National Services Division

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NHS National Services Scotland

Briefing Note

Subject: NIPT Implementation in Scotland
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This paper outlines the main issues around implementing Non Invasive Prenatal Testing (NIPT) as part of the existing Down's syndrome screening programme in Scotland. It should be noted that in England screening for Edwards' and Patau syndrome are part of the first trimester screening programme for Down's syndrome but this has still to be implemented in Scotland. A paper on the implementation of screening for these conditions is scheduled for the August meeting of the screening committee.

Background
NIPT is a test that can identify pregnant women who are at higher chance of having a baby with certain genetic and chromosomal conditions, such as Down's syndrome (also known as Trisomy 21), Edwards' syndrome (Trisomy 18) and Patau's syndrome (Trisomy 13). The test detects DNA fragments in a sample of blood taken from the mother. Most of the DNA fragments are from the mother but some are from the unborn baby, these fragments are called cell free fetal DNA (cffDNA). cffDNA is detectable from around 7 weeks of pregnancy and the amount of detectable DNA is thought to rise as the pregnancy continues. The test carries no risk of miscarriage.

All pregnant women in Scotland are currently offered screening for Down's syndrome either in the first trimester (11^{+2} -14^{+1} weeks' gestation) or second trimester (14^{+2}-20^{+0} weeks' gestation). Results indicating that the pregnancy is at a higher chance (more than a 1 in 150 chance) of having a baby with Down's syndrome are then offered follow-up diagnostic tests (amniocentesis or chorionic villus sampling). These diagnostic tests can tell whether the baby will have Down's syndrome but they are invasive and carry a small (generally quoted as 1-2%) risk of miscarriage.

NSC recommendation
In January 2016 the UK National Screening Committee (UK NSC) recommended an evaluative implementation of NIPT as an additional test into the Pregnancy Screening programme to assess what impact it would have. The evaluation aims to answer the specific questions raised by the UK NSC around behavioural choice, test accuracy for T18/T13, test failure rate and turnaround time. It is proposed that the evaluation period will take a minimum of 3 years. This approach will enable evaluation of the roll out at each stage ensuring that required changes can be made efficiently and effectively. If necessary the UKNSC would also be able to make a recommendation to cease use of NIPT as part of the screening pathway. See Annex A for more information on the recommendation.

The research findings that informed the NSC recommendation acknowledged the potential for NIPT to replace the current screening tests in the future. It concluded, however, that as the technology stood at the time of the study, it would not be cost-effective and the number of inconclusive tests would mean that more women would be offered invasive testing than the current screens. The UK NSC will continue to keep emerging evidence under review as this is a rapidly evolving technology.

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Formal announcement following the UKNSC recommendations was made by the Department of Health on 29 October 2016. Preparation for roll out in England has started with commencement of offer of NIPT as an additional screening test from April 2018.

The UK NSC recommend that NIPT should be offered to pregnant women whose chance of having a baby with Down's, Edwards' or Patau's syndrome is greater than 1 in 150 as an alternative to these invasive tests. Whilst NIPT is considered more accurate than the current screening tests it is not diagnostic and if the result still shows the pregnancy to be at higher chance of being affected by the condition screened for, then diagnostic testing should still be offered. The research commissioned by the UK NSC into the case for offering NIPT[1] concluded that the introduction of NIPT could result in the number of invasive tests in the UK falling from an estimated 7,900 to 1,400 each year and the number of miscarriages related to invasive tests would fall from around 46 to 3. The work done by the UK NSC also suggested that the reduced number of invasive tests would release enough money to cover the extra needed for the new test. So it should be cost neutral to the NHS. A summary of the report is attached at Annex B

The recommendation has proved to be controversial with some individuals and groups including the Down's Syndrome Society expressing concerns regarding the ethics in the use of NIPT in the NHS as it could lead to an increase in the number of terminations following a diagnosis of Down's, Edwards' or Patau's syndrome. As such the Nuffield Council on Bioethics were commissioned to produce a report to consider the ethical, legal and regulatory implications of recent and potential future scientific developments in NIPT, with regard to its use in both NHS and commercial services, including for whole genome/exome sequencing. Their report was published on 1st March 2017[2]. The report concluded that NIPT should be offered under certain circumstances with recommendations on how this should be offered in the NHS and commercial sector. See Annex C for a summary of the report.

NIPT for Down's syndrome screening has been available through the commercial sector as a primary screen, with costs ranging from £300-£600 since 2012. The availability of NIPT in the private sector has lead to inequalities in screening choices available to women in Scotland on the basis of ability to pay. Concerns about counselling inadequacies, in relation to the test within the private sector have also increased the demand that it should be made available within the NHS as soon as possible.

Implementation considerations

There are a number of areas to be considered before implementation could take place in Scotland. In terms of the numbers to be expected, in the year 2015/16 approximately 599 women were given a higher chance result from the Glasgow screening laboratory and 473 women were given a higher chance result from the Lothian laboratory. If all these women accepted the offer of NIPT then 1072 additional screening tests would have been carried out. This does not take into consideration of any repeat tests where no result is obtained on the initial NIPT. The tests would have to be carried out in a genetic laboratory and this would be an additional workstream to current practice and would need to be resourced accordingly.

Costs in relation to this are said to have been included in the cost per sample but this would need to be tested to ensure this was a true reflection of potential costs in NHS Scotland given the limited workload there would be. National guidance on the laboratory specification is being produced as part of the rollout in England. Whilst there are not going to be set workload throughput thresholds there will be cost and turnaround time standards which would restrict this to laboratories with a high throughput. In England it is anticipated that there would only be two or three laboratories providing the analytical service. Given the number of samples that would be generated in Scotland it would therefore be anticipated that one genetic laboratory would carry out the workload for the whole of Scotland to be cost effective and meet the turnaround requirements.

There are also clinical considerations that need to be taken into account as to whether a repeat NIPT screen or an invasive diagnostic test (CVS/amniocentesis) should be offered. Factors including the BMI of the woman, the gestation of the pregnancy, history of recent transfusion and the limitations of

[1] RAPID Non-invasive prenatal testing (NIPT) evaluation study (2015)
[2] Non-invasive prenatal testing: ethical issues. Nuffield Council on Bioethics (2017

NIPT itself will influence the decision making process of whether to repeat NIPT or go straight to the offer of CVS/amniocentesis. This would affect the number of NIPT tests to be carried out and the resources required. The costs quoted in the NSC report estimated Laboratory cost of NIPT to be £250 (plus additional costs of £30, including phlebotomy, counselling/feedback and repeat test costs) compared to £650 for the invasive tests. Additionally the transport costs for the sample to reach the designated laboratory did not been appear to have been included in the study. The prices quoted would also need to be assessed for accuracy with current prices.

The Public Health England draft national service specification is anticipated to be completed by April 2017. A challenging legal and commercial market for providing the tests and platform has already been experienced in NHS Wales and is impacting on the procurement in NHS England. NHS Scotland would be able to learn the lessons from these.

Costings for data collection are still to be established. In addition Quality Assurance measures shall be incorporated in to the current Downs Quality Assurance Statistical Service (DQASS). Details of this and any potential costs are still to be fleshed out. There would also be resource requirements for Health professional training and patient and professional information.

Recommendation
The Scottish Screening committee is invited to;

- note the UKNSC recommendation
- commission an outline business case to inform implementation and advise Scottish Ministers that NHSScotland should move towards planning for implementation of the NSC recommendations.

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UK National Screening Committee

January 2016

UK NSC non-invasive prenatal testing (NIPT) recommendation

The UK NSC recommended an evaluative implementation of NIPT to assess what impact it would have on the existing NHS Fetal Anomaly Screening Programme.

Pregnant women are already offered a screening test for Down's syndrome, Edwards' syndrome and Patau's syndrome from 10-14 weeks of pregnancy (the combined test, involving an ultrasound scan and blood test), or a screening test for Down's syndrome only (the quadruple test, involving a blood test alone) if booking between 14-20 weeks.

If the screening test shows that the chance of having a baby with Down's, Edwards' and Patau's syndromes is higher than 1 in 150, this is called a higher-risk result. Currently, women who have a higher risk result have the option of having an invasive diagnostic test (amniocentesis or CVS).

The proposed change is for Non-Invasive Prenatal Testing to be offered to women who are deemed at higher risk following the current primary screen. NIPT is not diagnostic and an invasive diagnostic test is still required to receive a definitive diagnosis.

Key findings supporting the UK NSC recommendation

- an invasive diagnostic test carries a small risk of miscarriage. The evidence suggests that NIPT will reduce the number of women being offered an invasive test
- however, while we know that the accuracy of NIPT is very good, we don't yet know how it will perform in an NHS screening programme pathway
- for women who choose to have NIPT, this will add in an extra step in the screening programme. The impact of this, and the choices women make at different points in the pathway, is something that we hope to gain a better understanding of through further research
- a recommendation has therefore been made to evaluate the introduction of non-invasive prenatal testing (NIPT) to Down's syndrome screening. This will include scientific, ethical and user input to better understand the impact on women, their partners and the screening programme around the offer of cfDNA or invasive testing following a screening test result where:
  - » the screening test risk score for trisomy 21 (T21) is greater than or equal to 1 in 150
  - » the combined test risk score for trisomy 18 (T18) and trisomy 13 (T13) is greater than or equal to 1 in 150

The UK NSC regularly reviews its recommendations on screening for different conditions in the light of new research evidence becoming available.

To find out more about the UK NSC's NIPT recommendation, please visit:

legacy.screening.nhs.uk/fetalanomalies

The UK National Screening Committee (UK NSC) advises ministers and the NHS in the 4 UK countries about all aspects of screening and supports implementation of screening programmes.

Find out more about the UK National Screening Committee at www.gov.uk/government/groups/uk-national-screening-committee-uk-nsc. The UK NSC evidence review process is described at www.gov.uk/government/publications/uk-nsc-evidence-review-process and a list of all UK NSC recommendations can be found at legacy.screening.nhs.uk/recommendations

The UK NSC secretariat is hosted by Public Health England (www.gov.uk/phe).

Annex B

Systematic review and cost-consequence assessment of cell-free DNA testing for T21, T18 and T13 in the UK – Final report

Plain English Summary

We investigated how well a new blood test (called cell-free DNA testing – cfDNA for short) for pregnant women works for detecting Down syndrome (trisomy 21), Edwards syndrome (trisomy 18) and Patau syndrome (trisomy 13) in the fetus. We systematically searched for published studies. We found high risk of bias in the research studies, meaning that test performance might be lower in real life than the studies suggest. We combined 41 different research studies to get an overall estimate of test accuracy. We found that test accuracy is very good but not 100%, so the test should not be used to give a final diagnosis. We estimated how well cfDNA would work if it was used in a high risk population of 10,000 pregnancies where 3.3% of fetuses have Down syndrome, 1.5% have Edwards syndrome and 0.5% have Patau syndrome. We predict that there would be 324 cases of Down syndrome detected, with 9 missed and 31 false positive results, 140 cases of Edwards syndrome detected with 11 missed and 26 false positive results, and 47 cases of Edwards syndrome detected, with 3 missed and 7 false positive results. One large study in the general pregnant population estimated that 19 in 100 pregnancies testing positive for Down syndrome did not actually have a baby with the condition. Because of the possibility of the test giving an inaccurate result cfDNA testing should not be considered as a diagnostic test for trisomies. Pregnant women with positive results should be offered an invasive diagnostic test (such as amniocentesis or chorionic villus sampling [CVS], which carry a small risk of miscarriage) to give a conclusive diagnosis.

We made an economic model to compare three options for the NHS. The first option is keeping the current NHS screening programme using the combined test (a combination of a blood test and ultrasound) with pregnant women given a screening risk of having a baby with Down's, Edwards' or Patau's syndrome of greater than 1/150 offered an invasive diagnostic test. The second option was using the combined test with women given a risk greater than 1/150 offered the new cfDNA test, and if they tested positive offered an invasive diagnostic test. This option resulted in similar numbers of trisomies detected, 43 fewer miscarriages of healthy pregnancies because of many fewer women choosing to have invasive tests than currently, and may cost approximately the same as currently. The third option is to use the new cfDNA test as the first test offered instead of the combined test. This option would cost an extra £105 million to the NHS, and would result in more invasive tests than the second option.

In summary, the new cfDNA test is very accurate, but does not give a definite answer. Offering the new cfDNA test to pregnant women who test positive using the current combined test could reduce the number of invasive tests, and therefore the number of miscarriages of unaffected fetuses caused by invasive testing. Because the cfDNA test cannot give a definitive answer as to whether the baby has a trisomy, a CVS or amniocentesis would be recommended before parents considered termination of pregnancy.

Copies of the full report are available from the Secretariat on request

NUFFIELD COUNCIL ON BIOETHICS

SUMMARY OF REPORT

Non-invasive prenatal testing: ethical issues

Published 1 March 2017

Non-invasive prenatal testing (NIPT) is a technique that can be used to test a fetus for genetic conditions and variations. It involves taking a blood sample from the pregnant woman at around 9 or 10 weeks of pregnancy. NIPT is more accurate than other screening tests, it carries no risk of miscarriage and, in some circumstances, NIPT can provide earlier results than current screening and diagnostic tests.

From 2018, NIPT for Down's, Edwards' and Patau's syndromes will be available to pregnant women as a second stage screening test in the NHS fetal anomaly screening programme. NIPT is already used in the NHS to diagnose fetuses for other genetic conditions, such as cystic fibrosis and achondroplasia, in women where there is a family history or another indication. NIPT for a range of genetic conditions, and for finding out fetal sex, is widely available through private healthcare providers. NIPT for more genetic conditions and variations is likely to be available in the future. Whole genome sequencing using NIPT has already been carried out in a research setting.

The Nuffield Council on Bioethics report considers, at this early stage of its use, how NIPT could change the way we view pregnancy, disability and difference, and what the wider consequences of its increasing use might be.

Key recommendations

Women and couples should be able to access NIPT to enable them to find out, if they wish, whether their fetus has a significant medical condition or impairment, but only within an environment that enables them to make autonomous, informed choices, and when the potential wider harms of NIPT are minimised.

- To offset the possibility that the increased use of NIPT might adversely affect disabled people, the Government and those subject to the Public Sector Equality Duty have a duty to provide disabled people with high quality specialist health and social care, and to tackle discrimination, exclusion and negative societal attitudes experienced by disabled people.
- Before the introduction of NIPT in NHS screening, Public Health England should produce accurate, balanced and non-directive information for women and couples about NIPT and the conditions for which it tests. High quality education and training must be compulsory for all NHS healthcare professionals involved in prenatal screening.
- The Committee of Advertising Practice should more closely monitor the marketing activities of private NIPT providers to ensure that they are not being misleading or harmful.
- Certification from information quality schemes should be sought by private NIPT providers to help women and couples to know that the information they provide has been quality checked.
- Private hospitals and clinics should be required by their regulatory bodies to only offer NIPT as part of an inclusive package of care that should include, at a minimum, pre- and post-test counselling and follow-up invasive diagnostic testing if required.