UK National Screening Committee (UK NSC)

Note of the meeting held on the 18 June 2015

at

Victoria Quay- Edinburgh

Members

Professor David Walker (Chair)	Medical Director, University Hospitals of Morecambe Bay Foundation Trust
Dr Sunil Bhanot	GP
Professor Martin Buxton	Emeritus Professor of Health Economics
Professor Alan Cameron	Consultant Obstetrician at Southern General Hospital, Glasgow
Professor Gareth R Evans	Consultant in Genetics Medicine, St Mary's Hospital, Manchester
Ms Jane Fisher	Patient and Public Voice

Observers;

Dr Hilary Angwin	Screening & Immunisation Lead, NHS England/PHE Chair of FMCH
Dr Stephen Bridgeman	Director of Public Health and CMO for Guernsey
Dr Margaret Boyle	Department of Health, Social Services and Public Safety Northern Ireland
Miss Sally Cartwright	Specialist Registrar
Mrs Carol Coquhoun (PM)	National Screening Co-ordinator, Scotland

Dr David Elliman	Clinical lead for Newborn Infant Physical Examination and Newborn Blood Spot, PHE
Mr Tim Elliott (Telecom PM)	DH Senior Cancer Policy
Dr Nick Hicks	National Co-ordinating Centre for HTA
Dr Rosemary Fox	Director of Screening Division, Public Health Wales
Dr Dorian Kennedy	Deputy Director, Sexual Health, Screening and Sponsorship Team, Department of Health
Ms Billie Moores	Director of QA North-East
Miss Nicole Redhead	Sexual Health, Screening and Sponsorship Branch Department of Health
Professor Julietta Patnick	Director of Cancer Screening Programmes, PHE
Dr Heather Payne (Video.Conf)	Senior Medical Officer for Maternal and Child Health, Welsh Government
Mrs Anne Stevenson	National Lead for Adult Screening Programmes
Mr Scott Sutherland	Scottish Government
Miss Jo Taylor	Sexual Health, Screening and Sponsorship Branch Department of Health

Secretariat

Mrs Jo Harcombe	Head of Professional and Public Information, education and training
Dr Anne Mackie	Director of Programmes - UK National Screening Committee
Mr John Marshall	Evidence Lead, PHE
Miss Zeenat Mauthoor	Secretariat, PHE

Apologies

Mr Andrew Anderson	Cancer Screening Communication Team, PHE
Ms Alison Brown	Patient and Public Voice
Dr Roger Brownsword	School of Law, Kings College London
Ms Majella Bryne	Director, National Cancer Screening Service, Republic of Ireland
Dr Surendra Kumar	GP
Dr Janet Little	Public Health Agency, Northern Ireland
Mr Terry O'Kelly	Senior Medical Officer, Scottish Government

Presenters;

Professor Lyn Chitty	Professor of Genetics and Fetal Medicine
Dr Mark Kroese	Programme Director, phg foundation
Professor Peter Scanlon	Consultant Ophthalmologist, Clinical Director of NHS Diabetic Eye Screening Programme
Dr Sian Taylor-Phillips	Warwick Medical School
Dr Fiona Ulph	Senior Lecturer in Qualitative Methods at University of Manchester

Welcome and Introductions

1. The Chair welcomed all to the meeting and a round of introductions were given including;

Agenda Item Presenters

Professor Lyn Chitty and Dr Mark Kroese presenting the RAPID report on NIPT.

Dr Fiona Ulph project lead for "The provision of antenatal information for the NHS Newborn Bloodspot Screening Programme (NBSP)" presenting her HTA research.

Dr Sian Taylor –Phillips presenting the Warwick Economic Model for the use of a new blood test called the cell –free fetal DNA testing (cfDNA) in an NHS setting.

Mrs Anne Stevenson and Professor Peter Scanlon presenting work undertaken to look at screening intervals in the Diabetic Eye Screening Programme (DES)

Resignations

The Chair informed members of Dr Eric Baijal (Joint Director of Public Health, NHS Borders) retirement.

Dr Baijal had been on the Committee since 2012 as a Scottish observer. The Committee agreed that a letter should be sent to thank Dr Baijal for his contribution on the Committee.

Action; The Chair to send letter of appreciation to Dr Baijal and for the Secretariat to liaise with the Scottish Department for a replacement observer

The Committee was also informed of Professor Patnick's impending leave to take early retirement at the end of summer. The Chair and Committee thanked Professor Patnick for all her hard work, contribution and dedication in progressing and influencing all three NHS Cancer Screening Programmes to be world leading and reputable programmes at the forefront of screening.

Apologies were noted.

Minutes and Matters arising

2. One amendment was identified from the last minutes;

- Page 8 Line 5 removal of *"RCPCH"*

Dr Bhanot also requested an update from the discussions noted on page 7 on how the statement that the UKNSC would look at programmes that resembles screening programmes was being actioned. Dr Mackie and the Chair responded confirming that work is being undertaken to address this but noted that this will not be straightforward.

There were six actions points identified from the last meeting;

1. Resignations

Professor Walker to send letter of appreciation to Moira Morris- COMPLETED

4.1 Directors Update

Dr Mackie to enquire if pulse oximetry could be used in home births - Confirmed that it is available.

5.2 Duty of Candour

An update on Duty of Candour to be brought to the UK NSC for information at a later date- ONGOING with discussions with CQC.

6 HPV Testing in Cervical Cancer

Dr Mackie to arrange for public and stakeholder consultation after pre-election period – To be discussed at the meeting

9 Annual Stakeholder Meeting

Committee members wishing to participate to contact Miss Mauthoor- COMPLETED

11.2 Galactosaemia

Recommendation to be considered further by the UK Health Departments- ONGOING

Director's Update

3. Dr Mackie gave an update as follows;

Pulse Oximetry

3.1 Six English hospitals have newly introduced the use of pulse oximetry screening in newborn babies to help detect congenital heart defects and six more have altered their existing testing with pulse oximetry in line with the national pathway. The pilot is progressing well and interim data from the pilot should be available for discussion at the next committee meeting.

Action; Dr Mackie to bring interim data for Pulse Oximetry to the November UK NSC meeting

Update on Reducing Inequalities

3.2With the current restructure of Public Health England bringing together all cancer, non cancer screening and QA teams into a single division, a key priority for PHE will be to

ensure that inequalities are uniformly addressed across all English National Screening Programmes. In order to achieve this and understand the work involved a national workshop is to be held in September. The aim of the workshop is to:

- Consider the roles and responsibilities of all those involved in the delivery of screening
- Consider effective evidence based actions to reduce health inequalities and improve health outcomes in screening programmes
- Share best practice
- Identify resources and support tools

A literature review has been commissioned from Professor Stephen Duffy to support this work. In addition two HTA trials are underway to research interventions in improving uptake in the Diabetic Eye Screening Programme (DES) and in NHS Cervical Screening Programme. Dr Bhanot expressed an interest in this workshop and requested an invitation to attend.

Action; Dr Bhanot to be invited to the workshop

Action: Dr Mackie to bring a detailed English paper on Inequalities to a future UK NSC meeting

Update on cessation of screening for Rubella susceptibility

3.2 Dr Mackie informed the Committee that, following the UK NSC recommendation in 2012, screening for rubella susceptibility does not meet the UK NSC criteria for a screening programme and that work was in hand to cease screening in England from April 2016 to enhance the current MMR programme. This was subject to the agreement of English Ministers who would make the final decision. The work will be supported by education and awareness for health professionals on the management of rash and contact with rash illness in pregnancy. A project group, which included representatives from each of the four UK countries, had been established to oversee the process. The Committee noted that there had been several cases of congenital rubella in England however it recognised that these cases had contracted rubella abroad and not in England. The Committee agreed that education, awareness and managing rash in pregnancies were imperative in understanding and treating rubella.

Action: Paper on Rubella cessation for England to be shared with the Four Countries

Review of the UK National Screening Programme

4 Miss Jo Taylor provided the Committee with a verbal update on the review of the UK NSCs.

4.1 Since the last UK NSC meeting the recommendations from the review group have been agreed by the four Chief Medical Officers. The recommendations were due to be published shortly alongside consultation responses and the newly produced UK NSC Code of Practice. The Secretariat was taking forward recommendations from both the review and the House of Commons Science and Technology Committee. A key priority was to appoint new members to the Committee. The Department of Health was overseeing the recruitment process and vacancies had been advertised.

4.2 In line with recommendations from the review, the Terms of Reference for the Committee are being revised. A draft version of the revised Terms of Reference will be shared with the Committee before final approval by the Four CMOs.

4.3 The Committee agreed that consideration should be given to the governance, Terms of Reference and membership of the Fetal Maternal and Child Health sub-committee.

Action: Jo Taylor, Hilary Angwin and John Marshall to take forward work on governance arrangements for the FMCH

HTA Presentation

5 At the March UK NSC meeting it was agreed that the Committee would benefit from having a research project presented in order to understand the research processes undertaken by Health Technology Assessment (HTA).

5.1 Dr Fiona Ulph presented her research on the provision of antenatal information for the Newborn Bloodspot Screening Programme (NBSP). The Committee thanked Dr Ulph for her presentation.

5.2 The Committee recognised many of the challenges outlined in the presentation, in particular that the process for giving screening information and ensuring informed choice is facilitated isn't always ideal in the newborn period and that although training is available to staff and information is provided to parents on newborn blood spot screening, not all parents engage in the same way. However, the Committee was clear that the current booklet "Screening Tests for You and Your Baby" had been thoroughly revised with input from key stakeholders including health care workers and parents to ensure that delivery of the screening offer was both practical for front line staff to deliver and acceptable to parents generally. It was also clear that all screening programmes are committed to ensuring that parents do fully understand the screening

offer. The Committee agreed it would be helpful if the National Screening Programme and the Information and Education for Patients and Professionals (IEPP) team in PHE could contribute to the research.

Action; Committee Members to forward on comments to Dr Ulph. The Screening Programme and the IEPP team would contact Dr Ulph to contribute to the research

Action; Dr Ulph to forward on a pre-publication report to the UK NSC

Fetal Maternal and Child Health subgroup

6 Dr Hilary Angwin provided the Committee with a verbal update from the FMCH and noted the Committee's intention to review the FMCH's membership and terms of reference as discussed earlier. The sub-committee had also discussed some evidence reviews to be discussed as main agenda items.

NIPT, cfDNA for T21, 18 and 13

Dr Mackie introduced this item which considered the use of Cell Free DNA (cfDNA) also known as Non-Invasive Prenatal testing (NIPT) to screen for Trisomies 21, 18 and 13 (Down's, Edward's and Patau's syndrome).

RAPID REPORT

7 Professor Lyn Chitty and Dr Mark Kroese presented the findings from the evaluation study (RAPID) which provided evidence for and practical implementation advice relating to non-invasive prenatal testing (NIPT) in the NHS.

7.1 The RAPID NIPT study evaluated the use of NIPT as part of the NHS Downs Syndrome Screening pathway, as a non-invasive method to improve the accuracy of the estimates given to parents about the risk of their baby being affected by Downs Syndrome. Professor Chitty emphasised to the Committee that the study evaluated the use of NIPT as a contingency test for trisomy 21 as part of the current pathway, rather than a diagnostic test. An NIPT result of 'high risk' would then result in the offer of a Chorionic Villus Sampling (CVS) or an amniocentesis to provide a definite diagnosis.

7.2 Based upon the results from the study there was evidence to conclude that parents took up the offer of NIPT when used as a contingent test in the current screening pathway, NIPT is more accurate than the combined test in detecting Down's syndrome. Consequently this significantly reduced the number of invasive prenatal diagnostic tests

which would lead to fewer miscarriages, whilst increasing the number of DS cases detected.

7.3 The Chair thanked both Professor Lyn Chitty and Dr Mark Kroese for their work.

7.4 The UK NSC concurred that the use of NIPT was a safe and efficient test.

Warwick Economic Model

7.5 Dr Sian Taylor- Phillips presented this item to the Committee. **Annex A**

7.6 The Warwick model investigated how a non-invasive method, can be used to detect Down's Syndrome, Edwards' syndrome and Patau's syndrome in pregnant women. The model took into account all published literature. The model considered three options;

i. To offer the combined test to all pregnant women at risk of greater than 1:150 and then offered an invasive diagnostic test (as is current practice)
ii. To offer the combined test to all pregnant women with a risk greater than 1:150 and the new cfDNA test, and if positive to offer an invasive diagnostic test
iii. To offer the cfDNA test only

7.7 The findings indicate that although the second option would detect a similar number of trisomies as the first option using the combined test, it would lead to less invasive testing and thus fewer miscarriages but would cost slightly more per year. Furthermore the use of cfDNA as a first line test for Downs's syndrome would incur a much heavier cost.

7.8 The Committee noted some remaining uncertainties about NIPT:

- there is a failure rate for the test which is between 1 and 12%;
- it is not yet clear how well the tests perform in relation to T13 and T18;
- how the offer of a test will affect initial uptake of trisomy screening, or
- how it will affect the proportion of people wishing to have an invasive test.

The Committee wished to ensure that information is gathered during the roll out to fill in the gaps in evidence.

7.9 The Committee did not agree that Turner's syndrome was part of the existing FASP pathway nor should it be part of the offer of NIPT. Furthermore the Committee noted that this test would not be relevant to multiple pregnancies.

7.10 The UK NSC agreed, based upon the Warwick Economic Model paper and the RAPID REPORT, to a three month consultation on a proposal to pilot cfDNA testing as a contingency to screen for Down's, Edward's and Patau's syndromes in pregnancy for women with a risk of greater than 1 in 150 before final recommendation is made at the UK NSC meeting on 19 November.

Action: The UK NSC to open public consultation to offer NIPT as a contingent test for Down Syndrome screening to women with a risk greater than or equal to 1:150

Screening for Fragile X syndrome in pregnancy

8 Mr Marshall presented this item to the Committee and outlined the severity of this genetic condition which can cause a range of developmental problems including learning disabilities to cognitive impairment.

8.1 The Committee noted that this condition was last reviewed in 2011. The recommendation was that screening should not be offered.

8.2 Mr Marshall informed the Committee that the 2014 review had not identified any new evidence to suggest a change to the previous recommendation. In addition, the current testing approach (southern blotting) was labour intensive and would therefore render it to be impractical for a universal screening programme. Comments received from the consultation concurred with the existing recommendation not to screen for Fragile X syndrome but noted that raising awareness of this condition was important to help clinicians detect the condition once a baby was born.

8.3 The Committee noted the feedback received from the Fetal Maternal and Child Health group (FMCH) that an alternative review, would be to consider Fragile X in newborn and to also consider the use of the two main treatments of folic acid and L-acetycarnitine in newborns. The Committee acknowledged that this could be a potential topic to review however highlighted that this would need to be introduced through the formal topic process route.

8.4 The UK NSC agreed that screening for Fragile X syndrome in pregnancy should not be recommended because a number of the criteria were not met:

- While the natural history and prognosis of Fragile X in males is well understood, it is not possible to predict whether a female fetus will be affected by learning difficulties or to what extent
- The current test is labour intensive and unsuitable for high throughput screening purposes
- There are no curative or preventive treatments that could be offered to those identified through screening

Criteria	UK NSC Comments
The Condition	
The condition should be an important health problem in which the epidemiology, prevalence and natural history is understood	While the natural history and prognosis of Fragile X in males is well understood, it is not possible to predict whether a female fetus will be affected by learning difficulties or to what extent
The Test	
Should be simple, safe, precise and validated screening test.	The current test is labour intensive and unsuitable for high throughput screening purposes. There are no curative or preventive treatments that could be offered to those identified through screening

Proposal to extend screening intervals in the Diabetic Eye Screening Programme (DES)

9. Mrs Anne Stevenson and Professor Peter Scanlon presented this item to the Committee. Diabetic retinopathy is a common complication of diabetes that if left untreated could cause blindness. Since the introduction of the NHS Diabetic Eye Screening Programme (DES) diabetic retinopathy is no longer the leading cause of blindness in the working age group in England.

9.1 The UK NSC had discussed the possibility of extending screening intervals from annually to every two years for those with low risk retinopathy in November 2014 and was supportive of this move. However, the Committee had requested that further work be undertaken in;

i. The requirement for strategies to be in place to ensure accurate and consistent grading was taking place in programmes.
ii. Robust data and IT processes to be in place to ensure the safe identification and management of patients along a pathway.
iii. Vital stakeholder and service user communication.

9.2 Mrs Stevenson said that the four nations group overseeing this work had developed a key set of principles and issues for each country to consider in order to address the issues raised by the UK NSC. However, it was recognised that different approaches to implementing change would need to be put in place for each country because of varying delivery models. For example, Wales has a single grading centre compared to England's where the programme is delivered across 83 local providers with each provider housing their own grading facility and Scotland having a single national programme. Each country would adopt its own process for assuring the quality of grading prior to the implementation of risk based intervals. Mrs Stevenson said that work was in hand to link the development of IT systems to support risk based intervals across the four nations in order to share development costs and ensure a consistent approach. In addition, all countries remained committed to using consistent outcome measures in order to assess continued user engagement.

9.3 The Committee agreed that extending screening intervals for those with low risk findings would be both cost and clinically effective, helping to minimise the demand of screening by 35% when compared to current annual screening. The Committee also agreed that the work in hand by the Four Nations group addressed its previous concerns.

9.4 The UK NSC agreed to a three month consultation on a proposal to pilot two yearly screening intervals for those who have a low risk of sight threatening retinopathy.

Screening for Risk of Sudden Cardiac Death

10. Dr Mackie presented this item. The Committee had reviewed the evidence for screening for hypertrophic cardiomyopathy, the most common cause of Sudden Cardiac Death in young people in 2008 and population screening was not recommended. Dr

Mackie confirmed that the latest review has expanded to include the major causes of SCD in young people between the ages of 12 – 39 years.

10.1 Dr Mackie noted that screening for the risk of SCD had been considered by the Committee at its March meeting however since that meeting a systematic review of test accuracy based on a larger body of evidence has been published and it had been agreed to include this in the review[1].

10.2 The Committee acknowledged that this is an extremely important public health problem as it affects young people even though it is rare and drew attention to the recent sportsmen who had collapsed as well as those who died.

10.3 Dr Mackie discussed risk of SCD and summarised that the epidemiology of these conditions is difficult to confirm and that there is very poor understanding of the course of the underlying disease.

10.4 The Committee recognised the screening programme in Italy and noted that the review had taken into account the three Italian papers based upon testing modalities and approaches in Italy. The latest review looked at evaluating the accuracy of an ECG to help identify a range of cardiovascular risks in young athletes as well as using family history and physical examinations as a testing method. The review identified that the use of an ECG was more effective to detect cardiovascular disease than any other test however to use an ECG alone would not be an adequate test. The Committee agreed that a combination of tests would necessary however would not be suitable for a population screening programme.

10.5 The Committee agreed that the inclusion of the additional systematic review did not alter the substance of the UKNSC review and it reiterated its advice that the evidence did not support the introduction of a systematic population screening programme for the risk of sudden cardiac death because:

[1] Harmon A, Zigman M, Drezner J., The effectiveness of screening history, physical exam, and ECG to detect potentially lethal cardiac disorders in athletes: a systematic review/meta-analysis. J. Electrocardiology 48(2015) 329-338

- While SCD is an important health problem, there is little peer reviewed evidence to enable an accurate assessment of the number of people suffering from SCD.

- The conditions that lead to sudden cardiac death are poorly understood and there is no evidence to guide clinicians regarding treatment or lifestyle advice when such a problem is found in a family member or when detected at a screening examination. Guidelines for the management of patients identified as being at risk are based on consensus of opinion due to a lack of high quality evidence.

- No studies reporting on test performance (sensitivity or specificity) were identified by the literature search so it is not possible to recommend its use in a national programme.

- The literature largely addresses screening in young people participating in sporting activity, and is predominantly not peer reviewed and the published outcomes have been questioned in peer reviewed literature.

- No direct evidence, for example, in a US population, was identified to conclude that an ECG or any other cardiovascular screening programme will reduce the incidence of SCD in any of the patient populations thought to be at increased risk.

Criteria	UK NSC Comments
The Condition	
The condition should be an important health problem in which the epidemiology, prevalence and natural history is understood	The conditions that lead to sudden cardiac death are poorly understood and there is no evidence to guide clinicians regarding treatment or lifestyle advice when such a problem is found in a family member or when detected at a screening examination. Guidelines for the management of patients identified as being at risk are based on consensus of opinion due to a lack of high quality evidence.
All cost-effective primary prevention interventions have been implemented as far as practicable	No studies reporting on test performance (sensitivity or specificity) were identified by the literature search so it is not possible to recommend its use in a national programme.

The Test	
Should be simple, safe, precise and validated screening test.	Current means would involve an array of tests which would not be feasible for a national programme
The distribution of test values in the target population should be known and a suitable cut-off level defined and agreed.	While SCD is an important health problem, there is little peer reviewed evidence to enable an accurate assessment of the number of people suffering from SCD. The literature largely addresses screening in young people participating in sporting activity, and is predominantly not peer reviewed and the published outcomes have been questioned in peer reviewed literature

HPV

11 Professor Julietta Patnick presented this item to the committee. HPV as a primary screen had been considered by the UK NSC at its last meeting in March 2015. Since that meeting further evidence on cost effectiveness had been commissioned for the committee to consider.

11.1 As discussed at the last committee meeting the Human Papilloma Virus (HPV) is associated with majority of cervical cancers. The use of HPV as a primary screen is supported by four large European randomised trials which reported that HPV and subsequent treatment reduces the risk of cervical cancer and is a more sensitive test than the current test of cytology. These findings are supported by a Randomised Trial of HPV Testing in Primary Cervical Screening (ARTISTIC) overseen by PHE. Professor Patnick said that the evidence showed that offering HPV as the primary test would not only provide women with a more sensitive test but it would also allow the screening interval to be extended for those women with a negative HPV result. Such a move would be both cost effective and cost saving with two economic analyses for HPV primary screening both illustrating an increase in QALY and a cost reduction. The committee considered the evidence; HPV primary screening is a more clinically and cost effective practice than the current cytology test.

11.2 Professor Patnick said there were some key risks relating to laboratory capacity and the workforce, as the reduction in cytology will require concentration in fewer laboratories and fewer staff. There is some concern that any announcement to roll out HPV primary screening may lead to premature flight from cytology. Work was in hand to look at how to mitigate these risks as any changes to the screening programme were rolled out. In England, the use of HPV was currently being piloted in six sentinel sites and if the move to HPV as a primary screen was recommended it was likely that these sites would become early implementers.

11.3 The UK NSC agreed a three month consultation on a proposal to roll out HPV as a primary screen, before a final recommendation on its use is made at the UK NSC meeting in November 2015.

FIT to replace FOBT

12 The item was presented by Professor Patnick who informed the committee that the Bowel Screening Advisory Committee (BSAC) had reviewed the findings from a pilot run by the NHS Cancer Screening Programme and concluded that faecal immunochemical testing (FIT) was a more suitable and sensitive test.

12.1 The FIT test is a self-sampling home kit which requires only one sample of stool instead of three, as currently required by the Faecal Occult Blood Test (FOBT). At the start of 2014, a six month FIT pilot began involving over 40,000 people from across England to assess what the implications may be to adopt FIT in England.

12.2 The results from the pilot studies clearly indicated that this new screening test was more sensitive and was more acceptable to the screened cohort, which resulted in an increase in participation of up to 10%. The Committee agreed with these findings and also agreed that such a move would be an easy transition as the screening pathway remains aligned with the current pathway for FOBT.

12.3 The economic model indicated that FIT was highly cost effective and had the potential to be cost saving depending on the cut off value. The Committee examined the varying cut off points and recognised that by using the current cut off point there would only be a minimum of 3% increase in the overall cost of implementing FIT. This would also manage capacity in colonoscopy clinics. Over the longer term, as endoscopy capacity

increase that the sensitivity of the test can be raised and more people with bowel cancer found and treated earlier. Though a move to FIT would be beneficial, the Committee noted that the IT infrastructure for the NHS Bowel Screening Programme would need to be reviewed if this was to be approved to ensure that the screening hubs could record the new test.

12.4 The Committee agreed a three month consultation on the proposal to offer FIT as the primary screen for bowel cancer in the NHS Bowel Screening Programme.

Action: Professor Patnick to provide Dr Mackie with the final FIT summary paper
Action: Miss Mauthoor to circulate the FIT cost effective paper to the committee

Updates

NIHR NETSCC Update (for information)

13 The Committee noted the updates

SIGN Update (for information)

14 The Committee noted the updates

Date of the next meeting

Thursday 19th November - London

ANNEX A

NSC UK National Screening Committee

WARWICK

NHS National Institute for Health Research

Cell free Fetal DNA for the detection of Down, Edwards and Patau Syndromes: Economic Model

Sian Taylor-Phillips

29/07/2015

NSC UK National Screening Committee

WARWICK

NHS National Institute for Health Research

Main models

- Current first trimester screening using combined test
- cffDNA added after combined test at 1/150
- cffDNA added after combined test at 1/1000
- cffDNA used as primary screen

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Economic Model Assumptions

NHS National Institute for Health Research

	Source	Cost	Sensitivity analysis
Total cost of combined test	NHS FASP decision planning tool 2011[50] (£26.10) inflated to 2014 prices	£27	NA
Cost of Amniocentesis	NHS FASP decision planning tool 2011[50] (£368.93) inflated to 2014 prices	£383	£515 Department of health reference costs for 2013/14
Cost of CVS	NHS FASP decision planning tool 2011[50] (£306.93) inflated to 2014 prices	£319	£515 Department of health reference costs for 2013/14
Cost of cffDNA testing	Hill et al. (2011)[49] lab costs UK	£232	£100-£500

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NHS National Institute for Health Research

Economic Model Assumptions

	Source	Estimate	Sensitivity analysis
Sensitivity of cffDNA	Our Meta-analysis pooled estimates	T21 97.1% T18 93.1% T13 82.7%	T21: 99.4% T18: 97.4% T13: 97.4%
Specificity of cffDNA	Our Meta-analysis pooled estimates	T21 99.8% T18 99.8% T13 99.8%	T21: 99.9% T18: 99.9% T13: 99.9%
Success rate of cffDNA testing in pregnancy with trisomy	Norton et al. (2015)[16] (largest study that reports failure by trisomy)	90%	NA
Success rate of cffDNA testing in pregnancy without trisomy	Norton et al. (2015)[16] (largest study that reports failure by trisomy)	97.0%	NA

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Economic Model Assumptions

	Source	Estimate	Sensitivity analysis
Acceptance of invasive test after combined	FASP 2012/13	72.4%	NA
Acceptance of cffDNA	Lewis et al. (2014)[45]	90.7% (2.9% invasive, 6.4% no further tests)	Gil et al. 57% (40% invasive, 3% no further testing)
Acceptance of invasive test after cffDNA	Gil et al. (2015)[48]	83.3%	NA

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NHS National Institute for Health Research

Results

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Economic Model Results

NHS National Institute for Health Research

	Combined test alone	cffDNA testing if combined >1/150	cffDNA testing if combined >1/1000	cffDNA testing as primary screen
Total cost (£m)	14.9 (14.9, 15)	15.1 (14.9,15.2)	22.7 (22.3,23.0)	107.8 (107.4,108.2)
Total trisomies detected	1032 (964, 1103)	1019 (600, 1256)	1129 (671,1389)	1273 (726,1568)
Test-related miscarriages of healthy pregnancy	46.1 (30,69)	2.8 (1,6)	9.7 (5,18)	8.2 (4,14)
Cost per trisomy detected through testing (£/trisomy)	14472 (13605, 15414)	14764 (12117, 24747)	20094 (16581, 33299)	84709 (68992, 148003)

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NHS National Institute for Health Research

Economic Model Results

	Combined test alone	cffDNA testing if combined >1/150	cffDNA testing if combined >1/1000	cffDNA testing as primary screen
Total cost (£m)	14.9 (14.8,15.0)	15.1 (14.9,15.2)	22.7 (22.3,23.0)	107.7 (107.3,108)
Total trisomies detected	1032 (964,1103)	1056 (626,1300)	1173 (701,1443)	1321 (762,1626)
Test-related terminations of healthy pregnancy	46.1 (30,69)	2.7 (1.1,5.6)	9.5 (4.3,17.7)	5.9 (3.1,10.3)
Cost per trisomy detected through testing (£/trisomy)	14,472 (13605, 15414)	14,265 (11707, 23746)	19,359 (15966, 31876)	81,517 (66412, 140734)

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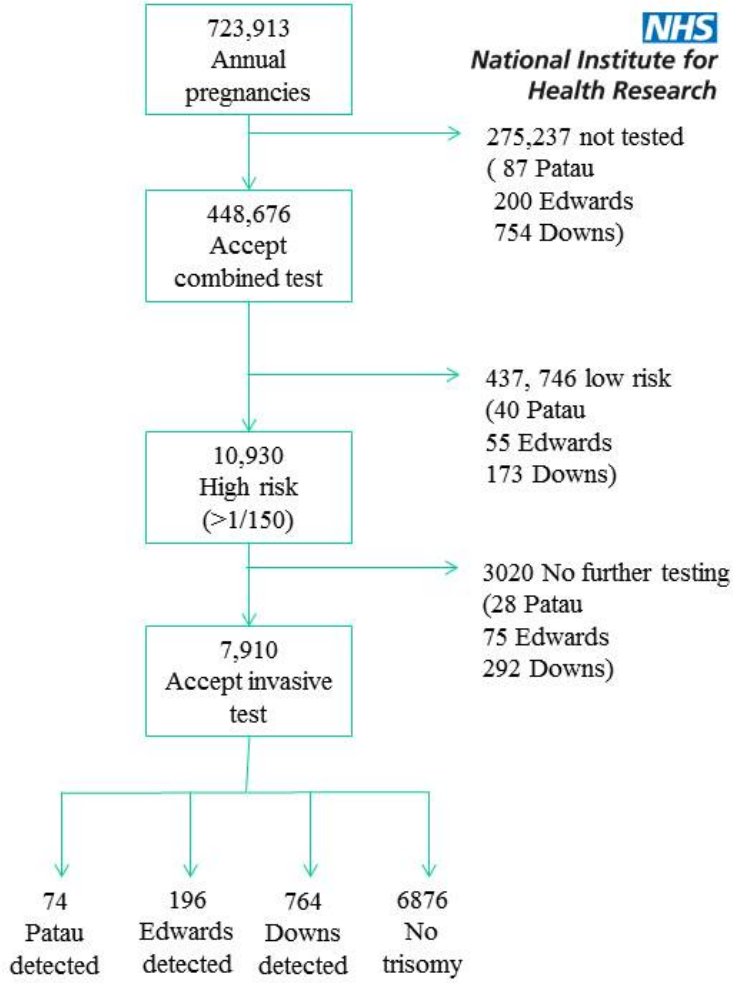
Combined test only

Outcome	Number
Test-related miscarriage	46
Downs cases identified	764
Downs cases undetected	1219
Edwards cases identified	196
Edwards cases undetected	331
Patau cases identified	74
Patau cases undetected	155
Invasive tests/trisomy detected	7.4
Cost per case detected	£14,472
Total cost (£millions)	14.9
cffDNA initial test failures	N/A



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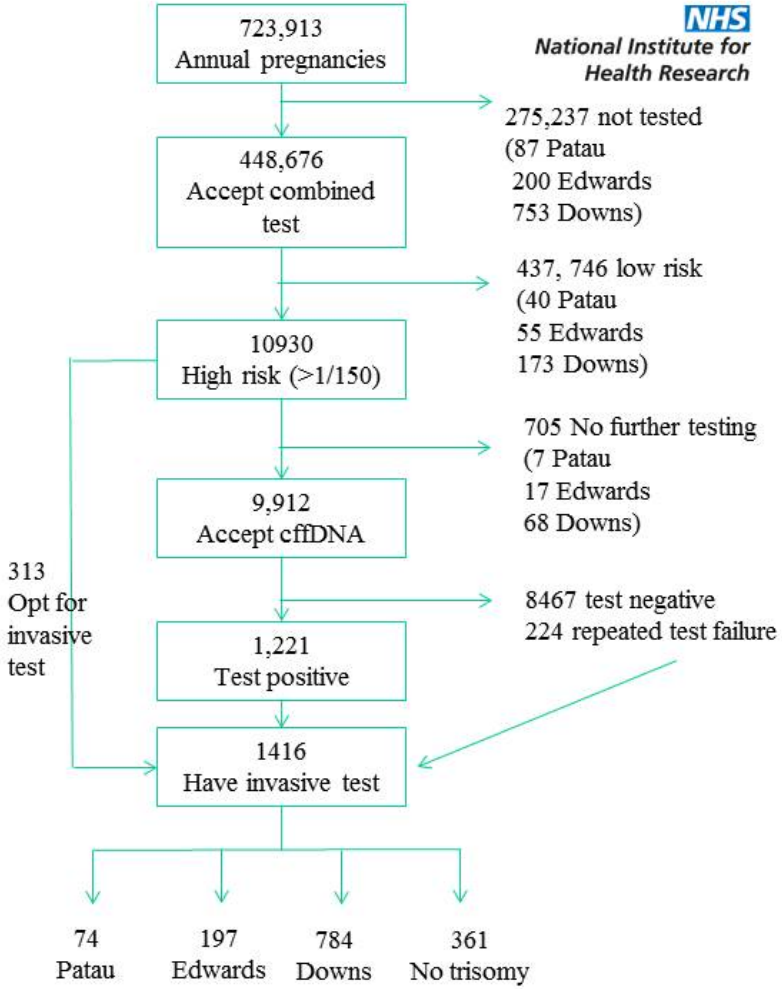
cffDNA after combined test at 1/150

Outcome	Number
Test-related miscarriage	3
Downs cases identified	784
Downs cases undetected	1198
Edwards cases identified	197
Edwards cases undetected	329
Patau cases identified	74
Patau cases undetected	155
Invasive tests/trisomy detected	1.4
Cost per case detected	£14,265
Total cost (£millions)	15
cffDNA initial test failures	385



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cffDNA as primary screen

Outcome	Number
Test-related miscarriage	6
Downs cases identified	962
Downs cases undetected	1019
Edwards cases identified	250
Edwards cases undetected	276
Patau cases identified	109
Patau cases undetected	120
Invasive tests/trisomy detected	1.7
Cost per case detected	£81,517
Total cost (£millions)	108
cffDNA initial test failures	13,410

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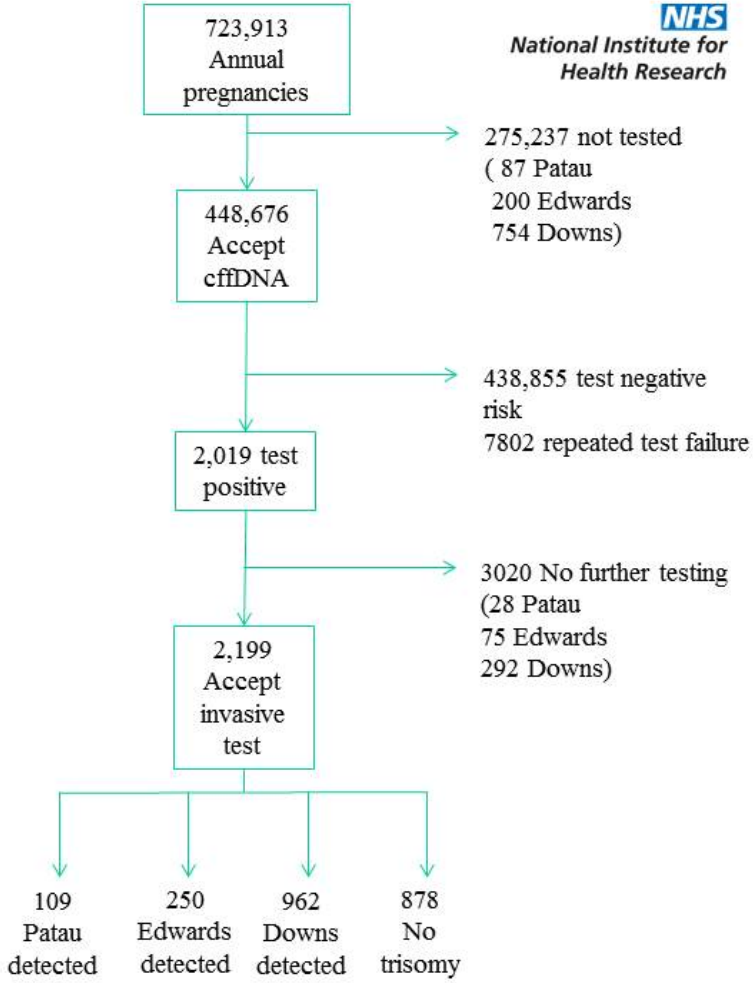

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Sensitivity analysis – change in miscarriage rate

	Combined test alone	cffDNA testing if combined test result >1/150
Reference case	46.0 (30,69)	2.8 (1.2,5.7)
Danish Registry Data	114.1 (107,121)	6.9 (3.3,12.9)
Akolekar et al. (2015)[53]	10.4 (0.6,61)	0.6 (0.03,3.6)

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Sensitivity analysis

- cffDNA £100 save £1.25m
- cffDNA £500 extra £3m
- Invasive test £515 save £1.1m
- cffDNA uptake just 55% test related miscarriages increases to 30, minimal effect on costs

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Sensitivity analysis

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- 1/150 then cffDNA scenario
- Overall proportion of pregnancies screened increased from 61% to 81%,
  - same cost per trisomy detected
  - 1.3x number of trisomies detected (extra 335)
  - 1.3x costs (extra £5m)

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Key Implementation Issues

- Economic model shows similar results over a range of possible assumptions
- Test performance excellent, but not diagnostic
- Variable failure rate
- We assumed you could block other results from cffDNA
- Combined test >1 in 5, NIPT negative

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Questions?