

EVIDENCE REVIEW

Decision-Making by Expectant Parents: NIPT, NIPD, and Current Methods of Prenatal Screening for Down's Syndrome

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Note

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Summary

The objective of this review is to examine research exploring the decisions that women and couples make about prenatal screening and testing and the factors that influence their decisions. This will inform and offer context for the Nuffield Council of Bioethics' inquiry on non-invasive prenatal testing (NIPT) and how its possible introduction into the NHS screening programme could affect decision-making in pregnancy.

Studies deemed eligible for inclusion were full-length peer-reviewed journal articles and other publications in the English language that present data on parental decision-making in the context of NIPT (for Down's syndrome [DS], Edward's syndrome [ES], and Patau syndrome [PS]), NIPD for other genetic conditions, and current prenatal screening and testing for DS. The shortage of studies about NIPT and NIPD means that sources are discussed from the UK and beyond. Publications that do not rely on primary empirical data were excluded. Given time and money constraints, publications were also excluded if focusing exclusively on scientific and clinical development and application, cost-effectiveness, marketing and commercial analysis, and bioethical considerations (although the latter topic is discussed in section five).

Thirteen studies were found that explore the decision-making experiences of women in the context of NIPT for DS, ES, and PS. Positive experiences were often reported with respect to NIPT's perceived accuracy, safety, and capacity to provide an earlier test result. However, women also identified several concerns requiring consideration before NIPT is introduced into the NHS screening programme. Both advantages and disadvantages of NIPT were also outlined in twenty-three studies examining peoples' views of, and attitudes towards, NIPT for DS, ES, and PS. Many more studies examine expectant parents' decision-making relating to *current* prenatal screening for DS and diagnostic testing, and whether to continue or terminate a pregnancy following a diagnosis of DS, ES, or PS. This literature from diverse disciplines sketches out key issues around choice, care, responsibility, parenting, and disability. After statistics of screening uptake and terminations of pregnancy in the UK are outlined, the evidence review identifies gaps in the literature that future research on NIPT could explore. The review concludes by suggesting that more research on the experiences and decision-making processes of expectant parents with respect to NIPT – and on the opinions, anxieties, and suggestions of healthcare professionals and policymakers, charities, academics, and the wider public – a matter of urgency. Such studies will likely ignite more reflective and collective dialogues, and better communication between expectant parents and professionals, around NIPT and its implementation in NHS prenatal care.

1. NIPT for DS, ES, and PS

1.1. Background

NIPT is used to analyse cell-free foetal DNA in a pregnant woman's blood at around ten weeks' gestation. It can accurately predict the chance of a foetus having a genetic condition such as Down's syndrome [DS], Edward's syndrome [ES], or Patau syndrome [PS]. For example, at least 99 percent of all pregnancies in which a foetus has DS can be detected using NIPT. Screening for sex chromosome disorders (e.g. Turner syndrome) is also possible by using NIPT. Although most pregnant women will receive a 'lower-risk' (lower-chance) result, some will receive a 'higher-risk' (higher-chance) result, meaning it is highly likely that a foetus has a genetic condition. In such instances, diagnostic testing (CVS or amniocentesis) is used to validate this (i.e. NIPT is not officially classified as a diagnostic test). As NIPT is non-invasive, it presents no risk of miscarriage or other adverse outcomes associated with diagnostic tests. If implemented in the NHS, NIPT is likely to be offered as a contingent screening test as this is viewed as being 'cost-effective' (Chitty et al. 2016).¹

It is worth clarifying the difference between NIPT and NIPD here. Both are based on a maternal blood test. However, in some cases (e.g. testing for achondroplasia), this test is diagnostic and will mean an invasive diagnostic test (amniocentesis or CVS) is not required to confirm a diagnosis. This is referred to as NIPD (outlined more fully in section 2). In other cases, such as testing for DS, this test is not diagnostic (i.e. it is a 'screening test'). This is referred to as NIPT. Since NIPT cannot provide a definite diagnosis, an invasive diagnostic test can be offered to confirm or refute a result.

1.2. NIPT uptake statistics

Statistics for NIPT uptake were difficult to locate, mostly since uptake is only available in commercial settings (so national screening statistics are not recorded) and a select few NHS hospitals. Some studies have provided uptake statistics for single settings, with Chetty et al. (2013) and Beamon et al. (2014) reporting a high uptake of NIPT in one hospital and Taylor et al. (2014) reporting a low uptake of NIPT in another hospital; the reasons behind these uptake rates are not empirically explored by any of these outputs. Chitty et al. (2016), however, provide more extensive uptake statistics as part of the RAPID (Reliable, Accurate Prenatal, Non-Invasive Diagnosis) programme. The RAPID research programme was a prospective cohort study performed in eight NHS hospitals from November 2013 to February 2015. The objective of the programme was to examine the potential costs and consequences of introducing NIPT in the NHS. Although NIPT may help detect other conditions – like ES and PS – the main aim of RAPID was to evaluate NIPT for DS.

¹ For further resources, consult the website for the NHS RAPID Project (RAPID 2016). This contains an extensive electronic library with links to publications on cell-free foetal DNA, NIPT for Down's syndrome [DS] and foetal sex determination, stakeholder views and ethical concerns relating to NIPT, NIPD for single gene disorders and foetal blood types, studies on subchromosomal changes and foetal genotyping, and research on the cost-effectiveness and implementation of NIPT.

During the RAPID study, 40,527 pregnant women booked for maternity care at units participating in the study and 30,790 (76.0%) opted for DS screening. NIPT was offered to 3,175 women who received a screening result of at least 1:1000 (i.e. a 1 in 1,000 chance of having a baby with DS). In this population, 934 had a result of higher than 1:150 (i.e. a 1 in 150 chance of having a baby with DS) and 695 (74.4%) of these consented to NIPT, with 166 (17.8%) choosing to have diagnostic testing only (amniocentesis or CVS) and 73 (7.8%) declining further testing altogether. Of the 2,241 women with a risk between 1:150 and 1:1000, 1,799 (80.3%) had NIPT and of the women with a positive result, 80.4% underwent confirmatory diagnostic testing. In the participating units, uptake of diagnostic testing before the availability of NIPT was 54% in women who received a (higher) risk result of at least 1:150. In the RAPID study, the uptake of follow-on testing overall (NIPT and diagnostic testing combined) in women with the same result was 92.5%. The RAPID programme suggests that NIPT uptake in the eight participating units was considerably higher than the national uptake rate for the current DS screening pathway (66.2%).

The RAPID study found that 71 women received a confirmed diagnosis of DS; 13 out of 42 women (31%) with a diagnosis after NIPT and 2 out of 29 women (7%) after diagnostic testing continued their pregnancy, resulting in 12 live births of children with DS. For Chitty et al. (2016), this indicates that expectant women had NIPT to 'prepare' and not necessarily for decision-making about termination. They also suggest that this highlights how the birth rate of infants with DS may not change significantly if NIPT is introduced more widely, an observation in keeping with two regional US studies suggesting that NIPT has not affected the number of infants born with DS (Warsof et al. 2015; Wax et al. 2015) and one UK study showing that some women continued the pregnancy with a diagnosis of DS after NIPT (Gil et al. 2016). However, given the small numbers of cases, any conclusions should be drawn tentatively and the concerns of disability rights groups such as Saving Down Syndrome and Don't Screen Us Out – that NIPT may lead to a reduction in the amount of children born with DS – are yet to be debated in extensive detail in the literature.

1.3. Decision-making and NIPT

Thirteen publications were identified that explored the decision-making processes of NIPT for DS, ES, and PS. Four of these publications draw on data from the UK (Gil et al. 2015; Lewis et al. 2016a, 2016b; Strange 2015), five from Hong Kong (Chan et al. 2015; Lau et al. 2012, 2016; Poon et al. 2014; Yi et al. 2013), three from the US (Chetty et al. 2013; O'Brien et al. 2014; Vahanian et al. 2014), and one from Taiwan (Li et al. 2015). Whilst five of the thirteen studies focus on the possible 'predictors' of decision-making using quantitative data (Chan et al. 2015; Chetty et al. 2013; Gil et al. 2015; Poon et al. 2014; Vahanian et al. 2014), eight studies draw on qualitative data from pregnant women themselves that explains why they do or do not consent to NIPT (Lau

et al. 2012, 2016; Lewis et al. 2016a, 2016b; Li et al. 2015; O'Brien et al. 2014; Strange 2015; Yi et al 2013).

Research on the possible predictors of NIPT uptake suggest that expectant parents are more likely to accept NIPT if it is a first pregnancy (Chan et al. 2015; Poon et al. 2014), if they receive an increased risk result for DS, ES, and/or PS (Gil et al. 2015), if they conceived via assisted reproductive procedures (Chan et al. 2015), if they are Caucasian or Asian (Chetty et al. 2013; Vahanian et al. 2014), if they have health insurance [mostly in the US] (Chetty et al. 2013; Vahanian et al. 2014), if they are older than 35 (Chetty et al. 2013; Gil et al. 2015), if they were university-educated (Gil et al. 2015), and if they are employed (Poon et al. 2014). Other predictors that were reported as influencing choices include timing of results (first or second trimester) and nuchal translucency size. Most of the studies predicted a large decrease in diagnostic testing after the introduction of NIPT, but acceptance rates varied among studies; Vahanian et al. (2014), for example, report that 60% of their sample declined NIPT (mostly since women did not have insurance to cover the cost).

Importantly, the research cited above does not ask *why* women have NIPT for DS, ES, and PS. This is explored by eight other studies (Lau et al. 2012, 2016; Lewis et al. 2016a, 2016b; Li et al. 2015; O'Brien et al. 2014; Strange 2015; Yi et al 2013). Several of these studies reported women's positive experiences of NIPT (often cited by authors by using the term 'overwhelmingly positive'). In Lau et al.'s (2012) study, for instance, over 95% of participants 'had complete or almost complete resolution of anxiety' and said they would recommend NIPT to others. This corresponds with suggestions from some women that NIPT should be offered to all pregnant women on a routine basis (Lewis et al. 2016b). Women who had NIPT regularly reported that the most important aspects of NIPT were accuracy, safety, and having an earlier result (and that ultimately reduces the possibility of a diagnostic test).

The reasons for women undertaking NIPT include seeking general reassurance and attempting to reduce uncertainty (Lewis 2016b; Yi et al. 2013; Strange 2015), a desire to obtain as much information about a foetus as possible (Lewis et al. 2016b), wanting to avoid anxiety about diagnostic testing that may cause a miscarriage (Lau et al. 2012, 2016; Li et al. 2015; O'Brien et al. 2014; Yi et al. 2013), perceiving themselves as being at 'advanced maternal age' (O'Brien et al. 2014; Yi et al. 2013), wanting access to a safer and more accurate test than current screening (Lau et al. 2016; Lewis et al. 2016b; Strange 2015; Yi et al. 2013), being designated as 'higher-risk' (Lewis 2016b), and informing decisions about further testing and continuing/terminating a pregnancy (Lewis et al. 2016b; Yi et al. 2013). Reasons for declining NIPT include testing causing anxiety (Lewis et al. 2016b), stating a preference for diagnostic testing that was seen as more accurate (O'Brien et al. 2014), the cost/lack of health insurance (O'Brien et al. 2014), a perception that an NIPT result would not change how they managed the pregnancy [e.g. they would not terminate following a diagnosis] (Lewis et al. 2016b; O'Brien et al. 2014), and satisfaction with earlier screening results (Lewis et al.

2016b)². In some studies, a small number of participants were more uncertain about whether to have NIPT, indicating anxiety and ‘decisional conflict’ (Lewis et al. 2016b).

On the issue of informed consent, Lewis et al. (2016a) reported that ‘rates of informed consent were high (89%)’, although they suggest that more research on this in other clinical settings is needed. They claimed that whilst many women demonstrated a good knowledge about NIPT, others deemed to not to have made an ‘informed choice’ often did not deliberate about the test and had poor knowledge of it. In a Hong Kong study, Lau et al. (2016) describe how women valued both ‘individual autonomy’ and ‘relational autonomy’ (i.e. with help from others such as doctors [as ‘experts’], partners, and other women on internet discussion groups) in decision-making for NIPT. Women in their study wanted more support from others to make sense of complex information and guide their decision, thereby highlighting how the concept of ‘non-directive care’ does not always translate to other contexts (e.g. rather than just providing expectant parents with clinical leaflets on NIPT).

Despite women’s positive experiences, several studies identify a number of concerns about NIPT including the presence of anxiety – even following a ‘lower-risk’ result (Lau et al. 2012; Strange 2015; Yi et al. 2013), worries about how commercial companies advertise NIPT (Yi et al. 2013), difficulty in interpreting risk-ratios that consist of a wide range of probabilities (Yi et al. 2013), a lack of knowledge about the conditions tested for (Strange 2015), the potential for health inequalities with the introduction of NIPT (Yi et al. 2013), a lack of follow-up care after a result (Yi et al. 2013), and the perception that the turnaround time for results was too short (Lau et al. 2012; Lewis et al. 2016b). In Lau et al.’s (2016) study, women reported that they were unaware that NIPT provides results for ES and PS and that doctors were unable to offer information about these conditions in a way that they could understand (likewise, Yi et al. claim that in their study, mothers were worried that their professionals were not well informed about NIPT). Others expressed ethical concerns, such as a possible increase in termination rates (Lewis et al. 2016b), an unease around whether NIPT will result in ‘eliminating’ DS (Lewis et al. 2016b), and whether women would feel pressure to accept NIPT since it is defined as lower-risk (Lewis et al. 2016b).

Furthermore, Strange’s (2015) study identifies how both healthcare professionals and expectant parents believe NIPT (and also NIPD) prompts deep critical examination of its moral, social, and political implications – not only of the technology but of the established clinical practices and specific policy contexts within which it has emerged. In one of the few studies to quote more ‘dissenting’ voices from women that are more critical of/ambiguous about NIPT, Strange shows how NIPT troubles the boundaries between screening and diagnostic testing, ignites worries about NIPT’s routinisation

² Other studies have *predicted* why NIPT is declined. For example, Taylor et al. (2014) deduce that in their US study, 72% of 961 expectant parents declined NIPT and elected for ‘standard’ screening processes because of no insurance coverage, a desire to undertake screening that includes ultrasound, not wanting to terminate a pregnancy, and a lack of recommendation from their healthcare professional.

and trivialisation, and provokes important ethical questions that demand attention. In addition, according to Strange, giving full responsibility for decision-making to women means that NIPT can cause them to feel silenced and stigmatised when deciding after diagnostic testing and a subsequent diagnosis to terminate a pregnancy.

1.4. Attitudes and views of NIPT

Twenty-three studies were identified which examined peoples' attitudes towards NIPT for DS, ES, and PS. Of this research, only one was undertaken with pregnant women who had already consented to NIPT in a current pregnancy (Lau et al. 2012). Fourteen of the twenty-two studies were carried out with pregnant women (Farrell et al. 2014; Floyd et al. 2016; Hill et al. 2012b, 2016; Kooij et al. 2009; Lewis et al. 2013, 2014b; Sahlin et al. 2016; Silcock et al. 2014; Tischler et al. 2011; van Schendel et al. 2015; Verweij et al. 2013a, 2013b; Yotsumoto et al. 2012), one with pregnant women *and* their male partners (van Schendel et al. 2014), one with mothers of children with DS (Kellogg et al. 2014), and five with members of the public (Allyse et al. 2015; Farrimond and Kelly 2011; Higuchi et al 2016; Kelly and Farrimond 2012; Sayres et al. 2014). One study was also identified which examined pregnant women's views of NIPT for sex chromosome conditions and microdeletion syndromes (Agatisa et al. 2015). There is also a small body of literature on the views of healthcare professionals in relation to NIPT including genetic counsellors, consultants, nurses, midwives, and obstetricians (Alexander et al. 2014; Buchanan et al. 2014; Hill et al. 2012a, 2013, 2016; Horsting et al. 2014; Musci et al. 2013; Sayres et al. 2011; van den Heuvel 2010). However, this work will not be summarised here as this review directs attention to the experiences and views of expectant parents.

Fifteen studies were carried out with pregnant women (one with pregnant women *and* male partners) to examine their views on NIPT. Many studies report that these women viewed NIPT as a positive development in prenatal care and that they would consider taking it themselves, even if they did not have screening in earlier pregnancies (Farrell et al. 2014; Kooij et al. 2009; Lewis et al. 2013, 2014b; Sahlin et al. 2016; Tischler et al. 2011; van Schendel et al. 2014, 2015; Verweij et al. 2013a, 2013b; Yotsumoto et al. 2012). They cited its positive qualities in relation to safety (Lewis et al. 2013, 2014b; Tischler et al. 2011; van Schendel et al. 2014), accuracy (Floyd et al. 2016; Lewis et al. 2013; Verweij et al. 2013b), timing (Farrell et al. 2014; Hill et al. 2012b; Lewis et al. 2013; van Schendel et al. 2014; Yotsumoto et al. 2012), its capacity to provide information (Lewis et al. 2014b; Sahlin et al. 2016) and potentially detect conditions beyond DS, ES, and PS (Farrell et al. 2014; Hill et al. 2012b, 2016; Sahlin et al. 2016; van Schendel et al. 2014), and allowing parents to prepare for diagnostic testing and possibly continuing or terminating a pregnancy (Floyd et al. 2016; van Schendel et al. 2015). Such statements were commonly made with reference to the disadvantages of invasive diagnostic testing. Expectant parents' hypothetical decision to have NIPT was influenced by the factors outlined above as well as maternal age (Tischler et al. 2011), education (Tischler et al. 2011), ethnicity (Tischler et al. 2011), perceptions of health

and the quality of life of a foetus/baby (Lewis et al. 2014b; Sahlin et al. 2016), whether they felt that they could bring up child with a disability (Lewis et al. 2014b), personal values and experiences of disability and/or termination (Lewis et al. 2014b; Sahlin et al. 2016; Tischler et al. 2011), conversations with a partner (Lewis et al. 2014b), and previous pregnancy experiences (Lewis et al. 2014b).

However, there were concerns about NIPT regarding diagnostic testing after a higher-risk result (Farrell et al. 2014), lack of knowledge about NIPT among pregnant women (Yotsumoto et al. 2012), compromising informed consent since women may just agree with a professionals' endorsement (Tischler et al. 2011), the routinisation and trivialisation of testing (Lewis et al. 2013; van Schendel et al. 2014, 2015; Yotsumoto et al. 2012), the possibility of inaccurate results (Floyd et al. 2016), unequal access because of cost (Yotsumoto et al. 2012), creating a pressure to have NIPT since it is seen as 'just a blood test' (Lewis et al. 2013; van Schendel et al. 2014), increasing anxiety even among low-risk populations (Floyd et al. 2016; Lewis et al. 2013), and the difficulty of determining quality of life and severity of a genetic condition in advance (van Schendel et al. 2014). Other concerns include ethical worries pertaining to 'eugenics' (Floyd et al. 2016), screening for late onset disorders and non-medical sex selection (Kooij et al. 2009), the continued stigmatisation/discrimination of disabled people and worries over DS being 'eliminated' (Lewis et al. 2013; van Schendel et al. 2014, 2015), where the medical profession 'draws the line' relating to prenatal testing (Lewis et al. 2013; van Schendel et al. 2014), and women not being able to fully realise the consequences and choices they will perhaps unexpectedly be confronted with (Kooij et al. 2009; van Schendel et al. 2014; Yotsumoto et al. 2012).

Whilst some expectant parents were generally uninterested or ambivalent about NIPT (Tischler et al. 2011), others wanted more clarification, such as what conditions could be screened for and the quality of life of the child born with a condition (Farrell et al. 2014). Others shown discrepancies between healthcare professionals and expectant parents. For example, in contrast to their providers, women in studies by Hill et al. (2012b, 2016), Silcock et al. (2014), and Yotsumoto et al. (2012) were willing to wait longer for test results with lower accuracy if the test had no miscarriage risk, whereas for health professionals, accuracy and early testing were of more importance.

Only one study was identified which examines the views of parents with DS regarding NIPT (Kellogg et al. 2014). They found that whilst many parents would perhaps use NIPT in future pregnancies, they were worried that NIPT could lead to increased terminations, increased stigma, and decreased availability of services for individuals with DS. Many also reported healthcare professionals giving biased, incorrect, and overly negative about DS in their pregnancy, suggesting that NIPT will only be useful if accompanied by accurate, complete, and impartial information about the condition. As for more 'general public' views, some studies reported that they believed women would decide on accepting/declining NIPT with reference to personal and religious beliefs (particularly relating to perceptions of disability and DS specifically), trust in the

medical system, attitudes towards risk, and knowledge about NIPT and the conditions possibly detected through its use (Allyse et al. 2015; Higachi et al. 2016).

Some members of the public supported NIPT use, particularly in terms of offering 'choice' through the use of a safer and more accurate test, and expressed an interest in it themselves (Higachi et al. 2016; Kelly and Farrimond; Sayres et al. 2014). But others voiced concerns over financial cost (Allyse et al. 2015), the value of prenatal genetic information (Allyse et al. 2015), the trivialisation of testing (Farrimond and Kelly 2011), possibly increased anxiety for women and partners (Kelly and Farrimond 2012), and the implications of commercial availability of NIPT (Farrimond and Kelly 2011; Kelly and Farrimond 2012). Others were worried about NIPT playing a role in creating a negative image of people with a diagnosis (Higachi et al. 2016) and its connection to eugenic reasoning (Kelly and Farrimond 2012), the speed at which NIPT is being developed which could outstrip the capacity of professionals to ensure that women are informed (Higachi et al. 2016), information and support requirements for expanded testing (Kelly and Farrimond 2012), and NIPT fostering a view that all women *should* undertake the procedure (Higachi et al. 2016). Research shows, then, how members of the public both support and question NIPT. Farrimond and Kelly (2011) found, for example, that NIPT is concurrently seen as a tool in the ongoing societal discrimination against the disabled (linked to the notion of 'eugenics'), a positive technique that can offer reassurance, a medical option only justified for 'severe' genetic conditions, and a valid expansion of personal choice.

Finally, one study was identified which examines pregnant/recently delivered women's views of NIPT for sex chromosome conditions and micro-deletion syndromes – i.e. not DS, ES, or PS (Agatisa et al. 2015). Although the women largely supported NIPT for sex chromosome conditions, they were more uncertain about NIPT for micro-deletion syndromes as it only reveals variable or unknown phenotypic expression of a condition in a child. That said, they would be keen to receive details of all conditions assessed by NIPT prior to testing. They also said in their own experience (10 of the 31 women had NIPT in an earlier pregnancy), they were familiar with DS, ES, and PS but not sex chromosome conditions or micro-deletion syndromes. Without knowledge of this, the women worried that others would not be able to make an 'informed' choice and Agatisa et al. suggest that this is problematic because NIPT is likely to increase the volume of information that must be conveyed during the counselling process.

1.5. NIPT in the commercial sector

Access to NIPT in the UK is primarily through the commercial sector. The numbers of expectant parents accessing NIPT in the commercial sector is unavailable. However, suggestions are that there has been an 'extraordinary uptake' of NIPT in the at-risk population worldwide (Gil et al. 2013; Larion et al. 2014; Sago et al. 2014; Warsof et al. 2015), with estimations that more than half a million NIPT procedures have been performed in over 61 countries (Chandrasekharan et al. 2014; Zhang et al. 2015). In

the UK, equally, whilst the average cost of NIPT in the commercial sector has not been calculated, it has been suggested that it can vary between £400 and £900 (ARC 2016; Morris et al. 2014). In their analysis of internet advertising by commercial companies and health providers for NIPT, Skirton et al. (2014) found that whilst several sites provide balanced and accurate information, most do not provide supporting evidence to underpin details, overstate the capabilities of NIPT (e.g. that it can ensure ‘normality of foetal chromosomes’), and do not always abide by professional recommendations. Many sites also include persuasive advertising, such as discussing NIPT’s benefits more than its limitations or the possible implications for expectant parents – this reflecting claims of a study on how the UK press media report advances in NIPT (Lewis et al. 2014a). It was noted that very little empirical research has been carried out on the implications for the NHS of women seeking NIPT in the commercial sector, such as how they attempt to access follow-up advice and/or care.

1.6. Conclusion

Studies on the experiences of expectant parents relating to NIPT are limited in scope and is often closely associated with scientific research programmes (e.g. RAPID). No data was identified on what expectant parents do following a higher-risk NIPT result for DS, ES, and PS (or any other genetic conditions) with respect to diagnostic testing and continuing or terminating a pregnancy. Chitty et al. (2016) outline some statistics relating to this, and Lewis et al. (2016a) suggest that uptake rates following a higher-risk result were high in their study, yet no studies were found that examine expectant parents’ decision-making processes in this context.

2. NIPD

2.1. Background

NIPD is a test that involves analysing cell-free foetal DNA (cffDNA) in maternal blood during pregnancy. It is offered in the UK (NHS) to determine foetal sex in pregnancies at risk of serious X-linked conditions (including Duchenne muscular dystrophy) and congenital adrenal hyperplasia (CAH). It is also used for RhD-women with a history of haemolytic disease in a newborn or with high levels of anti-D antibodies in pregnancy. The development of NIPD for single gene disorders is also progressing and available for a small number of genetic conditions, such as achondroplasia.

2.2. NIPD uptake statistics

No statistics were identified that recorded uptake rates of NIPD for different conditions in either the NHS or commercial sector. A possible reason for this is the wide range of conditions screened for with NIPD. However, research by Hill et al. (2014a, 2014b, 2015) suggests that introducing NIPD into routine practice may be accompanied by an increase in the uptake of prenatal testing for single gene disorders. Their survey study indicates that of 131 carrier or affected adults with cystic fibrosis [CF], only 43.5% participants would have diagnostic testing for CF. In contrast, 94.9% of the sample said they would hypothetically choose NIPD for CF – and that 90% would be prepared to pay for it. For Hill et al., this suggests that a high potential uptake of NIPD includes couples who would currently decline diagnostic testing (due to a miscarriage risk) but would have NIPD. Their work claims that introducing NIPD for CF would be welcomed and uptake is likely to be high, but they recognise that the predicted uptake may differ from actual uptake (linking to previous research showing that *hypothetical* interest is often only a modest predictor of *actual* uptake).

2.3. Parents' Views and Experiences of NIPD

Little research has established parental views and experiences of NIPD. Three studies were identified that explore NIPD experiences of pregnant women and/or partners (Lewis et al. 2012a, 2012b, 2014c) and five others examine the views of NIPD of those with direct experience of conditions (Hill et al. 2014a, 2014b, 2015; Oxenford et al. 2013; Skirton et al. 2014). No studies were identified that examine the decision-making processes of expectant parents after a positive NIPD result (i.e. whether they continue or terminate a pregnancy).

In a study by Lewis et al. (2012a, 2012b) on NIPD for foetal sex determination, they found that decision-making was influenced by several factors including the number of previous pregnancies, earlier pregnancy experiences (e.g. miscarriage, termination), and personal experience and perceived seriousness of the condition. The technology was viewed by women as 'overwhelmingly positive' because it expanded reproductive choice, was perceived as safe, and allowed them to receive an earlier result. The latter was seen as offering an opportunity to be reassured, delay attachment to a pregnancy,

and prepare for next stage of pregnancy and beyond. Other perceived benefits were it allowed men to be informed about being a carrier of a genetic condition and it could help with treatment of 'at-risk' women during a pregnancy (including CAH carriers). However, participants also recognised some potential disadvantages of using NIPD for foetal sex determination, such as feeling pressure from family members to have testing, concerns over foetal sexing and technology misuse, and increased anxiety.

In another study, Lewis et al. (2014c) reported on the experiences of eight women using NIPD who were at risk of single gene disorders such as achondroplasia, Apert syndrome, thanatophoric dysplasia, and a neuromuscular condition. They liked access to an accurate, safe, and early test and highlighted the benefits of NIPD over diagnostic testing, including minimising the risk of miscarriage and having earlier procedures which reduces uncertainty and worry in the first trimester. However, they also identified several concerns such as what conditions are tested for prenatally and how this is decided (recognising the importance of guidelines for this), who should be offered NIPD, and fears about the relative ease and risk-free nature of the test which may lead to the trivialising of NIPD. In all of these studies, they suggest that further research on stakeholders' views and experiences of NIPD is warranted to inform the possible widespread implementation of NIPD for a range of genetic conditions.

Five studies were found that explore the views of NIPD of those with direct experience of conditions. In their survey-based study on NIPD for CF, Hill et al. (2014b, 2015) found that common reasons for wanting NIPD for CF include preparing for the birth of a baby and to 'help make a decision about whether or not to continue the pregnancy'. Participants also described other 'benefits' of NIPD for CF including the reduced risk of miscarriage (since they would not be offered diagnostic testing), the perception that NIPD would be a safe and simple test, and that NIPD would be earlier in a pregnancy than diagnostic testing. Most concerns with NIPD, albeit small in number according to Hill et al. (2014b, 2015), include a worry about terminations for CF and the possibility of increasing pressure to terminate (more were worried about the routinisation of NIPD and pressure to have the procedure). Hill et al, (2014b) also identify a discrepancy in the preferences of potential users and healthcare professionals, with users preferring a test with no risk of miscarriage and professionals preferred a test that was accurate and early. Additionally, whilst most users thought NIPD for CF should be offered to all women, more health professionals thought NIPD should be reserved for known carrier couples.

Two papers examined the views of NIPD of 27 carriers of thalassaemia, sickle cell disease, CF, or spinal muscular atrophy (Hill et al. 2014a; Skirton et al. 2014). Using focus groups and interviews, they found participants gave 'overwhelming support' to NIPD for single gene disorders. Nonetheless, parents were wary of tests becoming routine, felt that the decision about NIPD should be made by both parents but that women ultimately have the right to make the decision, and believed that the interests of the mother and foetus outweigh fathers and that fathers who declined carrier testing

should be made aware that an NIPD result may reveal their carrier status (they were more divided on who should provide this information – i.e. the partner or professional). The participants' concerns also revolved around the accuracy of NIPD and that less thought may be afforded to having a blood test compared to a diagnostic test – and that the perceived ease of a blood test may subsequently bring increased pressure to have NIPD. However, they also felt that NIPD would eliminate the risk of miscarriage (and ease anxieties about current diagnostic testing) and could be carried out earlier in a pregnancy which allowed parents to 'prepare' for decision-making and/or their future child.

Finally, one paper was identified that examines women's preferences and needs for the routine implementation of foetal Rhesus-D (RhD) typing using NIPD (Oxenford et al. 2013). They perceived this as a positive development and that it should be offered to all RhD– women. Test accuracy was important to participants yet their knowledge was described as 'poor'. For example, although 90.7% of participants knew that the baby could have a different blood group from themselves, only 34% knew that blood groups are inherited from both parents. In addition, many women were uncertain about whether they would have NIPD for RhD themselves because they would not want an extra blood test and that they wanted more information on its benefits, risks, accuracy, and implications. Finally, Oxenford et al. warned that women may accept whatever is recommended to them and that NIPD could be presented as routine care, thereby undermining the principle of informed consent – concluding that this needs addressing before any test is fully introduced into clinical practice.

2.4. Conclusion

Although a number of studies highlight the benefits of NIPD for expectant parents, they also recognise the concerns of using it in routine prenatal care. Very little research is accessible at the moment and more is needed before the technique is possibly made more widely available.

3. Decision-Making and Current Screening/Testing for DS

3.1. Background

In this section, the evidence review revisits significant issues from previous debates about prenatal screening and testing for Down's syndrome [DS]. All expectant parents in the UK are offered screening for DS. The main objective of screening is to identify women in whom a risk factor is deemed high enough to warrant offering diagnostic testing. Screening should take place in a window of ten to twenty weeks during a pregnancy, although the preferred period of time is by the end of the first trimester. If expectant parents undertake screening, they receive a 'risk factor', a numeric ratio establishing the odds of a foetus having DS. This works by combining a prior probability – maternal age at expected date of delivery – with a likelihood ratio based on several factors such as weight, gestation, ethnicity, pregnancy history, smoking habits, the number of foetuses, whether it is an assisted conception, and nuchal translucency size. These create an estimate of whether a foetus has DS (and also possibly Edward's syndrome [ES] and Patau syndrome [PS]). In the UK, the cut-off point for categorising a pregnancy as 'at-risk' is 1:150 (a 1 in 150 risk of having a foetus with DS, ES, and/or PS). If expectant parents receive a risk factor that is numerically higher than 1:150 (e.g. 1:250), they are categorised as 'lower-risk' and they are not offered further treatment except for an ultrasound at twenty weeks to check for other potential problems (anomaly scan). In contrast, if expectant parents receive a risk factor that is numerically lower than 1:150 (e.g. 1:100), they are categorised as 'higher-risk' and diagnostic testing (i.e. amniocentesis or CVS) is offered to prove or refute a suspected diagnosis.

An amniocentesis involves taking a small sample of amniotic fluid by passing a fine needle through the abdomen of an expectant mother and drawing the fluid out using a syringe. During CVS, a small sample of placenta is taken either by passing a small needle through the abdomen of an expectant mother and drawing the fluid out using a syringe, or by passing a small tube through a vagina and cervix. CVS is carried out in the first trimester and an amniocentesis is often carried out in the second trimester. Both tests provide an accurate diagnosis but have a few possible complications such as causing miscarriage, infection, bleeding, and premature labour. The risk of causing miscarriage is reported as 1% due to amniocentesis and 2% due to CVS. Diagnostic testing is offered because of a possible indication of a genetic condition, previous or current pregnancy complications, a family history of a condition, and an advanced maternal age (although this last option is currently not common in UK medicine). After diagnostic testing is done, samples are sent to a cytogenetics laboratory for analysis. After a result is established, information is returned to professionals who must deliver this news to expectant parents. If a diagnosis is established, counselling is offered before a decision has to be made about whether to continue or terminate a pregnancy.

3.2. Decision-making and screening/testing for DS

There is a small collection of literature reviews and meta-syntheses that reflect on the factors that influence decisions related to current NHS screening and/or testing for DS (more on PS and ES later). The most comprehensive reviews of the literature on DS screening and testing (but mostly screening) include Reid et al. (2009), Skirton and Barr (2007), Crombag et al. (2013), and Thomas (2014b). The reviews show that much of the research on this topic derives from many different countries (and with diverse social, cultural, economic, political, medical contexts), uses qualitative and quantitative methods (but rarely together), focuses on screening and testing at different periods of gestation, and stems from scholarly roots such as sociology, public health, medicine (midwifery, nursing, genetics), anthropology, psychology, and bioethics. The quality of this evidence seems high, especially given the sheer amount of data from the UK and beyond – and that many studies from around the world report similar/related findings.

3.2.1. Accepting screening/testing for DS

According to the literature, common justifications for consenting to screening and/or testing include offering reassurance that a foetus is unlikely to have DS (Bryant et al. 2010; Etchegary et al. 2008; García et al. 2008; McNeill et al. 2009; Pilnick et al. 2004; Santalahti et al. 1998), satisfying curiosity about a foetus (Skirton and Barr 2007; van den Berg et al. 2005a), fulfilling demands of a partner (Helm et al. 1998; Jaques et al. 2004), a perceived negative attitude towards DS and disability more generally (García et al. 2008; Gottfreðsdóttir et al. 2009b), allowing expectant parents to ‘prepare’ for a possible diagnosis and to subsequently terminate early in a pregnancy (Etchegary et al. 2008; Williams et al. 2005), and a fear of supporting and parenting a child with a disability (Bryant et al. 2010; Chiang et al. 2006; García et al. 2008; Pilnick and Zayts 2012; Remennick 2006). This ‘tentativeness’ (Rothman 1986) is often felt by expectant mothers. Within a gendered context, responsible mothering implies the acquisition of all available medical information about the health of a foetus (García et al. 2012) and engaging with prenatal medicine to potentially produce a ‘normal’ baby (Gottfreðsdóttir et al. 2009b). This means that women are likely to shoulder a moral duty to prevent what is perceived to be the burden of a disabled child on their family – and, so, feel to blame if this is not achieved (Alderson 2001; Chiang et al. 2006; García et al. 2012; Ivry 2006; Landsman 2009; Reed 2012; Remennick 2006). A similar fear is reported by expectant parents with previous pregnancy complications or a family history of genetic conditions, citing this when accounting for a decision to have screening and/or testing (McNeill et al. 2009; Spencer 2002). One of the most common justifications for participating in screening and testing is that expectant mothers perceive themselves as being at an ‘advanced maternal age’ as this is the only known attribute increasing the risk of a foetus being diagnosed with DS (Kaiser et al. 2004; Lotto 2015; McNeill et al. 2009; Thomas in press).

In the context of diagnostic testing (CVS/amniocentesis), reasons for consenting to a test include – as well as many of the reasons outlined above – resolving uncertainty

and doubt, believing that it was recommended by a professional (either explicitly or implicitly), the belief that a prenatal diagnosis will help professionals to prepare for delivery and that it will help themselves to plan their future of parenting a child with a disability, perceiving that the 'risk' of miscarriage is low and/or that it offsets the 'risk' of having a child with DS, the strong influence of partners, the inclination to terminate a pregnancy if a diagnosis is established, and not wanting to 'disappoint' professionals (Browner and Preloran 1999; Markens et al. 2010; Press and Browner 1998; Rapp 2000; Rothman 1986). It should be noted here that decision-making processes are immensely complex, and expectant parents are likely to account for their decision with reference to many of these explanations. Indeed, they are frequently conflicted about 'whether to know or not to know' (Aune and Möller 2012; Kaiser et al. 2003; Markens et al. 1999).

Several studies appear to view consenting to DS screening and/or testing as a result of rational decision-making processes. However, others identify how screening (and testing in some cases too) is an instance of conformity instead of being an expression of choice (Chiang et al. 2006; Gottfreðsdóttir et al. 2009b; Markens et al. 1999; Marteau 1995; Pilnick 2004; Pilnick et al. 2004; Press and Browner 1997; Rapp 2000; Santalahti et al. 1998; Sooben 2010; Williams et al. 2005). Many studies suggest that expectant parents accept DS screening as it is perceived as a 'routine' procedure in prenatal care (Barr and Skirton 2013; Chiang et al. 2006; Markens et al. 1999; Pilnick et al. 2004; Thomas in press; Williams et al. 2005). Hunt et al. (2005) claim that expectant parents do not have a clear understanding of screening as they view it as a recommended part of prenatal care. This relates to them interpreting screening and/or testing as an advised part of pregnancy surveillance (Hunt et al. 2005; Vassy 2006), how expectant parents do not discuss screening and/or testing prior to the procedure (Gottfreðsdóttir et al. 2009b), how they can be overloaded with information which reduces the time to discuss and think more about screening (Barr and Skirton 2013), how they view professionals' offer of screening/testing as endorsing its acceptance (Heyman et al. 2006; McNeill et al. 2009; Remennick 2006), and how ultrasound scans used for screening can be seen, first and foremost, as offering a chance for 'meeting the baby' and to make a pregnancy seem more real rather than for prenatally detecting genetic conditions (Barr and Skirton 2013; Draper 2002; Heyman et al. 2006; Lupton 2013; Mitchell and Georges 1998; Reed 2012; Thomas in press; Williams et al. 2005).

In a similar vein, Tsouroufli (2011) claims that expectant parents accept screening because of their prompt processing in the hospital, because professionals endorse it as a safe test (no chance of miscarriage), and because professionals expect that that they will opt for the procedure. These studies collectively convey a concern that expectant parents do not perceive their care as non-directive; they argue that stating options does not always amount to the neutral provision of advice since some options have the force of an explicit instruction (Browner et al. 1996; Helm et al. 1998; Hunt et al. 2005; Lippman 1991; Marteau et al. 1993; Tsouroufli 2011; Williams et al. 2002c), so they may not feel empowered by screening or testing (Lippman 1994; Pilnick 2008;

Rapp 2000; Rothman 1986; Williams et al. 2002c). Baillie et al. (2000) and Åhman et al. (2010) believe that the routinisation of DS screening as a 'normal' part of pregnancy means that expectant parents are not always aware of, or prepared for, the complex information and choices associated with a result.

Many studies report how screening, for example, prompts feelings of anxiety among expectant parents before, during, and after receiving a lower-risk result or higher-risk result for DS (Aune and Möller 2012; Green and Statham 1996; Ivry 2006; Markens et al. 1999; Marteau 1995; Pilnick et al. 2004). For Heyman et al. (2006) and Hunt et al. (2005), this angst and upset frequently emerges following a higher-risk result and a decision needing to be made about diagnostic tests. In the case of a diagnosis being made after testing, parents may feel that they are becoming 'moral pioneers' who must make a decision about the value of their own child (Rapp 2000; Rothman 1986). This literature demonstrates that whilst expectant parents may engage with screening and/or testing to decrease anxiety and receive reassurance, it can also have the opposite effect: they can be anxious about waiting for results, confronted with distressing decisions that they may not expect, and apprehensive and fearful even after a lower-risk result (Burton-Jeangros et al. 2013; Marteau 1995; Pilnick et al. 2004; Remennick 2006; Williams et al. 2005).

3.2.3. Informed choice and non-directive care

Whilst some research shows that non-directive or informed choice are not 'achieved' when screening and/or testing for DS, others explain that this should not always be defined as bad practice (Williams et al. 2002b). During interviews with professionals, Schwennesen and Koch (2012: 283) recognise that by answering expectant parents' appeal for direction, professionals can move closer to promising 'informed choice' by supporting them to make decisions on the basis of uncertain knowledge. This shows how non-directive care may not always be the most suitable response to fully support expectant parents in decision-making. Nonetheless, many studies highlight how DS screening and/or testing presents problems such as how professionals have their own ambiguities and ethical concerns about screening and/or training (Thomas in press), are undertrained in communicating information (Cleary-Goldman et al. 2006; Sandall et al. 2001; Skirton and Barr 2007), and hold limited knowledge of DS (Dormandy et al. 2006; Skirton and Barr 2010) and screening for the condition (Ekelin and Crang-Svalenius 2004; Farsides et al. 2004; Hey and Hurst 2003; Samwill 2002; Smith et al. 1994; Williams et al. 2002c). This involves having little direct contact during medical training with people who have developmental disabilities (Cleary-Goldman et al. 2006; Driscoll et al. 2009; Skotko 2005).

3.2.2. Declining screening/testing for DS

Studies also report why expectant parents *do not* have DS screening. Common justifications include avoiding adverse health risks associated with diagnostic testing such as causing a miscarriage (Liamputtong et al. 2003; Markens et al. 1999; Pilnick

et al. 2004), the inaccuracies and unreliability of tests (Gottfreðsdóttir et al. 2009a), a lack of information on tests (García et al. 2008), concerns about the emotional impact of intervention (Markens et al. 1999; McNeill et al. 2009; Santalahti et al. 1998; van den Berg et al. 2005a), the complexity and inconclusiveness of information provided (Baillie et al. 2000; Heyman et al. 2006; Liamputtong et al. 2003; Markens et al. 1999; Remennick 2006), expectant parents ruling out the option of terminating a pregnancy (Etchegary et al. 2008; Heyman et al. 2006; Markens et al. 1999; McNeill et al. 2009; van den Berg et al. 2005a), friends' negative experiences of screening (Santalahti et al. 1998), personal and/or religious values about the worth of children with DS and other disabilities (Bryant et al. 2010; Gottfreðsdóttir et al. 2009a; Liamputtong et al. 2003; Remennick 2006), and a perception that DS is a condition not severe enough to terminate a pregnancy (Etchegary et al. 2008; García et al. 2008; Gottfreðsdóttir et al. 2009a; Santalahti et al. 1998).

Decisions for refusing diagnostic tests include concerns about miscarriage and other 'risks' (Browner and Preloran 1999; Browner and Press 1996; Lewando-Hundt et al. 2001; Markens et al. 1999), expectant parents' interpretation that they are 'low-risk' and a prenatal diagnosis is improbable (Markens et al. 2010), religious background (Press and Browner 1998), an objection to a termination of pregnancy on any grounds (Press and Browner 1998), and personal attributes of expectant parents such as social class, ethnicity, and social status (Rapp 2000; Remennick 2006). In their study on women's decision to accept or decline amniocentesis, Markens et al. (2010) claim that the hypothetical willingness to terminate a pregnancy was only a partial explanation of the decision to decline amniocentesis. Rather, they found that the decision to decline was often based on their scepticism towards doctors (e.g. they can make mistakes) and medical technologies and trust in their own embodied and experiential knowledge that the pregnancy is progressing well. In contrast, women who accepted diagnostic tests accounted for their decision by conveying a strong trust in doctors/medicine (and did not trust embodied or experiential sources) and by appealing for the information and reassurance that they expected the procedure to provide.

These studies identify how decision-making processes in the context of screening and testing for DS are complex and changing, with expectant parents likely to justify their choice with reference to any number of these rationalisations. Regarding the *quality* of information/counselling when expectant parents consider DS screening, studies claim that professionals have difficulty in communicating screening information whilst remaining non-directive and ensuring informed choice (García et al. 2008; Heyman et al. 2006; Pilnick et al. 2004; Thomas in press). This stems from the conflict between the time that professionals have available to explain screening and the time needed to discuss the procedure (Barr and Skirton 2013; Sooben 2010; Vassy 2006; Williams et al. 2002a), the trouble of conveying complex information (Burton-Jeangros et al. 2013; Ekelin and Crang-Svalenius 2004; Heyman et al. 2006; Hunt et al. 2005), communication breakdowns when expectant parents' first language is not the native language (Barr and Skirton 2013; Hey and Hurst 2003), and the different definitions

between expectant parents and professionals of what constitutes a 'normal result' and/or 'normal child' (Hunt et al. 2005; Vassy 2006; Williams 2006). Additionally, studies show how some professionals do not know how to best support higher-risk expectant parents (Getz and Kirkengen 2003; Williams et al. 2002a, 2002c), how some expectant parents are not fully aware of the key features of DS prior to screening and testing (Williams et al. 2002c), and how expectant parents may not fully understand screening (Burton-Jeangros et al. 2013; Gammons et al. 2010; van den Berg et al. 2005b).

3.3. Decision-making and continuing/terminating a pregnancy for DS

In their integrative review of decision-making after a prenatal diagnosis of DS, Choi et al. (2012) identify 11 studies (9 quantitative, 2 quantitative and qualitative) in 7 different countries that met their inclusion criteria. Whilst some of these studies were based on hypothetical situations (Bell and Stoneman 2000; Bryant et al. 2005; Lawson 2006; Lawson and Walls-Ingram 2010; Leung et al. 2004; Roberts et al. 2002), others concerned people who made a decision after a prenatal diagnosis (Britt et al. 2000; Korenromp et al. 2007; Quadrelli et al. 2007; Zlotogora 2002). Other studies not included in Choi et al.'s review examine how and why expectant parents choose to terminate a pregnancy after a diagnosis of DS (Helm et al. 1998; Skotko 2005; Tymstra et al. 2004) and the views of parents of children with DS around terminating for the condition (Ahmed et al. 2013)³.

Across the studies, a common reason for terminating a pregnancy after a diagnosis of DS was already having existing children and the perceived burden of a disabled child to parents, partners, and family members (Bryant et al. 2005; Britt et al. 2000; Korenromp et al. 2007; Lawson 2006; Lawson and Walls-Ingram 2010; Roberts et al. 2002). Other reasons for terminating a pregnancy include the perception that the child with DS would have a reduced 'quality of life', the prognosis of DS is too severe and uncertain, worry about what would happen to the child after the parent/s died, and negative personal and public attitudes of disability (Korenromp et al. 2007; Lawson 2006).

Reasons for continuing a pregnancy after a diagnosis of DS include religious beliefs (Bryant et al. 2005; Helm et al. 1998; Lawson 2006; Leung et al. 2004), not wanting to experience a termination or being unable to decide on it, seeing the foetus/baby on a monitor and feeling foetal movement/heartbeat (Helm et al. 1998), changing their view after meeting a child with DS (Tymstra et al. 2004), previous infertility (Helm et al. 1998), positive attitudes towards DS (Helm et al. 1998; Lawson 2006; Lawson and Walls-Ingram 2010), a perception that DS still entails a good 'quality of life' (Bell et al.

³ Lotto (2015) has carried out research on parents' decision-making after a suspicion or diagnosis of a 'severe congenital anomaly'. This includes DS, ES, and PS (as well as conditions such as anencephaly, spina bifida, and exomphalus). However, Lotto's study – whilst highlighting reasons for terminating a pregnancy – is not prominent in this review as the specific condition was not always clear in participants' accounts (and the focus in this review is specifically on DS, ES, and PS).

2000), and previous positive experiences of DS (Ahmed et al. 2013; Bryant et al. 2005; Helm et al. 1998; Lawson and Walls-Ingram 2010; Skotko 2005). Support from partners, family, friends, professionals, and others was also seen by most studies to influence the decision to continue or terminate a pregnancy. However, many parents also expressed doubt about the decision. Common reasons for this include conflicting feelings, disagreements with a partner, possible stigmatisation because of termination, and worries that they would be 'killing a baby' (Korenromp et al. 2007; Lotto 2015).

The studies on parental decision-making following suspicion or diagnosis of a genetic condition are small in number but it is worth noting that the reasons for terminating a pregnancy are multiple and are unlikely to be fully covered by the research cited in this evidence review.

3.4. Decision-making and Edward's syndrome/Patau syndrome

Many studies explore factors influencing decisions related to current NHS screening by only referencing DS. Whilst a small number of studies make reference to Patau syndrome [PS] and/or Edward's syndrome [ES], very few explore parents' experiences of being screened specifically for both genetic conditions. This reflects how DS is the primary 'target' of prenatal screening practices and how literature frequently still refers to screening/testing solely in terms of DS (Lotto 2015). Indeed, in one study (Walker et al. 2008), parents believed that they were being screened *solely* for DS and did not realise that they were also being screened for ES (but had a prenatal diagnosis of ES).

In the small amount of research carried out with parents whose child was prenatally diagnosed with ES or PS⁴, they suggest that whilst some healthcare professionals were empathetic, considerate, and supportive of decision-making (Adler and Kushnick 1982; Walker et al. 2008), others tried to coerce them into termination and claimed their child would probably die after birth (Guon et al. 2013; Janiver et al. 2012; Walker et al. 2008), despite recent evidence suggesting the condition is not *always* 'lethal'⁵ and up to 20% of children survive for more than a year (Wilkinson et al. 2014). The studies show how parents felt their child was not valued by healthcare professionals, felt poorly informed about screening and falsely reassured by professionals after initial results, were unhappy with how a diagnosis and prognosis were communicated (very negative), were not made aware of all options and were offered fewer treatments (e.g. C-section not being offered when the foetus/baby was in distress), and believed that some professionals were biased towards certain options (Guon et al. 2013; Janiver et al. 2012; Walker et al. 2008). Despite such experiences, a large number of parents continued with the pregnancy (for possible reasons for this, see: Guon et al. 2013).

⁴ Côté-Arsenault and Denney-Koelsch (2016) discuss both conditions but they categorise them with other 'lethal foetal diagnoses'. As such, it is impossible to distinguish ES and PS from their arguments.

⁵ Wilkinson et al. (2014) suggest avoiding the term 'lethal' when referring to conditions like ES or PS since there is no agreement about a definition of lethal malformations, nor which conditions should be included in this category. They suggest that counselling should be mainly focused on prognosis instead.

A small number of publications cite single cases relating to ES or PS (Heyman et al. 2006; Pilnick and Zayts 2016). Other single cases include parents' reflections about their experience of prenatal care when their child was diagnosed, or suspected as having, PS or ES. Whilst some parents felt well-supported (Locock et al. 2005), others felt judged by their decision to continue a pregnancy, believed that treatment to save their child's life was withdrawn, had insensitive and rude comments from professionals who did not look beyond their child's genetic label, and could only access accurate information online (Farlow 2009, 2011; Thiele 2010)⁶. In several of the studies cited above, parents that continued a pregnancy conveyed that they had 'few regrets' and that they lived happy, fulfilling lives with their child. This reflects positive accounts of parents who have a child with DS, documented in studies (Ahmed et al. 2013; Flaherty and Glidden 2000; Skotko 2005; Solomon 2012; Thomas 2014a; Van Riper and Choi 2011) and autobiographies (for references to these books, see: Thomas in press).

However, in many of the same accounts, parents of children with DS suggested that their experiences of healthcare professionals during screening and testing was mixed. Some professionals were empathetic and supportive; they conveyed a diagnosis in person, provided informed information on the condition, and referred parents to a local support group (Skotko 2005). Other parents, however, explain that some professionals did not support their decision to continue a pregnancy and felt judged for doing so, they delivered a diagnosis via telephone rather than in person (seen as inconsiderate), they expected parents to terminate a pregnancy and focused mostly on termination in conversations with them, they held negative attitudes about DS and used problematic language (e.g. apologising when delivering a diagnosis, using negative terms such as 'mongoloid'), they focused solely on 'negative' biomedical information and screening for DS as opposed to the condition itself, and they provided inaccurate, insensitive, inconsistent, and outdated information about DS (e.g. Skotko 2005; Tymstra et al. 2004; Williams et al. 2002b). This correlates with studies arguing that leaflets for DS screening contain false, misleading, and inconsistent information on DS (Bryant et al. 2001; Murray et al. 2001; Williams et al. 2002b).

4. Statistical Data on Current Screening/Testing for DS, ES, and PS

The most recent official statistics report that roughly 74% (N=542,312) of all expectant mothers accessing NHS services in England and Wales in 2011 opted to be screened for DS (NHS FASP 2012)⁷. The uptake in screening increased annually in England

⁶ Other experiences of parents whose child was diagnosed with ES/PS are reported in HealthTalk.org, an online resource that provides 'free, reliable information about health issues by sharing people's real life experiences'. For people who continued or terminated a pregnancy after a diagnosis of ES, see: Healthtalk.org (2016a, 2016b, 2016e, 2016f, 2016g, 2016h). For people who continued or terminated a pregnancy after a diagnosis of PS, see: Healthtalk.org (2016c, 2016d).

⁷ DS screening uptake statistics in Scotland or Northern Ireland could not be identified. However, the National Services Division (2011) claims that 34,768 expectant mothers in Scotland were screened for

and Wales between 2007 (53%) and 2011. Whilst 2008 and 2009 saw uptake rates of 57% and 62% respectively, an uptake rate of 70% was recorded in 2010 (NHS FASP 2012)⁸. The UK NSC (2013) claims that around 567,000 women in England and Wales were screened for DS in 2013 (uptake rate is not officially recorded, but the reported birth rate of 698,500 in 2013 suggests this is around 81%). More recent publications claim that the current national uptake rate for both the first trimester combined screen and second trimester quadruple test is 66% (Chitty et al. 2016), although the source of this is unclear. Research suggests around two to three percent of pregnant women in England and Wales that consent to screening receive a higher-risk result (Chitty et al. 2016; NHS FASP 2012) and approximately 54% of expectant parents will undertake invasive prenatal testing after a positive screen result (Chitty et al. 2016). According to Buckley and Buckley (2008), between 1 in 20 and 1 in 30 higher-risk results lead to a diagnosis of DS⁹. Annual statistics on the average gestational age of women having diagnostic testing, the exact number of diagnostic tests performed, and the number of women receiving a confirmed diagnosis after diagnostic testing could not be identified.

A report conducted by the National Down's Syndrome Cytogenetic Register (Morris and Springett 2014) claims that in 2013 in England and Wales, there were 1,886 diagnoses of DS, 65% of which were prenatal (N=1,232), a rate of 2.7 per 1,000 births. The number of diagnoses has increased gradually over the years, as has the number of those detected prenatally. There were 1,066 diagnoses in 1989 (30% detected prenatally), 1,228 diagnoses in 1994 (49% detected prenatally), 1,313 diagnoses in 1999 (55% detected prenatally), 1,417 diagnoses in 2003 (59% detected prenatally), 1,791 diagnoses in 2007 (62% detected prenatally), and 1,959 diagnoses in 2011 (65% detected prenatally). There was also an estimated 728 live births (live birth rate of 1.0 per 1,000 live births). This has varied over the years but has remained consistent. Estimated live births of babies with DS were 750 in 1989, 639 in 1994, 604 in 1999, 616 in 2003, 723 in 2007, and 758 in 2011.

Both prenatal and postnatal diagnoses of PS in England and Wales have remained fairly stable since 2004 (when statistics were first collected). There were 145 diagnoses in 2004 (92% detected prenatally), 189 in 2006 (90% detected prenatally), 189 in 2008 (90% detected prenatally), 221 in 2010 (90% detected prenatally), and 180 in 2013 (91% detected prenatally). Estimated live birth rates have been stable. There were an estimated 14 live births in 2004, 25 in 2006, 24 in 2008, 28 in 2010, and 19 in 2013. Between 2004 and 2013 in England and Wales, there have been 1,892 diagnoses of PS and an estimated 233 live births. Both prenatal and postnatal diagnoses of ES in England and Wales have also remained stable since 2004 (when statistics were first collected). There were 356 diagnoses in 2004 (90% detected

DS in 2010-2011. It is worth noting, however, that such statistics do not represent all procedures in Scotland since it is limited to those collected by nationally designated laboratories.

⁸ These statistics do not include those who accessed prenatal screening in privately-funded clinics.

⁹ Suspicions of DS can also be established during an anomaly scan that is performed at twenty weeks gestation.

prenatally), 454 in 2006 (87% detected prenatally), 489 in 2008 (92% detected prenatally), 542 in 2010 (90% detected prenatally), and 474 in 2013 (93% detected prenatally). Estimated live birth rates have also been stable. There were an estimated 40 live births in 2004, 69 in 2006, 48 in 2008, 66 in 2010, and 40 in 2013. Between 2004 and 2013 in England and Wales, there have been 4,818 diagnoses of ES and an estimated 524 live births.

Of the 1,232 prenatal diagnoses of DS, 90% were terminated (N=925), 8% were live births (N=82), and 2% were natural miscarriages or stillbirths (N=20); the outcome of 205 prenatal diagnoses is unknown (Morris and Springett 2014). The proportion of terminations after a diagnosis of DS in England and Wales has remained steady for over twenty years (and the miscarriage/stillbirth and live birth rates have subsequently remained steady too). From the first report in 1989 until 2013, the annual rates for termination in England and Wales have ranged from 89% to 95% (the mean rate is 92%). Termination statistics for PS and ES could not be identified.

5. Gaps in the Evidence

Given that the introduction of NIPT (and NIPD) into clinical practice is in its infancy, the current lack of studies around expectant parents' experiences of the procedure is understandable. More research is needed to ensure that the opinions, concerns, and suggestions of expectant parents, healthcare professionals, and others (policymakers, disability rights groups, etc.) are identified. The current research shortage ensures that there are many gaps in the analysis of NIPT that merit attention.

For instance, exploring the use of NIPT with respect to the characteristics of mothers (class, ethnicity, age, education, etc.) and studying the perspectives of others such as partners, who are often overlooked in studies on NIPT (Skirton and Patch 2013), could provide interesting insights. It could also be useful to explore what implications the availability of NIPT in commercial settings has for those involved, such as how NIPT is delivered, how it is marketed and regulated, and what effects private provision has for training healthcare professionals to offer this service. It could be useful to explore whether people can access NIPT owing to financial restrictions (Chandrasekharan et al. 2014; Rolfes and Schmitz 2016).

In addition, current gaps in the research include explorations of whether much-debated issues in prenatal care, such as the capacity to offer expectant parents truly 'informed consent' and 'non-directive care' and how screening can create anxiety for parents, emerge in undertaking NIPT. Since NIPT is reported as having a 99 percent detection rate for DS, for example, it could be productive to get a grasp of how this knowledge is managed by pregnant women. There are concerns that rolling out NIPT for 'low-risk women' (as research has mostly been carried out among 'high-risk' populations so far), which involves screening at an earlier gestation and reducing possible 'risks' such as miscarriage via diagnostic testing, may create added pressure to have NIPT. Thus, studies may profit by examining how much expectant parents reflect on undertaking NIPT before consenting to the procedure and what happens when there is a higher-risk result. Current research also overlooks how expectant parents do (or would) understand and deal with inconclusive results, 'variants of uncertain significance' (i.e. variation in the normal gene sequence, the significance of which is unknown), and 'incidental findings' (undiagnosed medical conditions that are found unintentionally). Such research could be carried out using observational qualitative data since this is not used in any current publications on NIPT – and could highlight issues that emerge when professionals and expectant parents interact with one another in the clinical setting (e.g. what 'informed choice' in the context of NIPT looks like in practice).

Another gap in the research is the various ethical issues of NIPT *in practice*. There is a relatively large literature on the ethical issues of NIPT from scientists, bioethicists, healthcare professionals, and academics (Benn and Chapman 2009; Chapman and Benn 2013; Bryant 2014; de Jong and de Wert 2015; de Jong et al. 2010, 2011, 2015; Deans and Newson 2012; Deans et al. 2012, 2015; Dickens 2014; Dondorp et al.

2015; Gekas et al. 2016; Hall et al. 2010; Munthe 2015; Newson 2008; Rolfes and Schmitz 2016; Schmitz et al. 2009; Tasinato et al. 2011; Thomas and Rothman 2016; Twiss et al. 2014; Verhoef et al. 2016). However, all of these are not grounded in empirical data and, for the most part, do not figure in many public debates about NIPT, with 'ethics' predominantly being discussed in relation to the bioethical principles of reproductive autonomy and informed consent.

What could also be profitable for future research on NIPT is how expectant parents and healthcare professionals manage the capacity of NIPT to detect genetic conditions other than DS, ES, and PS, and how they feel about the possibility of expanding NIPT to include next-generation sequencing¹⁰ or microarray testing¹¹ which make it feasible to screen for deletions and duplications in the foetal genome. This could explore their views of who decides what conditions to screen for, what information will be shared (and if expectant parents have the 'right to (not) know'), whether the technology may be used for other purposes (e.g. sex selection), and what support is needed in order to fully understand different results. This also relates to a current dearth of studies on incidental maternal cancer diagnoses following discordant NIPT results (Bianchi et al. 2015). More research could examine the possible psychosocial effects of this and the impact of 'over-diagnosis' for women who must respond to this information.

Of interest could be how much training professionals receive before delivering NIPT and how they respond to concerns raised by disability rights groups that NIPT extends an 'informal' eugenics. On this point, a current gap in the research is a consideration of the possible values that are embedded in NIPT (with the exception of Strange 2015). Future studies could attend to expectant parents' and healthcare professionals' attitudes toward disability in the context of NIPT to ensure that information about conditions is accurate, informative, and as impartial as possible to help expectant parents come to a decision from a more nuanced and knowledgeable position. This is important amidst concerns that prenatal settings offer little opportunity for people to discuss and explore their beliefs about disability (Bryant et al. 2006; Farrelly et al. 2012).

Finally, a current research gap is the relationship of NIPT with pregnancy termination and how this is regularly divorced from public debates about reproductive techniques, despite being intimately tied up with them. Research captures, both in the context of NIPT and earlier prenatal techniques, that termination is located in a context of secrecy and shame (Lotto 2015; Strange 2015). Whilst termination is a difficult and problematic topic, studies on NIPT have not explored it in detail. Doing so could also help

¹⁰ Next-generation sequencing (NGS) is a catch-all term used to describe a range of different techniques that allow for DNA sequencing (defined as the process of separating the different pieces of DNA). The sequence reveals the kind of information that is carried in a particular DNA segment.

¹¹ Chromosomal microarray analysis is a technique used to identify extra or missing chromosomal segments. It can be used with living individuals who do not have a specific diagnosis but who have attributes such as unexplained developmental delay and intellectual disability.

policymakers think about whether current regulatory frameworks (e.g. Abortion Act 1967) should be revisited owing to NIPT being introduced into clinical practice.

6. Conclusion

This review has identified the current research on expectant parents' decision-making in relation to NIPT (for DS, ES, and PS), NIPD (for rare genetic conditions), and earlier forms of prenatal screening/testing (for DS, ES, and PS) – together with the current research gaps. With NIPT minimising physical risks (such as reducing the number of diagnostic tests and miscarriages as a result of having this test) and offering an earlier result, one could reasonably deduce that the number of expectant parents that choose to undertake screening will expand. If we also consider the pace of developments in prenatal care in recent years, the widespread implementation of NIPT for DS and other conditions may occur sooner than expected. Therefore, more studies on the opinions, anxieties, and suggestions of expectant parents and healthcare professionals along with policymakers, charities, academics, and the wider public – with respect to NIPT – is a matter of urgency. This is particularly important in the knowledge that there were 687,852 births in England and Wales in 2015 (ONS 2016), highlighting the large number of pregnant women that would be offered NIPT in the future. Many of the gaps identified in section five currently sit at the margins of public debate and offer starting points for future research. This will ignite more reflexive and collaborative dialogues – and better communication between professionals and parents – around NIPT and its implementation in NHS prenatal care.

3.5. Summary

The many considerations identified above highlight how healthcare professionals play a key role in screening and testing for genetic conditions – and how a suspected or concrete diagnosis is communicated. This offers vital key points for consideration with respect to the future of NIPT. This is particularly important in light of research findings suggesting that some expectant parents do not differentiate between the results from screening and diagnostic testing – such as interpreting a higher-risk screening result as a definitive diagnosis (Levenson 2014; Lewando-Hundt et al. 2001; Pilnick et al. 2004) – with this distinction becoming even more blurred in the context of NIPT and subsequent highly accurate results (e.g. reported as 99% for DS).

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