UK National Screening Committee

UK National Screening Committee (UK NSC)

Request for the UK NSC recommendation of a major modification to the NHS Fetal Anomaly Screening Programme:

quadruple screening test to be added to the antenatal screening pathway for Edwards' syndrome (Trisomy 18 or T18) in response to the public consultation on the rapid review

Date: 21 March 2024

Contents

1 Aim

To ask the UK National Screening Committee (UK NSC) to make a recommendation of a major modification to the NHS Fetal Anomaly Screening Programme (NHS FASP), by adding the quadruple screening test to the antenatal screening pathway for Edwards' syndrome (Trisomy 18 or T18). This is based on the evidence presented in this document.

2 Background

In 2019, the Wolfson Institute of Preventive Medicine (WIPM) submitted a proposal to the UK NSC to modify NHS FASP by using analytes from the quadruple test in the second trimester to screen for Edwards' syndrome (Trisomy 18 or T18).

The international evidence base relating to this proposal was summarised in UK NSC evidence review which reported to the FMCH in January 2021.(See Appendix A, separate document). This suggested that further work was required to understand the accuracy of the test at a threshold of 1 in 150 to align with UK practice. The FMCH agreed that, given the proposal was to offer the test in a small subset of the

screening population, the use of retrospective FASP data might be a proportionate mechanism to achieve this.

FASPs Down's syndrome Quality Assurance Support Service (DQASS) agreed to provide an analysis and in January 2022, a paper was presented to the Fetal, Maternal and Child Health Reference Group (FMCH). This summarised the modelling of the existing data on the detection of Edwards' syndrome (Trisomy 18 or T18) using the quadruple test. The existing parameters of the NHS FASP screening gestational age window, and chance cut-off, were used. The authors were asked to update the paper to include Patau's syndrome (Trisomy 13 or T13) along with Edwards' syndrome (Trisomy 18 or T18) so that the quadruple test mirrors screening in the first trimester using the combined test.

The updated April 2023 paper, referred to as the rapid review, includes modelling data for Patau's syndrome (Trisomy 13 or T13) as well as Edwards' syndrome (Trisomy 18 or T18), suggests that the quadruple screening test, which is offered to pregnant women who miss the first trimester combined screening test, can be used to screen for Edwards' syndrome (Trisomy 18 or T18) in addition to Down's syndrome (Trisomy 21 or T21).

The paper is presented in the next section.

3 The rapid review of modelled data on screening for Edwards' syndrome (T18) using the quadruple test

(Sourced from the Edward's syndrome quadruple test consultation page on GOV.UK.)

The quadruple test uses maternal age and 4 biochemical markers to calculate the chance of a baby having Down's syndrome (T21). The test is offered within NHS FASP between 14^{+2} and 20^{+0} weeks of pregnancy to those who miss, or do not complete, the first trimester combined test. There is no evidence that Inhibin levels differ between T18 and euploid pregnancies but alpha-fetoprotein (AFP), human chorionic gonadotropin (hCG) and unconjugated oestriol (uE3) have lower levels in T18 pregnancies than in euploid pregnancies. This means that the quadruple test could be undertaken using chance results specific to T18. For T13, the evidence is that Inhibin is increased but, for other quadruple test markers, levels are not substantially different from euploid pregnancies.

The UK NSC commissioned an evidence review, which found one low quality systematic review and 13 moderate to high quality observational studies showing sensitivity was variable while specificity was consistently high across chance thresholds. When using a patient-specific chance threshold of 1 in 100, sensitivity was above 65% in most studies (ranging from 57.1% to 100%) and specificity was

above 99%. However, there were applicability concerns as none of the studies were performed in the UK and none used the threshold of 1 in 150 as used in the UK.

There may be additional reasons to consider this proposal for earlier T18 and T13 detection and termination choice:

- this test would not be offered to the whole screening population of pregnant women, only a subset of women who miss first trimester screening
- women do have the opportunity to undergo additional testing for T18 and T13 at their ultrasound scan, which may help compensate for the moderate test sensitivity
- a modelling study from WIPM using serum analyte samples from T18-affected pregnancies in the UK reported a triple test sensitivity of 57% and false positive rate (FPR) of 0.19% using a ≥1 in 150 risk threshold, which is consistent with data identified by this rapid review

Current FASP pathway

There are 3 points in current pathways where it is possible to detect T18 and T13:

1. Dating scan – the primary screening method for T18 and T13 in the first trimester is the combined test. A dating scan is a necessary component of the combined test; required to measure the crown rump length and nuchal translucency (NT). T18 and T13 may be detected by ultrasound at this point but it should be noted that there is no formal first trimester fetal anomaly ultrasound screening programme in England for T18 and T13.
2. Combined test – uses maternal age, NT and 2 biochemical markers to identify the chance of T21 and T18/T13. The test is offered within NHS FASP between 10^{+0} and 14^{+1} weeks of pregnancy. The biochemical markers are free beta human chorionic gonadotropin (bhCG) and pregnancy associated plasma protein-A (PAPP-A). The combined test accounts for 86% of all tests within the programme. The detection rate (DR) for T18 exceeds the 80% target and the programme detected 89.4% (95% CI; 86.2-92.7%) of babies with T18 in 2019/20. The target detection rate (DR) for T13 is set at 80% and the programme detected 74.9% (95% CI; 67.5-82.3%) of babies with T13 in 2019/20 [footnote 1].
3. The 20-week screening scan – NHS FASP has a target DR of 95% for T18 and T13. Table 1 shows the DRs for T18 and T13 using data from the National Congenital Anomaly and Rare Diseases Registration Services (NCARDRS) for pregnancies with an expected date of delivery (EDD) 1 April 2019 to 31 March 2020.

Table 1: Detection rate for T18 and T13 2019-2020 EDD

Condition	FASP target DR	DR 18^{+0} to 20^{+6}	DR 18^{+0} to 23^{+6}	Up to 23^{+0} inc early detections
T18	95%	73.7% (CI 61.0-83.4)	79.7% (67.7-88.0)	97.7%
T13	95%	91.7% DR (CI 74.2-97.7)	92.0% (75.0-97.8)	98.9%

As shown in figures 1 and 2 below, when early detections are included the DRs exceed the 95% NHS FASP threshold.

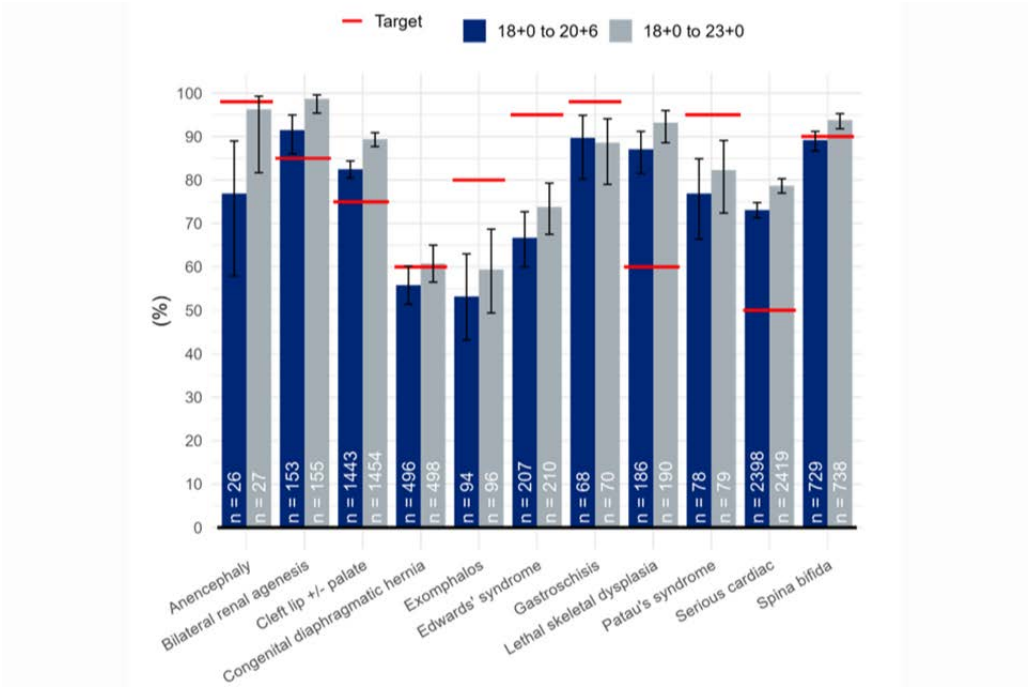

Figure 1: 18^{+0} to 20^{+6} week screening scan detection rates (%): conditions screened for as a minimum in England by gestational window, national, pooled EDD 2017/18 – 2019/20.

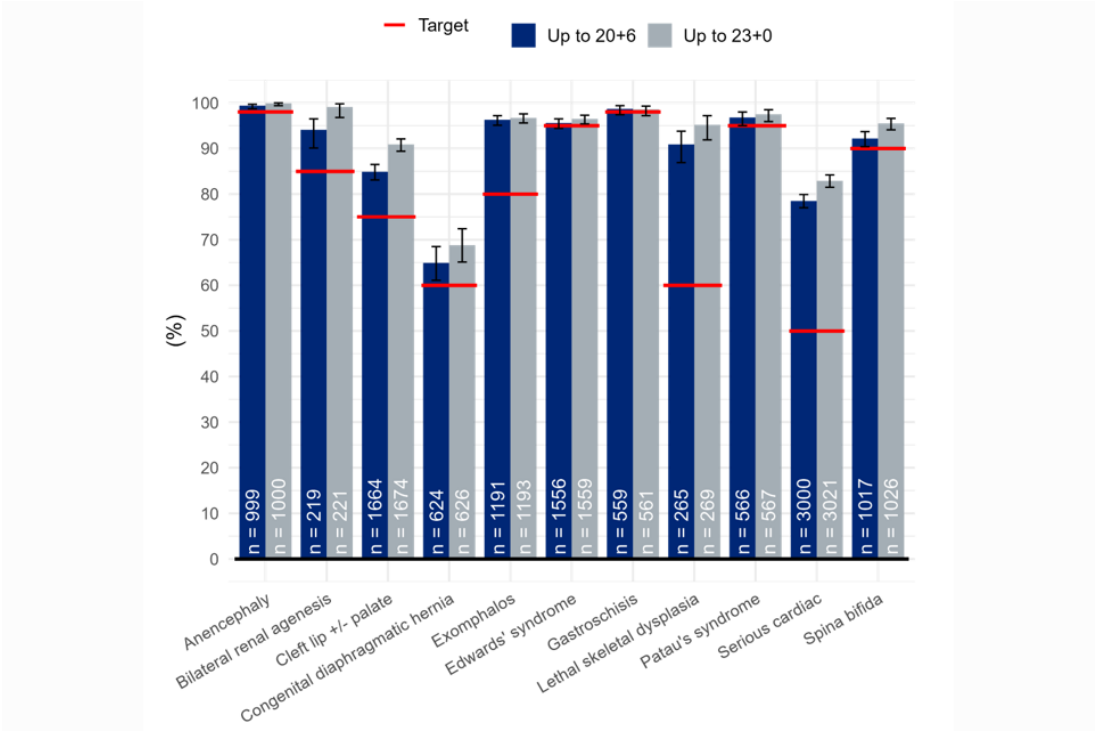

Figure 2: 18^{+0} to 20^{+6} week screening scan detection rates including early detections (%): conditions screened for as a minimum in England by gestational window, national, pooled EDD 2017/18 – 2019/20.

There is a proportion of babies with T18 and T13 who are undetected by the 20-week screening scan (Figures 3 and 4). Some women also booked too late to have a 20-week screening scan and some of these would also be too late to have the quadruple test.

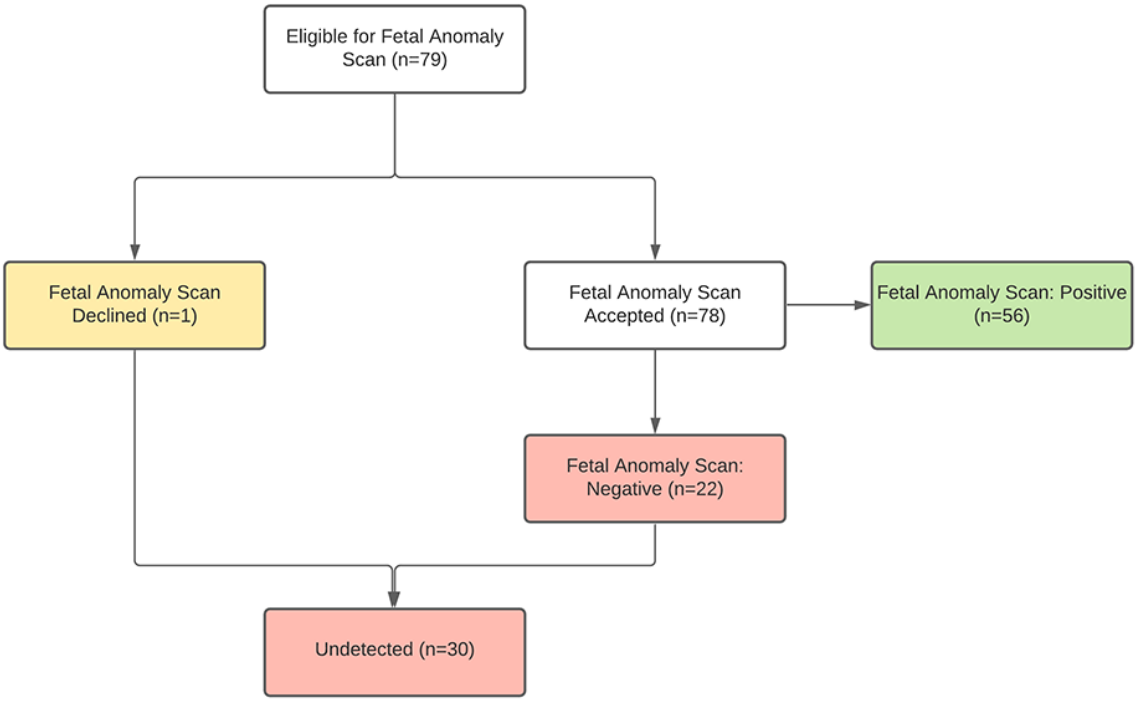

Figure 3: Babies with T18 who had a negative 20-week screening scan 2018/19. NCARDRS data.

Seven women were too late to have the 20-week screening scan.

Of the 22 women with a negative 20-week scan:

- 7 declined the combined test
- 11 had a lower chance combined test result
- 1 booked too late for the combined test and had a quadruple test
- 3 had failed combined tests because the NT was not measurable, and all went on to have quadruple test

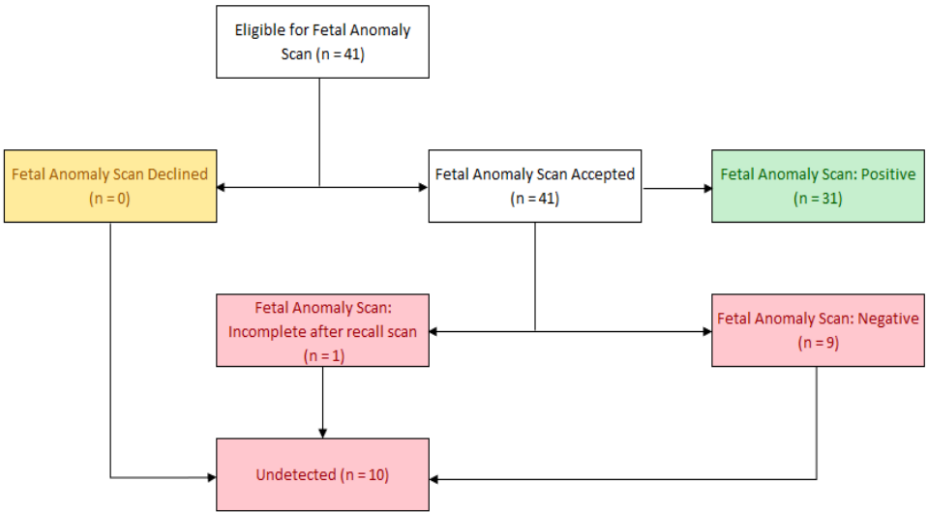

Figure 4: Babies with T13 who had a negative 20-week screening scan 2018/19 and 2019/2020 NCARDRS data.

Of the 9 women with a negative 20-week scan:

- 2 declined combined test
- 2 booked too late for combined screening
- 5 had a lower chance combined result

The quadruple test population within the screening programme

For the 14% of women who for some reason are ineligible (for example, present after 14^{+1} weeks of pregnancy) for combined testing, the second trimester quadruple test is offered for T21 but not for T18 or T13. The quadruple test population each year comprises around 70,000 women. Among these, 78 would be expected to have a T18 pregnancy and 25 would be expected to have a T13 pregnancy (Table 2).

	All	Combined	Quad	%
Unaffected	497,930	428,220	69,710	99.6%
Down's syndrome	1,334	1,147	187	0.3%
Edwards' syndrome	558	480	78	0.1%
Patau's syndrome	178	153	25	0.04%

	All	Combined	Quad	%
Total	500,000	430,000	70,000	100%
		86%	14%	

Table 2: Modelled T21/T18/T13 screened population for NHS England

Performance of quadruple testing for T18

Methodology

Screening performance was obtained from a simulation model with distributional parameters taken from the literature [footnote 2]. Data were simulated from the multivariate Gaussian distribution of log transformed multiples of the median (MoM) values of AFP, uE3 and hCG in T13, T18 and T21 pregnancies. These were then used to compute likelihood ratios for T13, T18 and T21 relative to euploid pregnancies. Bayes theorem was used to compute chance results for T18 and T13 by combining the likelihoods for the biomarkers with the maternal age specific prior probabilities. These resultant chance results for T21 and T18/T13 were compared with cut-offs of 1 in 150 to determine an age specific DR for each year of maternal age from 12 to 50. The weighted average of these age specific rates was then computed to produce a standardized DR. The weights used were obtained from the maternal age distribution of pregnancies in England and Wales in 2011 and the maternal age specific probability of euploid, T13, T18 and T21.

Similarly, standardized FPRs were computed by obtaining the likelihoods in unaffected pregnancies and then applying these to each year of maternal age from 12 to 50 years to estimate the age specific FPRs. These were then weighted according to the maternal age distribution of euploid pregnancies in England and Wales in 2011.

Results

Performance of screening depends on maternal age, for the population overall, the DR of T18 using the quadruple test is estimated to be around 75% and the FPR is estimated to be around 0.1% using a 1 in 150 at term cut-off.

The modelled performance of screening using the quadruple test with a cut-off of 1 in 150 applied separately to probabilities for T21 and T18/T13 are given in Table 3. This gives the proportions of screen positives for T21 alone, T18/T13 alone, both T21 and T13/T18 and of any of these. Performance for T13 is relatively poor

and the majority of T13 pregnancies that screen positive do so for T21, not for T18/T13. Including T13 along with T18 in the quadruple test increases the modelled detection rate of T13 by less than 1%.

Condition	+ve for T21 alone	+ve for T18/T13 alone	+ve for both	+ve for any
T21	75.6%	0.1%	4.5%	80.2%
T18	1.6%	62.1%	10.6%	74.3%
T13	21.6%	0.9%	8.0%	30.5%
Euploid	3.2%	0.1%	0.0%	3.3%

Table 3: Performance of screening (screen +ve proportions) for the quadruple test obtained using a term cut-off of 1 in 150 for the probability of T21 and T18/T13.

The poor performance of screening for T13 is a consequence of low prior probability for T13 and the distribution of markers in T13 pregnancies. The prior probabilities of T13, T18 and T21 for maternal ages 20, 21, 22, 23 and 24 are shown in Table 4. For T18, they are about one twelfth as high as those for T21. For T13 they are about one thirtieth of those for T21. This means that the markers must be strongly informative of T18 or T13 relative to T21 to make the posterior probability of T18 or T13 higher than that of T21.

The median MoM levels for T13, T18 and T21 are shown in Table 5. The median marker profile for T18 is very distinct from that of T21 and from euploid pregnancies. As a consequence of this, T18 pregnancies are well distinguished from both T21 and euploid pregnancies in the probability calculations. The median profile for T13 is not that distinguishable from euploid pregnancies, nor from T21 pregnancies. This, together with the low prior probability for T13 relative to T21, is why the majority of T13 pregnancies detected are detected based on the T21 probability rather than T18/T13 probability.

Maternal age (years)	T21	T18	T13
20	1 in 1500	1 in 18000	1 in 43000
21	1 in 1300	1 in 16000	1 in 38000
22	1 in 910	1 in 11000	1 in 25000

Maternal age (years)	T21	T18	T13
23	1 in 380	1 in 5000	1 in 11000
24	1 in 110	1 in 1000	1 in 3000

Table 4: Maternal age specific prior probabilities

Marker	T21	T18	T13
AFP	0.74	0.72	–
uE3	0.70	0.47	–
hCG	2.05	0.36	–
Inhibin	2.18	–	1.61

Table 5: Median MoM values for second trimester MoM values. The symbol – indicates that there is no evidence that the medians differ from Euploid pregnancies.

Conclusion

It is possible to produce quadruple test probabilities for T21 and for T18/T13 so the quadruple test in the second trimester is aligned with the combined test in the first trimester. However, with the quadruple test markers T13 is not well distinguishable from euploid pregnancies nor from T21 pregnancies. This means that screening performance for T13 is relatively poor and that the majority of T13 pregnancies that are screened positive do so for T21, but not for T18/T13.

We conclude that the option of screening for T18 could be made available in the NHS FASP second trimester quadruple test, but not screening for T18/T13.

Authors

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Original paper January 2022, updated April 2023

1. Data source – NCARDRS data 2019/20. ↩

2. Bestwick JP, Huttly WJ, Wald NJ. Detection of trisomy 18 and trisomy 13 using first and second trimester Down's syndrome screening markers. J Med Screen. 2013 Jun;20(2):57-65. doi: 10.1177/0969141313484904. Epub 2013 May 28. Erratum in: J Med Screen. 2015 Mar;22(1):52-4. PMID: 23761419. ↩

4 Consultation

The UK NSC consulted on the rapid review of modelling data and sought views from stakeholders and the public on the question:

Does the evidence from this rapid review demonstrate that the quadruple test is accurate enough to be added to the antenatal screening pathway for Edwards' syndrome (Trisomy 18)?

A 2-week consultation was hosted on the GOV.UK website and publicised on the UK NSC blog. Direct emails were sent to 57 stakeholders. (Annex A)

The public consultation opened on 21 February and ended on 6 March 2024.

The total number of consultation responses received was 10.

Comments were received from the following 10 stakeholders (see Annex B for comments):

- Society of Radiographers
- Antenatal Screening Wales, Public Health Wales
- Illumina
- Genetic Alliance on behalf of Genetic Alliance, SOFT UK and Antenatal Results and Choices (ARC)
- The Royal College of Midwives
- One professor of preventative medicine
- One antenatal and newborn specialist screening midwife
- One antenatal and newborn screening co-ordinator on behalf of an antenatal and newborn screening team
- Two antenatal and newborn screening co-ordinators

Key points raised by stakeholders are summarised below:

- All the antenatal and newborn screening co-ordinators and midwives who responded stated they were supportive of the introduction of the quadruple test to the Edwards' syndrome (Trisomy 18 or T18) screening pathway. Reasons cited included that this would enable early diagnosis, support women's choice, and enable equitable screening.
- The Society of Radiographers was supportive of the introduction of the quad test as an option for screening for Edwards' syndrome (Trisomy 18 or T18). The Society's response included the suggestion for additional training to

explain the rationale for the quadruple test being included in the Down's syndrome (Trisomy 21 or T21) and Edwards' syndrome (Trisomy 18 or T18) screening pathways, but not Patau's syndrome (Trisomy 13 or T13).

- Genetic Alliance responded on behalf of 3 stakeholders who said that the introduction of the quadruple test to the Edwards' syndrome (Trisomy 18 or T18) screening pathway would enable earlier diagnosis, which is important to parents.
- The response from Antenatal Screening Wales noted the differences between the screening pathways in England and Wales, but confirmed the rapid review demonstrates that the quadruple test is accurate enough to be added to the antenatal screening pathway for Edwards' syndrome. The response also noted that England offers quadruple testing for Down's syndrome (Trisomy 21 or T21) to twin pregnancies whereas Wales does not and raised the question as to whether this test has been considered for multiple pregnancies.
- The response from Illumina cited the high detection rate and low false positive rate of non-invasive prenatal testing (NIPT) for Edwards' syndrome (Trisomy 18 or T18). A selection of examples of published literature were cited to support the accuracy of NIPT in detecting Edwards' syndrome. There was a request to consider NIPT as the primary screening test at different points in the FASP pathway however this is outside the scope of this review and would require fundamental overhaul of the screening programme. This would require a separate submission and the Secretariat will contact this stakeholder regarding this. There was also a request for further information to be made available relating to the evidence underlying the rapid review, including the one low quality systematic review and 13 moderate to high quality observational studies. The Secretariat will send the initial (2021) UK NSC review to this stakeholder.

Concerns raised by stakeholders on the consultation included:

- **Antenatal Screening Wales noted that the modification was a relatively minor change and that the consultation question was narrow in scope. The timescales of the consultation and the narrowness of the consultation question prevented feedback being obtained from biochemistry and clinical advisors about any other implications of the proposed programme modification, including cost implications.**

- **The Illumina response requested an opportunity to open the discussion on the use of NIPT as the primary screening test at different points in the FASP pathway and this has been addressed above.**

Responses by stakeholders which were not in response to the rapid review:

- The professor of preventative medicine stated his support for the introduction of the quadruple test to the Edwards' syndrome (Trisomy 18 or T18) screening pathway. This was based on his review of published evidence. It was not in response to the rapid review.

The Royal College of Midwives stated it was not in a position to comment on the rapid review.

5 Recommendation for the UK NSC

In summary, the responses to the consultation question were limited in number, perhaps reflecting the uncontroversial nature of the modification. Eight were explicitly supportive of the introduction of the quadruple screening test to the antenatal screening pathways for Edward's syndrome (Trisomy 18 or T18). One response was on behalf of 3 stakeholders. One of these responses was in response to published literature rather than the consultation rapid review itself.

One stakeholder was not in a position to comment on the consultation, although no reason was provided for this. One response was from a company with a stake in NIPT, the in-service evaluation of which ends in June 2024.

In light of the above, the UK NSC is requested to make a recommendation in support of a major modification to the NHS Fetal Anomaly Screening Programme (NHS FASP) by adding the quadruple screening test to the antenatal screening pathway for Edwards' syndrome (Trisomy 18 or T18).

This is based on the evidence presented in the rapid review paper detailed in this document, along with the responses to the public consultation, also included in this document.

Annex A: List of Organisations Contacted

1. Antenatal Results and Choices
2. BLISS
3. British Heart Foundation
4. British Pregnancy Advice Service
5. CDH UK
6. Child Growth Foundation
7. Children's Heart Federation
8. CLAPA
9. Contact a Family
10. CRUSE
11. DIPex
12. Down's Heart Group
13. Down's Syndrome Association
14. Down Syndrome Education International
15. Down Syndrome Research Foundation UK
16. Elfrida Society
17. Faculty of Public Health
18. Genetic Alliance UK
19. Little Hearts Matter
20. Marie Stopes International
21. MENCAP
22. NHS England NHS ANNB Screening Programmes
23. PHG Foundation
24. Restricted Growth Foundation
25. Royal College of General Practitioners
26. Royal College of Midwives
27. Royal College of Obstetricians and Gynaecologists
28. Royal College of Physicians
29. Royal College of Physicians and Surgeons of Glasgow
30. Royal College of Physicians of Edinburgh
31. Screening information inbox
32. SHINE Charity
33. Society of Radiographers
34. SOFT UK
35. Stillbirth and Neonatal Death Charity
36. Tiny Tickers
37. Together for Short Lives
38. Wolfson Institute of Preventive Medicine

UK National Screening Committee

Annex B: Consultation Responses (in order of receipt)

, Professional Policy Advisor, The Royal College of Midwives

The RCM have received an invitation to respond to a consultation on the on the addition of the quadruple test to the antenatal screening pathway for Edwards' syndrome (T18).

Unfortunately, we are not in a position to respond on this occasion.

, Antenatal and Newborn Screening Co-ordinator on behalf of , Antenatal and Newborn Screening Co-ordinator; , Deputy Screening Midwife; , Midwife; , Midwife; , Failsafe Officer; , Failsafe Officer and , Screening Administrator, West Suffolk Hospital Antenatal & Newborn Screening Team

Following reading the consultation information the ANNB screening team at West Suffolk Hospital would support Edwards' syndrome being added to quadruple screening. We feel the evidence supports increased detection and choice for our families.

, Professor of Preventative Medicine, UCL Institute of Health Informatics

I strongly support using the Quadruple test markers in antenatal screening for trisomy 18 (Edwards' syndrome). The screening performance is good and there is, in my view, no valid reason for not using the Quadruple test markers in antenatal screening for trisomy 18. The Alpha software from Logical Medical Systems Ltd. has done so for over 10 years and such screening has been undertaken since then in many countries.

This assessment arises from evidence in the published literature. I am not commenting on the consultation ""rapid review"" that was attached to your email

[redacted], Antenatal & Newborn Screening Co-ordinator, UCHL

Having read the rapid review evidence, I think there is a strong case for including T18 in the quadruple test. I think it will also be welcomed by women – particularly those who attend for CST but are unable to have it, particularly if the NT is not measurable or if they have CRL >84mm (which is the most common reason for women needing quad unexpectedly at our unit).

Availability of more screening through quad will also help reduce the inequalities between units that do carry out more early anomaly screening at dating scan and those that don't, as women attending units who do no extra anomaly screening will potentially be given more information earlier than they currently would be, whereas in a unit that is looking for more fetal anomalies at early scan would likely pick up more of these cases earlier thus getting the woman into the FMU pathway outside of FASP which is great for them but not equitable.

[redacted], Antenatal & Newborn Screening Specialist Midwife, Queen Alexandra Hospital

Having read the rapid review evidence and from the data presented at the recent ANNB FASP forum, I agree that the option of screening for T18 should be made available in the NHS FASP second trimester quadruple test but not screening for T13. In my experience of counselling women who have missed 1st trimester screening and are offered 2nd trimester screening this would be an acceptable, and in many cases preferable, option.

[redacted], Antenatal & Newborn Screening Co-ordinator

As an antenatal and newborn screening coordinator, I think the evidence presented does demonstrate that the quadruple test is accurate enough to screen for T18. The detection rate is comparable with that of T21 for the quadruple test and with a lower false positive rate.

From experience, I think the test would be welcomed for the group of women who are either ineligible for/or unable to complete the first trimester screen; and am aware of several cases within my own Trust where quadruple screening for T18 may have led to an earlier diagnosis.

I look forward to seeing it implemented.

[redacted], Consultant in Public Health, Antenatal Screening Wales, Public Health Wales

The consultation question itself is quite narrow but, in answer to that, we think that the review does demonstrate that the quad test is accurate enough to be added to the antenatal screening pathway for Edwards' syndrome.

From conversations outside this consultation, we understand that there are differences in test performance with maternal age, which would need to be considered but is not explored in the consultation document.

The implication for us in Wales would be that women who had initial opted for Downs syndrome, Edwards' syndrome and Patau's syndrome screening would have two opportunities to undergo the screening, at 12 weeks and at 15+ weeks, and then also at the 20 week anomaly scan. It would be a minor change to the pathway in terms of implementation and would allow earlier detection for some. Whilst our standards say that the detection rate should achieve a minimum of 80% which this does not, we think that it does add benefit.

There are some differences between the antenatal screening pathways in England and Wales which, whilst small, would have implications for the implementation of any changes. In Wales women are consented for screening for the three trisomies as a group, unlike in England. We know that some women consented for Edwards' syndrome screening are not actually having it if they cannot have the combined test, so this additional offer would be beneficial. Another difference between England and Wales is that England offer quad testing for Down's syndrome to twin pregnancies whereas Wales do not. Has this test been considered for multiple pregnancies?

We would have liked to get feedback from biochemistry and our clinical advisors about any other implications of this, including cost implications, but timescales did not allow and this is outwith the scope of the question.

[redacted], Genetic Alliance, Policy and Stakeholder Engagement Manager, Genetic Alliance response on behalf of Genetic Alliance, SOFT UK and Antenatal Research and Choices (ARC)

Having considered and consulted with our member organisations Antenatal Research and Choices (ARC) and Soft UK, we are supportive of the proposals. The addition of a quadruple test means it can diagnose Edwards' syndrome significantly earlier and we know this is very important to parents.

[redacted], Professional Officer on behalf of the Ultrasound Advisory Group, Society of Radiographers

The Ultrasound advisory group at the Society of Radiographers support the introduction of the quad test as an option for screening for trisomy 18.

It was suggested that additional training for staff to explain why it can be offered for T18 and not T13, along with the value of the 20 week scan is important and that should include sonographers.

[redacted], Senior Manager, Market Access EMEA, Illumina

Please find the Illumina response to the “Edwards’ syndrome screening quadruple test consultation”, closing today March 6 ,2024. Illumina would like to highlight the high detection rate and low false positive rate of non-invasive prenatal testing (NIPT) for Edwards’ syndrome, and to clarify the evidence base underlying the consultation to allow more meaningful input from stakeholders. We look forward to feedback and further discussion on this consultation, the value of non-invasive prenatal testing in the second trimester for Edwards’ syndrome (in addition to other common trisomies), as well as across gestational ages.

Response to “Edwards’ syndrome screening quadruple test consultation” UK National Screening Committee Department of Health and Social Care

To whom it may concern,

Thank you for giving stakeholders the opportunity to comment on the proposed amendments to the fetal anomaly screening program to allow the use of the quadruple test in the second trimester to screen for Edwards’ syndrome (Trisomy 18 or T18)[1] .

Illumina is a global leader in DNA sequencing and array-based technologies, serving customers in the research, clinical and applied markets with the aim to improve human health. Our products are used for applications in the life sciences, oncology, reproductive health, and other emerging segments. Illumina is one of the manufacturers of an in-vitro diagnostic (IVD) NGS-based Non-Invasive Prenatal Test (NIPT) VeriSeq NIPT Solution v2 currently used in the UK national health service as part of the prenatal screening programme. Illumina’s NGS-based NIPT solution is based on whole-genome sequencing (WGS) and intended for use as a screening test for fetal aneuploidies from maternal peripheral blood in pregnancies of at least 10 weeks gestation. NGS-

based NIPT provide information on the aneuploidy status of chromosomes: 21, 18, 13, X, and Y.

Illumina would like the steering committee consider the use of non-invasive prenatal testing (NIPT) for this population to ensure more accurate screening of T18 (as well as T21 and T13). Studies have shown NIPT has a higher detection rate, and lower false positive rate compared to the quadruple screen for T18 and represents a better use of resources for pregnant women in second trimester for women who have missed first trimester combined screening, as well as across all gestational ages.

Non-Invasive Prenatal Testing (NIPT)

Illumina would propose to use NIPT as a first-tier test for women between 14+2 and 20+0 weeks of pregnancy who miss, or do not complete, the first trimester combined test. It is more accurate, is used in clinical routine or in clinical settings in many countries including the UK (through the ongoing evaluative rollout) and can be implemented using existing infrastructure resulting in a more efficient use of resources in this population. The available evidence for the diagnostic accuracy of NIPT for the detection of T18 is much more robust, is validated, and is built upon extensive clinical experience.

A brief summary of selected studies highlighting the high detection rate and low false positive rate of NIPT in large populations in clinical practice:

La Verde et al 2021[2]

- o This study describes the clinical practice and performance of NIPT as a screening method for T21, 18, and 13 in a general Italian pregnancy population comprising 36,456 patients referred between April 2017 and September 2019

- o The authors highlight the excellent detection rates and false positive rates of whole genome sequencing-based NIPT reporting ▪ Sensitivity of NIPT of 100.00% for T21, T18, and T13, with false positive rate of 0.02% for T18 –

Borth et al 2021[3]

- o This study describes the performance of NIPT in 13,607 pregnancies in a single centre in Germany using the VeriSeq NIPT Solution v2 assay from Dec 2017 to April 2019

- o The authors report high sensitivities and specificities of ≥98.89% for T13, T18 and T21 and a positive predictive value of 82.6% for T18 –

Gil et al 2017[4]

- o This meta-analysis synthesised evidence between January 2011 and 31 Dec 2016 comprising of 35 studies reporting on clinical validation or implementation studies of maternal blood cell-free DNA analysis and the performance of screening for trisomies 21, 18 and 13 and sex chromosome aneuploidies
- o In a total of 563 cases of trisomy 18 and 222,013 non-trisomy 18 singleton pregnancies, the weighted pooled detection rate and false positive rate were 97.9% (95% confidence interval 94.9-99.1%) and 0.04% (95% CI, 0.03-0.07%), respectively
- o The authors conclude screening by analysis of cfDNA in maternal blood in singleton pregnancies could detect >99% of fetuses with trisomy 21, 98% of trisomy 18 and 99% of trisomy 13 at a combined false positive rate of 0.13%
  - ▪ Note this meta-analysis does include several NIPT technologies and types of studies, although does support the value of NIPT broadly as a very accurate screening test

A protocol that maximises detection of common trisomies across all gestation by using first-tier NIPT (in place of quadruple test for T21 as well as the proposed use for T18) would be implementable within the existing infrastructure for NIPT in the UK through the evaluative rollout. a. Many professional societies are now recommending NIPT as a first line screening test [5,6] . Reorganization of laboratory infrastructure to shift from quadruple testing to NIPT may help provide necessary resources for efficient implementation of NIPT alongside current pathways for women who missed first trimester screening.

Illumina would like to request further information be made available relating to the evidence review underlying this consultation, including the one low quality systematic review and 13 moderate to high quality observational studies. It would be important to have consultation on the interpretation, and applicability in UK practice of modelling done on the basis of these studies, versus available evidence of the accuracy of NIPT in similar clinical settings. Illumina applauds the NSC for looking for new ways of providing aneuploidy screening for women in the UK. We have intended to summarize relevant up-to-date information in our response for your consideration and would welcome the opportunity to provide further evidence as required to demonstrate the value of broadened access to NIPT across all gestational ages including for women presenting at week 14+2 to 20+0 weeks who miss or do not complete the first trimester combined test. Illumina has extensive experience in the implementation of a

regulated product for NIPT and we look forward to working in partnership with the NSC and to continue this dialogue. Our contact details are available below.

With regards

[1] UK National Screening Committee. Open Consultation- Edwards' syndrome screening quadruple test consultation. Feb 2024. Available online at: https://www.gov.uk/government/consultations/addition-of-quadruple-test-to-edwards-syndrome-screening-pathway/edwards-syndrome-screening-quadruple-test-consultation#fnref:2

[2] La Verde et al. Performance of cell-free DNA sequencing-based non-invasive prenatal testing: experience on 36,456 singleton and multiple pregnancies. BMC Med Genomics. 2021; 14(1):93

[3] Borth et al. Analysis of cell-free DNA in a consecutive series of 13,607 routine cases for the detection of fetal chromosomal aneuploidies in a single center in Germany. Arch Gynecol Obstet. 2021; 303(6): 1407-1414.

[4] Gil et al. Analysis of cell-free DNA in maternal blood in screening for aneuploidies: updated meta-analysis. Ultrasound Obstet Gynecol. 2017; 50(3):302-314

[5] American College of Obstetricians and Gynecologists' Committee on Practice Bulletins—Obstetrics; Committee on Genetics; Society for Maternal-Fetal Medicine. Screening for fetal chromosomal abnormalities: ACOG practice bulletin, number 226. Obstet Gynecol. 2020;136(4):e48–e69

[6] Dungan J.S. et al. Non-invasive prenatal screening (NIPS) for fetal chromosome abnormalities in a general-risk population: an evidence-based clinical guideline of the American College of Medical Genetics and Genomics (ACMG) Genet Med. 2023;25(2)