Non-invasive prenatal diagnosis (NIPD) for single gene disorders: cost analysis of NIPD and invasive testing pathways

Talitha I. Verhoef1†, Melissa Hill2,3*, Suzanne Drury2, Sarah Mason2, Lucy Jenkins2, Stephen Morris1 and Lyn S. Chitty2,3

1Department of Applied Health Research, University College London, London, UK
2North East Thames Regional Genetics Service, Great Ormond Street Hospital for Children NHS Foundation Trust, London, UK
3Genetics and Genomic Medicine, UCL Institute of Child Health, London, UK
*Correspondence to: M. Hill. E-mail: melissa.hill@ucl.ac.uk
†These authors contributed equally to this work.

ABSTRACT

Objective Evaluate the costs of offering non-invasive prenatal diagnosis (NIPD) for single gene disorders compared to traditional invasive testing to inform NIPD implementation into clinical practice.

Method Total costs of diagnosis using NIPD or invasive testing pathways were compared for a representative set of single gene disorders.

Results For autosomal dominant conditions, where NIPD molecular techniques are straightforward, NIPD cost £314 less than invasive testing. NIPD for autosomal recessive and X-linked conditions requires more complicated technical approaches and total costs were more than invasive testing, e.g. NIPD for spinal muscular atrophy was £1090 more than invasive testing. Impact of test uptake on costs was assessed using sickle cell disorder as an example. Anticipated high uptake of NIPD resulted in an incremental cost of NIPD over invasive testing of £48 635 per 100 pregnancies at risk of sickle cell disorder.

Conclusion Total costs of NIPD are dependent upon the complexity of the testing technique required. Anticipated increased demand for testing may have economic implications for prenatal diagnostic services. Ethical issues requiring further consideration are highlighted including directing resources to NIPD when used for information only and restricting access to safe tests if it is not cost-effective to develop NIPD for rare conditions. © 2016 The Authors. Prenatal Diagnosis published by John Wiley & Sons, Ltd.

INTRODUCTION

Non-invasive prenatal diagnosis (NIPD) based on the analysis of cell-free DNA (cfDNA) in maternal plasma is now available in clinical practice for a small number of single gene disorders and the potential to test for a wide range of conditions has been demonstrated.1 NIPD allows parents with high risk pregnancies the option of safer testing with a maternal blood sample rather than invasive prenatal diagnosis that carries a small miscarriage risk.2 Women who have used NIPD,3 carriers of single gene disorders4–6 and health professionals7 welcome the safety of NIPD and suggest uptake will be high with couples using NIPD to prepare for the birth of an affected child as well as to inform decisions about termination of pregnancy.

A key challenge for the development of cfDNA-based prenatal tests is the low level of fetal cfDNA present alongside the high background of maternal cfDNA in maternal plasma. In addition, there are many different single gene disorders, each with their own technical challenges for NIPD. The first NIPD tests to enter clinical practice have been for autosomal dominant conditions that are paternally inherited or arise de novo such as achondroplasia and thanatophoric dysplasia.8,9 In these cases technical approaches are straightforward as the causative mutation is not present in the mother, but could be present in the fetus. NIPD has also been used for paternal exclusion in autosomal recessive conditions where parents carry different mutations, including directing resources to NIPD when used for information only and restricting access to safe tests if it is not cost-effective to develop NIPD for rare conditions. © 2016 The Authors. Prenatal Diagnosis published by John Wiley & Sons, Ltd.
and cystic fibrosis (CF). If NIPD detects the paternal mutation, invasive testing is required to determine inheritance of the maternal allele. The most technically difficult NIPD tests are for X-linked conditions or autosomal recessive conditions where parents carry the same mutation, as the levels of the mother’s alleles must be taken into account before accurate fetal diagnosis can be made. Using technologies such as digital PCR or massively parallel sequencing, which allow accurate quantification of specific sequences, proof-of-concept studies have been performed using approaches such as relative mutation dosage for beta thalassaemia and sickle cell disorder or analysis of single-nucleotide polymorphisms (SNPs) by whole genome sequencing and relative haplotype dosage analysis for beta-thalassaemia and CAH. Practical limitations, such as estimation of fetal fraction, that have prevented clinical implementation are being addressed and NIPD will soon be available for a wider range of conditions. It is important to note that NIPD for the direct diagnosis of single gene disorders is used in high risk pregnancies, either because of a family history or sonographic findings, and is considered diagnostic. It can be considered a replacement for invasive testing as, unlike non-invasive prenatal testing (NIPT) for aneuploidy where confined placental mosaicism or detection of unexpected maternal chromosomal abnormalities may confound results, these factors do not complicate prenatl diagnosis for monogenic disorders, whether invasive or NIPD based on analysis of cfDNA. Thus there is no need to confirm NIPD with invasive testing. When NIPD is performed for the exclusion of paternal mutations, invasive testing is required for definitive diagnosis if the paternal mutation is detected to confirm whether or not the maternal mutation has also been inherited.

Evaluation of the costs associated with implementing NIPD into routine care is important to inform service delivery, particularly in state funded healthcare such as the United Kingdom’s National Health Service (NHS). A number of studies have investigated the costs of introducing NIPT for Down syndrome, Costs of offering NIPD for fetal sex determination and NIPD for CF have also been explored, but studies looking more broadly at the costs of NIPD for single gene disorders have not been undertaken. Here we undertake a preliminary assessment of the costs of offering NIPD for a set of representative single gene disorders drawing comparison to current invasive testing pathways.

| Table 1 | Characteristics of the single gene disorders included in the cost analysis |
|---------|-------------------------------------------------------------------------|
| Condition | NIPD approach | Test characteristics |
| Achondroplasia | MPS Panel | Maternal sample |
| | | Detects presence/absence of the main causative mutation and three additional mutations |
| Thanatophoric dysplasia | MPS Panel | Maternal sample |
| | | Detects presence/absence of 14 possible causative mutations |
| Sickle cell disorder | RMD | Maternal and paternal sample |
| | | Fetal fraction estimate required for RMD analysis |
| Congenital adrenal hyperplasia (CAH) | RHD0 | Maternal, paternal and proband sample |
| | | As pseudogene present a proband sample is required to construct mutant alleles for RHD0 |
| Spinal muscular atrophy (SMA) | RHD0 | Maternal, paternal and proband sample |
| | | As pseudogene present a proband sample is required to construct mutant alleles for RHD0 |
| Haemophilia | RMD | Maternal sample |
| | | Fetal fraction estimate required for RMD |
| Duchene Muscular Dystrophy (DMD) | RHD0 | Maternal and proband sample required |
| | | As causative mutations have a high incidence of deletion/duplication plus 10% recombination rate a proband sample is required to construct mutant alleles for RHD0 |

MPS, massive parallel sequencing; RMD, relative mutation dosage; RHD0, relative haplotype dosage.
METHODS

Representative single gene disorders
The conditions included in our cost analysis are described in Table 1. Two autosomal dominant conditions were included: achondroplasia and thanatophoric dysplasia. NIPD for these conditions is available in clinical practice in the UK. Three autosomal recessive conditions were included: sickle cell disorder, CAH and spinal muscular atrophy (SMA). Sick cell disorder can be identified by NIPD using relative mutation dosage, whilst for CAH and SMA relative haplotype dosage analysis is required. As CAH is a sex linked condition and only female fetuses are at risk of genital virilization, fetal sex determination using NIPD would be performed followed by diagnostic testing for female fetuses. Two X-linked conditions were included: haemophilia and Duchene muscular dystrophy (DMD). Haemophilia can be identified using relative mutation dosage and DMD by relative haplotype dosage analysis. As both conditions primarily affect males only, fetal sexing would be performed followed by diagnostic testing for male fetuses. Achondroplasia, thanatophoric dysplasia and haemophilia can be diagnosed using a maternal blood sample only. All other conditions require a paternal blood sample. Tests using relative haplotype dosage analysis also require a proband sample and NIPD could only be used if the family already had a child with the condition or if samples were available from grandparents for parental haplotype construction.

Costs of NIPD versus invasive testing
Our perspective for the cost analysis was that of the prenatal screening department of a local hospital in a cash-constrained publicly funded health care system like the English NHS. We considered a narrow range of costs, focusing on the costs of the NIPD and invasive testing pathways only. We did not include childbirth costs, or costs beyond childbirth such as health care costs associated with looking after a child with a single gene disorder as these are unlikely to be relevant for the perspective taken. In addition lifetime costs for treatment and care of children affected with single gene disorders are not available in the UK, and inclusion of these costs requires several complex assumptions about whether or not an affected pregnancy is terminated, and whether or not a replacement pregnancy follows termination. The total costs of diagnosis using NIPD and invasive testing for each single gene disorder were calculated. Input parameters are listed in Table 2. Where possible local unit costs or published costs were used. For conditions where NIPD is not yet available in clinical practice, costs were estimated by our laboratory based on current service costs and costs of consumables, equipment and staff time derived from developing these tests in a research setting. In the analysis two assumptions were made: (1) invasive testing is not required to confirm a positive NIPD result, and (2) for sex-linked disorders fetal sex determination using NIPD is performed as a first step and diagnosis using invasive testing or NIPD is only performed in 50% of cases (female fetus for CAH, male fetus for haemophilia and DMD). As the accuracy of NIPD for fetal sex determination is high (99.5%), possible discordance was not factored into the analysis.

Differences in uptake of NIPD versus invasive testing
Many parents are reluctant to undergo invasive testing for prenatal diagnosis, mainly because of the small risk (0.5–1%) of miscarriage related to the invasive procedure. Evidence from questionnaire and interview based studies indicates that the uptake of diagnostic testing may be higher if NIPD is offered. To determine how differences in uptake would influence total costs we used sickle cell disorder as an example.
and calculated total costs of diagnostic testing using sickle cell disorder in a population of 100 eligible pregnancies. Estimates of uptake for testing with NIPD (95%) or invasive testing (if NIPD was not available) (65%) were obtained from recent research with carriers and affected adults with sickle cell disorder (n=64) recruited whilst waiting for a clinical appointment at one London hospital (Hill et al. unpublished data). In further sensitivity analyses we also varied uptake and costs of invasive testing and NIPD in a scenario analyses to check the robustness of the results. It was not possible to perform this analysis for other conditions as reliable estimates of uptake of NIPD or invasive testing were not available.

RESULTS

Costs of NIPD versus invasive testing

Costs of each component of invasive testing and NIPD, the total costs and the difference between NIPD and invasive testing are presented in Table 3. Total cost of invasive testing was £1020 for most conditions, but lower (£793) when fetal sex determination was performed as a first step. For achondroplasia and thanatophoric dysplasia total costs of NIPD were £706, which was £314 less than invasive testing. NIPD for autosomal recessive conditions and X-linked conditions was more expensive, for example sickle cell disorder (£1210, £190 more than invasive testing), CAH (£1385, £591 more than invasive testing), SMA (£2110, £1090 more than invasive testing), haemophilia (£935, £141 more than invasive testing) and DMD (£1135, £341 more than invasive testing).

Table 3 Costs of invasive testing, NIPD and differences in costs for each selected condition

|                  | Autosomal dominant | Autosomal recessive | X-linked |
|------------------|--------------------|--------------------|---------|
|                  | Achondroplasia     | Thanatophoric dysplasia | CAH | SMA | Haemophilia | DMD |
| Invasive testing |                    |                    |         |     |             |     |
| Fetal sex determination | —               | —                  | £283   | —   | £283        | £283 |
| Counseling, invasive test, sample transport, cytogenetics and feedback | £650           | £650               | £650   | £325 | £650        | £325 |
| Molecular test on amniocentesis or CVS sample | £370            | £370               | £370   | £185 | £370        | £185 |
| Total invasive testing | £1020           | £1020              | £1020  | £793 | £1020       | £793 |
| NIPD             |                    |                    |         |     |             |     |
| Fetal sex determination [including phlebotomy and sample transport] | —               | —                  | —      | —   | —           | —   |
| Phlebotomy       | £3                | £3                 | £3     | £3  | £3          | £3  |
| Sample transport | £5                | £5                 | £5     | —   | £5          | —   |
| Counseling and feedback | £98            | £98                | £98    | £98 | £98         | £98 |
| Molecular test on maternal plasma sample | £600            | £600               | £1100  | £1000 | £2000       | £550 |
| Total NIPD       | £706              | £706               | £1210  | £1384 | £2110       | £935 |
| Difference (NIPD-invasive testing) | —£314       | —£314              | £190   | £591 | £1090       | £141 |

Accounting for differences in uptake of NIPD versus invasive testing

In 100 pregnancies at risk of sickle cell disorder we estimate that 95 women would undergo NIPD compared with the 65 who would currently accept invasive testing. The total costs of diagnostic testing for sickle cell disorder would increase from £66 300 to £114 935 if NIPD was available (Table 4). When we assumed an uptake of invasive testing as high as 95% or uptake of NIPD as low as 65%, the difference in total costs between invasive testing and NIPD would be smaller (£12 340 to £18 035) (Supporting Information—Table 1). The costs per test performed did not have a large influence on the results.

DISCUSSION

Offering NIPD for single gene disorders will have a significant impact on the costs of diagnostic pathways. For the autosomal dominant conditions, achondroplasia and thanatophoric dysplasia, which utilize the most straightforward technical approaches, NIPD was £314 less than invasive testing. These tests are available in clinical practice and current prices were used in the analysis. Women who have had NIPD for skeletal dysplasias have been extremely positive towards these tests which are diagnostic, safe and can provide reassurance early in pregnancy. For the autosomal recessive and X-linked disorders, which require technically more difficult approaches, NIPD increases the costs of diagnostic testing pathways. NIPD for these conditions is not yet available in clinical practice, so costs were estimated by our laboratory based on current prices.
research setting costs. Costs of diagnostic pathways for sex-linked conditions are reduced by using fetal sex determination as a first step. Previous work found that NIPD for fetal sex determination itself was cost neutral for the NHS as the cost of NIPD was balanced by the reduction in invasive testing.\textsuperscript{23,28}

In cash-constrained publicly funded health care system such as the English NHS decisions about the broad programme of NIPD tests that could be offered are likely to be largely dependent upon on their relative costs. The technical difficulties of performing NIPD for autosomal recessive and X-linked conditions are the primary reason NIPD is predicted to be more expensive than invasive testing. Other factors influencing NIPD costs include the number of cases and opportunities to perform batch testing. For relatively common conditions such as CF or sickle cell disorder batch testing may lower costs. It may also be possible to test for several different conditions and include multiple causative mutations in a single assay. For example, testing for skeletal dysplasias in our laboratory uses a massively parallel sequencing panel that includes several conditions and multiple mutations.\textsuperscript{9} The large number of different single gene disorders presents another challenge for service delivery and costs for laboratories. For rare single gene disorders there is a question as to the cost and benefits of developing NIPD when tests are performed so infrequently, an issue that raises ethical concerns regarding restricting access to safer testing.\textsuperscript{29} Our laboratory currently offers a bespoke NIPD service for individual families at risk of paternally inherited autosomal dominant conditions or recessive conditions where parents carry different mutations. Even in cases that involve simple molecular techniques and the cost of the NIPD approach is relatively low, the overall cost increases because of the time and consumable costs needed to develop and validate NIPD for an individual family.

Ultimately, a significant contributing factor to NIPD costs relative to invasive testing will be test uptake as the safety and ease of testing associated with NIPD means that uptake is likely to be higher than for invasive testing and include many couples that would not have previously considered prenatal testing because of miscarriage risk from invasive testing. This assumption is supported by research exploring the views of women using NIPD for skeletal dysplasias\textsuperscript{37} and potential service users who are carriers of single gene disorders.\textsuperscript{46} If this is the case, more couples will undergo testing and total costs will increase. Analysis of costs for sickle cell disorder in a population of 100 eligible pregnancies suggests that NIPD would be significantly more expensive than invasive testing, largely because of the predicted high uptake of NIPD. This is comparable with our previous exploration of the cost of NIPD for CF which found that a likely increased uptake of NIPD (94.4\%) compared to invasive testing (43.5\%) would increase overall costs.\textsuperscript{24} As hypothetical uptake of genetic tests can differ from actual uptake, uptake and total costs must be reassessed once NIPD for these disorders is available in clinical practice. In addition, whilst our analysis shows that women can have NIPD for the autosomal dominant conditions achondroplasia and thanatophoric dysplasia at lower cost for the NHS, this would only be the case if NIPD was generally restricted to women who would have had invasive testing. For achondroplasia and thanatophoric dysplasia total numbers having prenatal testing may increase as women with a previous affected pregnancy and a low recurrence risk may chose NIPD, when in the past they would have declined invasive testing because of miscarriage risk.\textsuperscript{3} In our laboratory the total number of prenatal tests performed for achondroplasia and thanatophoric dysplasia has steadily increased following the introduction of NIPD in 2011/2012 (North East Thames Regional Genetics Laboratory–personal communication); this increase is largely reflected in an increase in the number of NIPD tests whilst invasive testing rates have stayed the same or decreased (Supporting Information—Table 2).

The expected increased uptake of NIPD over invasive testing and the impact of on the cost of diagnostic pathways highlight the ethical issues associated with using NIPD for information only and the appropriateness of directing resources to a test that would not change pregnancy management in state funded health systems.\textsuperscript{30} Decisions about how NIPD is offered will need to take this concern into consideration, keeping in mind that decisions may vary from the couple’s initial intention following receipt of results, as well as the clinical and psychological benefits afforded by NIPD which include early the possibility of reassurance or provision of information for planning and preparation of the birth of an affected child, as well as the potential of access to surgical termination of pregnancy.\textsuperscript{3,4}

\textbf{Study limitations}

The main uncertainties in our analyses were NIPD uptake in clinical practice and test costs, both of which have been estimated. Costs may change when NIPD enters clinical practice, for example costs may fall if volume increases. In addition, we assumed 50\% of couples with pregnancies at risk of sex-linked conditions would go on to diagnostic testing following fetal sex determination. In clinical practice this figure

\textbf{Table 4 Total costs of invasive testing versus NIPD for sickle cell disorder in a population of 100 eligible pregnancies, including uptake of testing}

| Parameter                              | Invasive testing | NIPD          |
|----------------------------------------|------------------|---------------|
| Number of eligible pregnancies         | 100              | 100           |
| Number taking up the test              | 65               | 95            |
| Total costs per test performed         | £1020            | £1210         |
| Total costs per 100 pregnancies        | £66 300          | £114 935      |
| Additional costs for NIPD compared to invasive testing | –                | £48 635       |

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may vary. For example, our UK audit of NIPD for fetal sex determination found that invasive testing was performed in 46% of referrals for DMD (n = 92), 33% of referrals for CAH (n = 61) and 16.1% of referrals for haemophilia (n = 112). Care pathways may also change when NIPD is introduced, but major changes are unlikely as both service users and providers emphasize the need for NIPD to be offered through genetics services. Another potential limitation is our narrow costing perspective, which meant that we did not consider costs beyond the delivery of the prenatal diagnostic service. However, this perspective was selected as it is likely to be highly relevant for decision makers considering implementing NIPD for single gene disorders in the English NHS. The population based cost analysis for sickle cell disorder included an estimate of test uptake derived from a questionnaire study conducted in one London hospital and may not be generalizable to a wider population. Furthermore, as the questions on test uptake were hypothetical, choices may vary from those made in real life.

Further research is needed to investigate the costs associated with NIPD for individual conditions as they enter clinical practice and the broader implications for service programmes. Over time with increasing implementation of NIPD more data will become available on test uptake and pregnancy outcomes in clinical practice, including miscarriages averted. This analysis should be then be repeated to deliver a cost-effectiveness or cost-consequences analysis of NIPD for single gene disorders in clinical practice. Until then, the work we present here highlights some of the issues that may arise and we suggest that careful audit of any NIPD service should be put in place from the outset in order to collect the data required to address these issues.

CONCLUSION
We have explored the costs of NIPD for a range of single gene disorders, for some disorders NIPD is considerably cheaper than invasive testing, but for conditions requiring more technically challenging approaches costs were greater. Moreover, the likely increase in uptake when NIPD becomes available will be a major contributing factor to the cost of prenatal diagnostic services. These findings highlight the need for prospective consideration of both the economic issues that may arise as more tests are developed, as well as the ethical aspects around the potential for an increase in the number of couples choosing NIPD for information only.

WHAT’S ALREADY KNOWN ABOUT THIS TOPIC?
- Non-invasive prenatal diagnosis (NIPD) for some single gene disorders has entered clinical practice and NIPD for other conditions is in development.
- Studies exploring the costs and benefits of implementing NIPD for a range of single gene disorders have not been undertaken.

WHAT DOES THIS STUDY ADD?
- For single gene disorders where technical approaches are straightforward, NIPD was considerably cheaper than invasive testing, but for conditions that need more technically challenging approaches NIPD was more expensive.
- The anticipated increase in test uptake following the introduction of NIPD will be a major contributing factor to the cost of a genetic service offering prenatal diagnosis for single gene disorders in clinical practice.
- Prospective monitoring and audit of uptake following clinical implementation is required to allow full consideration of the economic, social and ethical issues that will arise.

REFERENCES
1. Lench N, Barrett A, Fielding S, et al. The clinical implementation of non-invasive prenatal diagnosis for single gene disorders: challenges and progress made. Prenat Diagn 2013;33(6):555–62.
2. Tabor A, Allfirevic Z. Update on procedure-related risks for prenatal diagnosis techniques. Fetal Diagn Ther 2016;37(1):1–7.
3. Lewis C, Hill M, Chitty LS. Non-invasive prenatal diagnosis for single gene disorders: experience of patients. Clin Genet 2014;85(4):336–42.
4. Hill M, Compton C, Karunaratna M, et al. Client views and attitudes to non-invasive prenatal diagnosis for sickle cell disease, thalassaemia and cystic fibrosis. J Genet Couns 2014;23(6):1012–21.
5. Hill M, Suri R, Nash E, et al. Preferences for prenatal tests for cystic fibrosis: a discrete choice experiment to compare the views of adult patients, carriers of cystic fibrosis and health professionals. J Clin Med 2014;3(1):176–90.
6. Skirton H, Goldsmith L, Chitty LS. An easy test but a hard decision: ethical issues concerning non-invasive prenatal testing for autosomal recessive disorders. Eur J Hum Genet 2015;23(8):1004–9.
7. Hill M, Karunaratna M, Lewis C, et al. Views and preferences for the implementation of non-invasive prenatal diagnosis for single gene disorders from health professionals in the United Kingdom. Am J Med Genet A 2013;161A(7):1612–8.
8. Chitty LS, Griffin DR, Meaney C, et al. New aids for the non-invasive prenatal diagnosis of achondroplasia: dysmorphic features, charts of fetal size and molecular confirmation using cell-free fetal DNA in maternal plasma. Ultrasound Obstet Gynecol 2011;37(3):283–9.
9. Chitty LS, Mason S, Barrett AN, et al. Non-invasive prenatal diagnosis of achondroplasia and thanatophoric dysplasia: next-generation sequencing allows for a safer, more accurate, and comprehensive approach. Prenat Diagn 2015;35(7):656–62.
10. Chiu RW, Lau TK, Cheung PT, et al. Noninvasive prenatal exclusion of congenital adrenal hyperplasia by maternal plasma analysis: a feasibility study. Clin Chem 2002;48(5):778–80.
11. Gonzalez-Gonzalez MC, Garcia-Hoyos M, Trujillo MJ, et al. Prenatal detection of a cystic fibrosis mutation in fetal DNA from maternal plasma. Prenat Diagn 2002;22(10):946–8.
12. Galbiati S, Brisci A, Lalatta F, et al. Full-COLD-PCR protocol for noninvasive prenatal diagnosis of genetic diseases. Clin Chem 2011;57(1):136–8.
13. Lun FM, Chiu RW, Allen Chan KC, et al. Microfluidics digital PCR reveals a higher than expected fraction of fetal DNA in maternal plasma. Clin Chem 2008;54(10):1664–72.
14. Barrett AN, McDonnell TC, Chan KC, Chitty LS. Digital PCR analysis of maternal plasma for noninvasive detection of sickle cell anemia. Clin Chem 2012;58(6):1026–32.
15. Lam KW, Jiang P, Liao GL, et al. Noninvasive prenatal diagnosis of monogenic diseases by targeted massively parallel sequencing of maternal plasma: application to beta-thalassemia. Clin Chem 2012;58(10):1467–75.
16. New MI, Tong YK, Yuen T, et al. Noninvasive prenatal diagnosis of congenital adrenal hyperplasia using cell-free fetal DNA in maternal plasma. J Clin Endocrinol Metab 2014;99(6):E1622–30.
17. Futch T, Spinosa J, Bhatt S, et al. Initial clinical laboratory experience in noninvasive prenatal testing for fetal aneuploidy from maternal plasma DNA samples. Prenat Diagn 2013;33(6):569–74.

18. Wang JC, Sahoo T, Schonberg S, et al. Discordant noninvasive prenatal testing and cytogenetic results: a study of 109 consecutive cases. Genet Med 2015;17(3):234–6.

19. Ohno M, Caugey A. The role of noninvasive prenatal testing as a diagnostic versus a screening tool—a cost-effectiveness analysis. Prenat Diagn 2013;33(7):630–5.

20. Morris S, Karlsen S, Chung N, et al. Model-based analysis of costs and outcomes of non-invasive prenatal testing for Down’s Syndrome using cell free fetal DNA in the UK National Health Service. PLoS One 2014;9(4):e93559.

21. Fairbrother G, Burigo J, Sharon T, Song K. Prenatal screening for fetal aneuploidies with cell-free DNA in the general pregnancy population: a cost-effectiveness analysis. J Matern Fetal Neonatal Med 2016;29(7):1160–4.

22. Chitty LS, Wright D, Verhoef TI, et al. A prospective cohort study and economic model to evaluate costs and benefits, acceptability and implications at a population level of implementing non-invasive prenatal testing for aneuploidy into routine NHS maternity care. BMJ 2016 (In press).

23. Hill M, Tafinder S, Chitty LS, Morris S. Incremental cost of non-invasive prenatal diagnosis versus invasive prenatal diagnosis of fetal sex in England. Prenat Diagn 2011;31(3):267–73.

24. Hill M, Twiss P, Verhoef TI, et al. Non-invasive prenatal diagnosis for cystic fibrosis: detection of paternal mutations, exploration of patient preferences and cost analysis. Prenat Diagn 2015;35(10):950–8.

25. Meng M, Li X, Ge H, et al. Noninvasive prenatal testing for autosomal recessive conditions by maternal plasma sequencing in a case of congenital deafness. Genet Med 2014;16(12):972–6.

26. Curtis L. Unit costs of health and social care. Personal Social Services Research Unit; University of Kent, 2014. Available from: wwwpssruacuk/project-pages/unit-costs/2013/Accessed October 2015.

27. Department of Health. National schedule of reference costs 2013/14. Available from URL: https://www.gov.uk/government/publications/nhs-reference-costs-2013-to-2014. 2015. Accessed October 2015.

28. Hill M, Finning K, Martin P, et al. Non-invasive prenatal determination of fetal sex: translating research into clinical practice. Clin Genet 2011;80(1):68–75.

29. Wright CF. Cell-free fetal nucleic acids for non-invasive prenatal diagnosis. Report of the UK expert working group. PHG Foundation [online], http://www.phgfoundation.org/reports/4985 2009. Accessed November 2015.

30. Deans Z, Hill M, Chitty LS, Lewis C. Non-invasive prenatal testing for single gene disorders: exploring the ethics. Eur J Hum Genet 2012;21(7):713–41.

31. Lewis G, Hill M, Skirton H, Chitty LS. Fetal sex determination using cell-free fetal DNA: service users’ experiences of and preferences for service delivery. Prenat Diagn 2012;32(8):735–41.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of this article at the publisher’s web site.