sites3/Documents/898/CP37%20Pre-implantation%20Genetic%20Diagnosis%20policy%20v4.0.pdf> [Accessed 25 April 2014].

decisions.’ PGD is further described here as allowing couples, ‘the opportunity to have a child free of the condition’.<sup>27</sup>

The list of conditions for which PGD is licensed in the UK runs to several pages and includes sensory conditions, such as retinitis pigmentosa, and also late onset conditions such as breast cancer.<sup>28</sup> The attitude study reported earlier suggested that many people would not consider such conditions ‘serious’ enough to justify pregnancy termination, raising the now-familiar question about how individuals might be trading off means and ends. A preliminary attitude study<sup>29</sup> was therefore devised based on five conditions, chosen to be of differing perceived severity according to the 30-condition IHT study.<sup>30</sup> Participants were randomly divided into two groups and asked, for each condition, *either* about the acceptability of pregnancy termination following PND, *or* about avoiding implantation following PGD. The results supported our hunch that technology makes most difference at intermediate levels of perceived severity:

For the most and least severe conditions, the number of women choosing to terminate/avoid implantation was similar in both groups. For conditions in the middle range of severity significantly more women said that they would avoid implantation.

These results strongly suggest the existence of a very active trade-off system, responding to the new contingencies created by technological advance.

In other words, for the majority of people, whether they would wish to avoid the birth of a child with a particular condition or not *depended on the condition AND on the action they would have to take*. In a general sense, that conclusion is perhaps unsurprising: for a condition perceived to be very serious, people tended to consider that either action would be justified; and for a condition perceived to be very mild, neither action to be justified – but in the middle of the ‘seriousness’ spectrum, that sense of a consensus was lost and different people drew different conclusions.

Participants’ reactions to completing the questionnaire were also very revealing: some people were quite shocked to realize they might prefer to avoid the birth of children with less ‘serious’ kinds of disability. Hitherto, avoiding a birth could only have been achieved by having a

termination, so if the latter was unacceptable, underlying wishes and preferences could remain unexamined. In the language used earlier, the avoidance of termination had provided another ‘psychological shelter’.

Technological advances continue to create new contingencies. In the early months of 2013, the UK HFEA licensed selected clinics to perform an IVF technique called mitochondrial replacement, which in effect introduces DNA from a third person into an embryo.<sup>31</sup> A public consultation conducted prior to that decision found ‘that there is broad support for permitting mitochondria replacement, to give families at risk of mitochondrial disease the chance of having a healthy child.’ In the later months of 2013, the UK national press reported on ‘Crispr’, an IVF technique in which the genome is ‘edited’, in order to ‘correct’ individual patient mutations.<sup>32</sup> In the words of one advocate:

It would be difficult to argue against using it if it can be shown to be as safe, reliable and effective as it appears to be. Who would condemn a child to terrible suffering and perhaps an early death when a therapy exists, capable of repairing the problem?<sup>33</sup>

## KEY CHALLENGES: INFORMATION AND DECISION MAKING

From a service providers’ point of view, if people want very different things, how can each individual’s information and decision support needs be met? Genetic counsellors talking to high risk families can adapt what they say to the family’s specific circumstances and to the preferences that emerge during counselling, but that is not an option in the screening context.

Non-invasive add-on screening for Down’s syndrome is essentially an extension to the existing way of doing things, so while the new pathway will need to be properly explained and presented to women, and support services put in place, the *information* challenges are not themselves unfamiliar. Multiple conditions are a different matter. Even without NIPT or Next Generation Sequencing, screening programmes already face major challenges in respect of giving adequate information,

<sup>27</sup> Genetic Alliance UK. 2012. *Preimplantation Genetic Diagnosis (PGD)*. London: Genetic Alliance. Available at: <http://www.geneticalliance.org.uk/aboutpgd.htm#Question4> [Accessed 25 April 2014].

<sup>28</sup> de Jong et al. *op. cit.* note 21.

<sup>29</sup> C. Miller, J. Hewison & S.A. Morley. Comparison of decisions about prenatal diagnosis and pre-implantation genetic diagnosis. *J Reprod Infant Psychol.* 2012; 30: 377–387.

<sup>30</sup> Hewison et al. *op. cit.* note 22.

<sup>31</sup> Human Fertilisation and Embryology Authority (HFEA). 2013. *HFEA sends finalised mitochondria consultation report and advice to Government*. London: HFEA. Available at: <http://www.hfea.gov.uk/7796.html>. [Accessed 25 April 2014].

<sup>32</sup> The Independent. 7 November 2013. ‘Jaw-dropping’ breakthrough hailed as landmark in fight against hereditary diseases as Crispr technique heralds genetic-revolution. Available at: <http://www.independent.co.uk/news/science/exclusive-jawdropping-breakthrough-hailed-as-landmark-in-fight-against-hereditary-diseases-as-crispr-technique-heralds-genetic-revolution-8925295.html> [Accessed 25 April 2014].

<sup>33</sup> *Ibid.*

and offering the choices people want, e.g. in relation to chromosomal conditions ('trisomies') other than Down's syndrome, Trisomy 21.<sup>34</sup> In this case, the UK National Screening Committee has accepted that many women are likely to differentiate between the trisomies in terms of their attitudes to testing, so implementing this programme will entail providing information about each condition and asking women to make a number of separate test uptake decisions. It goes without saying that this approach cannot be extended indefinitely.

In the UK, information about the availability of prenatal testing has to be given to all pregnant women. The information challenge is daunting but inescapable. As mentioned earlier, the degree of complexity of the test pathway is not dissimilar to that associated with routine ultrasound screening, so the approach taken there will probably be the place to start. Essentially, any information that is provided to all pregnant women, but which aims to meet the needs of individuals, must have three essential properties: first, it must make absolutely clear that all points of view and all decisions will be respected; second, it needs to give enough information, at each stage of the pathway, to make meaningful the decisions that women have to take at that stage; and third, it needs to make clear that support in reaching a decision, and after it has been made, will be available as and when required.

The first of these will not be changed by the advent of risk-free testing. The second will probably be made more difficult: testing for a single condition will become easier to explain, but nobody yet knows how a national screening programme can deliver meaningful individualized choice in the era of multiple testing. Providing support may also become harder, and more women may find themselves in need of it, e.g. when a risk-free test carried out 'only for information' identifies an affected pregnancy.

In comparison with risk-free prenatal testing, pre-implantation technologies have few immediate implications for the general pregnant population, but remind us powerfully of the need to distinguish means from ends: attitudes to termination of pregnancy cannot be taken as a measure of attitudes to avoiding having a child with a disability.

<sup>34</sup> UK National Screening Committee (UK NSC). 2014. *The UK NSC policy on Trisomy 18 and Trisomy 13 Syndromes (policy currently in consultation)*. London: UK NSC. Available at: <http://www.screening.nhs.uk/t18andt13> [Accessed 25 April 2014].

## SUMMARY

What, *if anything*, is an individual prepared to do to avoid the birth of an affected baby? Reproductive technologies have changed the options dramatically, but the fundamental task for individuals remains the same: how to juggle – or 'trade off' – some very complicated means against starkly simple ends. That trade-off will be:

- Finely balanced for some *conditions*, obvious for others . . . and for any one condition . . .
- Finely balanced for some *technologies*, obvious for others.
- And for any *combination* of technology and condition, finely balanced for some *people*, obvious for others.

Obtaining diagnostic quality information by non-invasive means is already possible for some conditions.<sup>35</sup> This is undoubtedly a real breakthrough for some of the high risk families seeking help in avoiding future affected births. However, by their very presence in genetics clinics, such families are already providing some indication of the options they would consider, and the same is true of low risk families with the resources and the willingness to pay for NIPT or even PGD out of their own pockets.

The range of views held by the pregnant population – the target of screening programmes – will be much wider. With new technologies, decision-making for many people may become easier in terms of its cognitive demands, but it will not necessarily become less stressful in emotional terms. The avoidance of miscarriage risk and the unacceptability of termination have simplified decision making for many people in the past. Taking away such 'psychological shelters' may have the effect of confronting some people with their own, newly exposed, attitudes to different disabling conditions, an encounter which for some will be psychologically quite disturbing. We know surprisingly little about the complex relationship between the information an individual would like to have and the 'price' she is prepared to pay to obtain it. By changing the price, reproductive technologies change the equation, but the effect on preferences and choices is harder to predict, and the task of informing and supporting individual choice may become harder rather than easier.

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<sup>35</sup> Lench et al. *op. cit.* note 18; Srinivasan et al., *op. cit.* note 18.