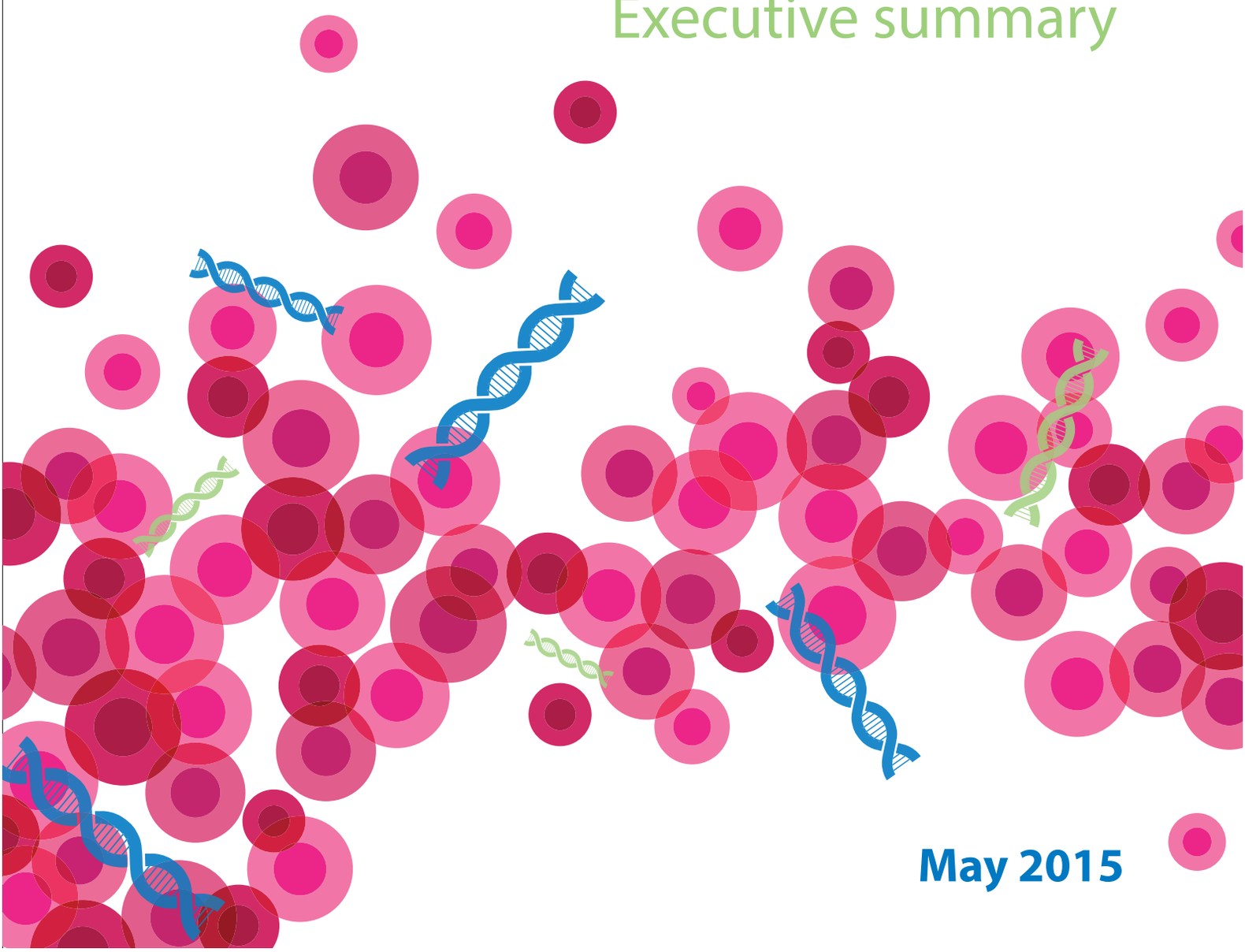
RAPID non-invasive prenatal testing (NIPT) evaluation study:

a report for the UK National Screening Committee

Executive summary



May 2015

Authors

Professor Lyn Chitty, Ms Louise Cameron, Ms Rebecca Daley, Ms Jane Fisher , Dr Melissa Hill, Mrs Lucy Jenkins, Dr Mark Kroese, Dr Alec McEwan, Ms Fiona McKay, Professor Steve Morris, Dr Talitha Verhoef, Professor David Wright.

Acknowledgements

The RAPID NIPT evaluation study was funded by the National Institute for Health Research (NIHR) through the Programme Grants for Applied Research (PGfAR) Programmme (RP-PG 10107-0707).
Great Ormond Street Children's Charity provided funds for the HiSeq and partly funds LSC. The NIHR Biomedical Research Centre at Great Ormond Street provided funds for the development of the laboratory test and partly funds LSC. The NIHR LCRNs in North Thames, South Thames and Wessex provided support to recruit to the study. We would also like to thank all the women who participated in the study and the staff in participating units who helped recruit them.

NHS
National Institute for Health Research

Great Ormond Street Hospital for Children NHS
NHS Foundation Trust

Correspondence to:
rapid@ucl.ac.uk

How to reference this report:
***RAPID Non-invasive prenatal testing (NIPT)* evaluation study Executive summary (2015)**

ISBN 978-1-907198-17-5

Executive summary

Non-invasive prenatal testing (NIPT) involves the analysis of cell free DNA (cfDNA) in maternal blood and allows detection of genetic problems and aneuploidy in the fetus. The RAPID NIPT evaluation study has investigated the use of NIPT to detect fetal aneuploidy as part of the NHS Down syndrome (DS) screening pathway, and to establish the following:

What is the optimal method of utilising NIPT in the NHS DS screening pathway?

In an NHS study population, is test performance comparable with published data, and how acceptable is the test to patients and health professionals?

What are the benefits and costs of implementing NIPT in the NHS DS screening programme?

What are the implications for implementation at a population level?

Study design

The RAPID NIPT study has specifically evaluated NIPT as a contingent test, with a risk cut-off chosen to provide evidence on the balance between improved detection of DS cases, reduction of invasive testing and overall screening programme costs. The study has run from November 2013 to February 2015. To maximise pregnancy outcome data, the results presented in this report are from women recruited from four centres in the first eight months of the study between November 1st 2013 and June 30th 2014.

The study protocol has offered NIPT to all eligible women with a standard DS screening risk of trisomy 21 (T21) of greater than 1:1000, based on the combined or quadruple test. Those women with a risk of greater than 1:150 were offered NIPT or invasive prenatal diagnosis (IPD). At some participating centres, women were also given a risk for trisomy 18 (T18) and trisomy 13 (T13) and offered further testing if their risk was greater than 1:1000. In line with national policy, women with an increased DS screening risk and a nuchal translucency >3.5mm were also offered NIPT which, for these cases, included screening for monosomy X. All women with a positive NIPT result were offered IPD to confirm the diagnosis.

Study results

One thousand, one hundred and sixty four women who were found to have a risk of between 1:2 and 1:1000 for either T21 and / or T18 / T13 across the four recruitment sites, were eligible and accepted NIPT testing. In total, 89 invasive tests were carried out (60 without prior NIPT), and 32 T21 pregnancies were detected. That is 2.8 invasive tests for each T21 pregnancy diagnosed. These figures should be compared with the combined test where, at best, with a risk cut-off of 1:150, over 10 invasive tests are carried out for each T21 pregnancy detected. The improvement is a reflection of a reduction in uptake of IPD in women with risks greater than 1:150 and increased detection from the offer of NIPT to women with risks of 1:151 - 1:1000.

Uptake of NIPT (77% in the greater than 1:150 risk group) was higher than the uptake of further testing at study centres prior to the study (60%), and indicates that NIPT removed a barrier to further testing which invasive procedures represent for some women. Uptake in the 1:151-1:1000 risk group was higher at 84%. The slightly lower uptake in the group of women with a risk greater than 1:150 reflects the concurrent offer

of IPD as a first line test in the research context, and is skewed towards higher uptake among women with the highest risks in the sub-group. Overall 95% of women with a risk of greater than 1:150 accepted further testing, compared with 60% before the study.

NIPT detected T21 pregnancies in 100% of cases (95% CI: 88% - 100%). No false negative results have been identified in the study results reported, with outcome data available in 91% of NIPT negative cases. There were eight (0.7%) failed or inconclusive tests which required a re-draw of maternal blood. The performance of NIPT as provided by the NHS laboratory in this study and in this intermediate risk population was comparable to that cited in the literature.[3,9,11-14]

Implementation scenario

The real-life implications of the RAPID study findings will be influenced by factors such as the number of pregnancies, demographic factors, and service delivery models. Study uptake data were used to estimate the likely impact at a national level in terms of costs and outcomes if NIPT was implemented in the screening pathway. Table 3.1 provides a summary of the overall costs and key outcomes of implementing NIPT as a contingent test in the NHS DS screening pathway at three different risk cut-offs with no access to direct IPD. The implementation scenario is based on the following assumptions:

Assuming a pregnant population of 698,500*

DS screening uptake in the current pathway is 66.2% (national data)

The proportion of women with a DS risk of: greater than 1:150 is 2.3%, greater than 1:500 is 5.7%, greater than 1:1000 is 9.8% (national data)

There is no option to proceed directly to IPD in the NIPT pathways

Uptake of NIPT in women with a DS risk of greater than 1:150 is 95% , greater than 1:500 is 88.1%, greater than 1:1000 is 86.2% (study data, assuming no direct IPD)

NIPT positive T21 after NIPT accepted with DS risk of greater than 1:150= 9.5%, with DS risk greater than 1:500= 4.1%, with DS risk greater than 1:1000= 2.4% (study data)

Uptake of IPD in women with a DS risk of greater than 1:150 in the current screening pathway is 53.8% (national data)

Uptake of IPD in women with positive NIPT is 88.9% (study data)

DS detected refers to cases identified by NIPT or IPD

DS confirmed by IPD assumes a specificity of 90% for NIPT for T21 (based on BGI / Next studies) and assumes a miscarriage rate of 0.5% (national data)

Laboratory cost of NIPT is £250 (additional costs of £30, including phlebotomy, counselling / feedback repeat test costs) (study data)

Cost of IPD is £650 (study data)

*ONS 2013 live birth figures for England and Wales

Table 3.1 (p.78) Comparison of outcomes for current DS screening pathway compared to proposed screening pathway in the England and Wales population

Pathway	Pregnant population*	No. accept DS screening	Cost of DS screening (£000s)	No. risk above risk cut-off	No. accept NIPT	Cost of NIPT (£000s)	No. NIPT +ve T21	No. IPDs (first line only)	No. IPDs (second line only)	IPDs (first or second line only)	DS detected by NIPT or IPD	DS confirmed by IPD	Cost of IPD (first or second line £000s)	Procedure related miscarriage	Total cost (£000s)
Current	698,500	462,060	£13,301	10,627	0	£0	0	5721	0	5721	855	855	£3,719	29	£17,020
NIPT>1:1000 No first line IPD	698,500	462,060	£13,301	45,282	39033	£10,932	1031	0	916	916	1031	820	£596	5	£24,829
Difference with current										4805 less	176 more	35 less		24 less	£7,809 more
NIPT>1:500 No first line IPD	698,500	462,060	£13,301	26,337	23216	£6,502	1007	0	895	895	1007	802	£582	4	£20,385
Difference with current										4826 less	152 more	53 less		25 less	£3,365 more
NIPT>1:150 No first line IPD	698,500	462,060	£13,301	10,627	10099	£2,829	957	0	851	851	957	762	£553	4	£16,682
Difference with current										4870 less	102 more	93 less		25 less	£337 less

*ONS 2013 live birth figures for England and Wales

Perspective from healthcare professionals and parents

The study has successfully developed a training programme and validated training materials for healthcare professionals and parent information materials, which could be utilised for wider implementation of NIPT in DS screening. The evaluation showed that parents and health professionals were very positive about the possible introduction of NIPT into NHS care. Overall most parents felt that any additional anxiety and the length of time required for results were overcome by the benefits of the test, which were considered to include its safety, accuracy and simplicity, along with the reduced need for invasive procedures. Feedback from healthcare professionals has shown that NIPT was easily integrated into existing screening arrangements.

Conclusion

The results presented support the use of NIPT as a contingent test in the NHS DS screening pathway. As illustrated in Table 3.2, the use of NIPT with a risk cut-off of 1:150 increases the number of DS cases detected slightly, the estimated costs would be marginally lower and the number of invasive tests and procedure-related miscarriages would fall dramatically. Lowering the risk cut-off will increase the number of DS cases detected, and increase the overall costs, whilst maintaining a significant reduction in IPDs and procedure-related miscarriages

Table 3.2 (p.85) Summary comparisons of the outcomes for the proposed screening pathway including NIPT compared to the current NHS DS screening pathway in the England and Wales population

Testing strategy	DS detected compared to current	Less IPD compared to current	Less IPD related miscarriage compared to current	Additional cost of implementing NIPT testing strategy (test cost - £250)
>1:1000 No direct IPD	176 more	4,805 less	24 less	£7,809,000 more
>1:500 No direct IPD	152 more	4,826 less	25 less	£3,365,000 more
>1:150 No direct IPD	102 more	4,870 less	25 less	£337,000 less

It should be noted that it has not been possible to capture in this study the additional benefits to women of avoiding an unnecessary invasive prenatal diagnosis procedure apart from the miscarriage risk. These additional benefits have therefore not been included in the health economics analyses presented in this report but should be taken into account when considering implementation costs.

This study has shown that NIPT can be provided safely and effectively as part of the NHS DS screening programme in the four clinics involved in the study. This included the use of NIPT in the different NHS antenatal care service models and the provision of NIPT testing by an NHS laboratory. There is therefore a strong case for the implementation of NIPT as part of the NHS DS screening programme to improve the quality of care for pregnant women and the performance of the programme as a whole.