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Guidance

Screening for Down’s syndrome, Edwards’ syndrome and Patau’s syndrome: NIPT

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This operational guidance is for people offering non-invasive prenatal testing (NIPT) screening for Down's syndrome (T21), Edwards' syndrome (T18) and Patau's syndrome (T13) and includes information on:

- eligibility for NIPT within NHS FASP
- laboratory requirements for NIPT
- blood sampling and transport
- reporting NIPT results

This guidance should be read alongside the FASP programme handbook (https://www.gov.uk/government/publications/fetal-anomaly-screening-programme-handbook).

In this publication, we use the terms 'woman' and 'women' to refer to anyone able to become pregnant, including trans men. Trans men who are pregnant should be offered the same antenatal and newborn screening tests as other pregnant individuals.

PHE Screening recommends the offer of NIPT screening for T21, T18 and T13, following a higher chance result from the combined or quadruple test in singleton and twin pregnancies. A higher chance result is between 1 in 2 and 1 in 150.

As part of the NHS FASP care pathway (https://www.gov.uk/government/publications/fetal-anomaly-screening-care-pathways) NIPT screens for T21, T18 and T13 and will not screen for other chromosomal conditions or assess the baby's sex.

Following a higher chance result from the combined or quadruple test, women must have a discussion with a healthcare professional about their results. Women can choose to have:

- no further testing
- NIPT screening
- prenatal diagnosis (PND), such as chorionic villus sampling (CVS) or amniocentesis (https://www.gov.uk/government/publications/cvs-and-amniocentesis-diagnostic-tests-description-in-brief)

For women choosing to have NIPT, the options would be:

- T21, T18 and T13
- T21 only
- T18 and T13 only

NIPT screening will report individual chance results for T21, T18 and T13.

During this discussion, women should be informed that the laboratory may keep NIPT screening samples for quality assurance (for example, validation) and testing development purposes for up to 5 years. The healthcare professional should inform the laboratory if a woman does not want her sample to be kept for these purposes. These discussions (including the decision on the retention of samples) must be recorded in the woman's maternity notes.

1. Eligibility

1.1 Inclusions

As part of the NHS FASP evaluative rollout, NIPT can be offered and performed:

- when a woman receives a higher chance result for T21 or a joint higher chance result for T18 and T13 from the combined test
- when a woman receives a higher chance result for T21 from the quadruple test
- in both singleton and twin pregnancies
- up to 21 weeks and 6 days (21^{+6}) of pregnancy

Women with in-vitro fertilisation (IVF) or donor egg pregnancies are eligible for the offer of NIPT. The relevant details must be recorded accurately on the NIPT screening request form.

1.2 Exclusions

As part of the NHS FASP evaluative rollout, NIPT cannot be offered and performed:

- when a woman receives a lower chance result for T21, T18 or T13 from the combined or quadruple test
- in higher multiple pregnancies (triplets or more)
- after 21^{+6} weeks of pregnancy

Also, NIPT cannot be offered and performed as part of the NHS FASP pathway when a pregnant woman has:

- cancer, unless in remission, as NIPT may detect cell free DNA (cfDNA) in the maternal blood which is released by a cancerous tumour
- received a blood transfusion in the previous 4 months, as studies show that donor DNA in blood transfusion recipients lasts for several months, sometimes longer
- had bone marrow or organ transplant, as donor DNA will be present
- immunotherapy in the current pregnancy, excluding intravenous immunoglobulin (IVIg) treatment
- had stem cell therapy, as this will depend on whether she has received her own stem cells or stem cells from a donor (certain methods of NIPT are not suitable for stem cell transplants)
- a vanished twin pregnancy (an empty second pregnancy sac or a second pregnancy sac containing a non-viable fetus), as there is evidence to suggest that the placenta can continue to shed cell free fetal DNA (cffDNA) even after the baby has died
- Down's syndrome or a balanced translocation or mosaicism of T21, T18 or T13

1.3 Uncertain eligibility criteria

To confirm eligibility for NIPT screening, contact the laboratory before taking a NIPT sample when the woman has any other chromosomal condition other than T21, T18 or T13. This is because it may affect the analysis of NIPT.

2. Laboratory requirements

Genomic laboratories performing NIPT screening must be accredited by the UK Accreditation Service (http://www.ukas.com/) (UKAS) and participate in Genomics Quality Assessment (https://www.genqa.org/) (GenQA).

2.1 Data fields for the NIPT laboratory request form

NIPT laboratory request forms must include, as a minimum, the required data fields outlined in NIPT screening request form: minimum data field requirements (https://www.gov.uk/government/publications/screening-for-downs-syndrome-edwards-syndrome-and-pataus-syndrome-non-invasive-prenatal-testing-nipt).

NHS FASP recommends these minimum data fields are included when request forms are developed. Software and data entry methods may vary.

2.2 Blood sampling and transport

Blood sampling

The process for obtaining an NIPT blood sample is as outlined below.

1. Take blood sample using cell stabilising tube provided by the individual laboratory, in line with the requirements outlined below.
2. Mix immediately by inverting at least 10 times for all samples.
3. If the venepuncture is unsuccessful or if you obtain less than the required full sample at the first attempt, discard and start again with a fresh cell stabilising tube.
4. After a second attempt if you are still unable to obtain a full sample, contact the individual laboratory for further guidance.

The individual laboratory blood sample requirements are outlined below.

Central and South GLH (Birmingham)

One full Streck cell stabilising tube (minimum 7ml of blood)

South East Thames GLH (St. George's)

One full Streck cell stabilising tube (minimum 10ml of blood)

North Thames GLH (Health Service Laboratory (HSL))

Two full tubes (minimum 6ml of blood in each), in either:

- Roche CE-IVD Cell-Free DNA (white cap) collection tube
- Streck (tiger cap) cell stabilising tube

NIPT samples must not be refrigerated.

If the sample is not transported to the laboratory immediately, store at room temperature and then send as soon as practically possible. NIPT samples should be received by the laboratory in ≤ 2 working days of sample draw (FASP NIPT-S02 (https://www.gov.uk/government/publications/screening-for-downs-syndrome-edwards-syndrome-and-pataus-syndrome-non-invasive-prenatal-testing-nipt/experimental-fasp-nipt-metrics#fasp-nipt-s02-test-timely-receipt-of-nipt-sample)).

Transporting the sample

NIPT laboratories are responsible for providing:

- specialist cell stabilising tubes
- NIPT request forms
- packaging for sample transport
- the method of sample transport from the maternity service to the laboratory

The process for transporting an NIPT blood sample is outlined below.

1. Place the NIPT blood sample (specimen tube) into protective packaging provided by the individual laboratory. Do not refrigerate.
2. Put the protective packaging, with the NIPT laboratory request form, into P650 and UN3373 compliant transport packaging provided by the individual laboratory. Do not refrigerate.
3. The requestor should inform the NIPT laboratory that a sample is being sent to them for analysis. The laboratory should confirm that the sample has arrived.
4. Samples should be received by the NIPT laboratory in ≤ 2 working days from the day of collection. Day of sample draw is counted as day 0.

NIPT samples must not be refrigerated.

Local guidance should be in place between the NIPT laboratory and maternity service to make sure samples are processed in a timely manner. The laboratory must have processes in place for:

- recording receipt of the NIPT sample
- contacting the provider if the sample is not received within 5 calendar days of dispatch
- dealing with incomplete information on the request form
- dealing with any unacceptable samples that require a repeat (all requests including repeat samples should be tracked from request until maternity services have confirmed receipt of the results)

3. Reporting NIPT results

All women who receive a higher chance NIPT result must be offered the option of:

- PND
- no further testing

In some cases, NIPT may fail to give a result. 'No result' is where a 'fit for analysis' sample was received in the laboratory and it has failed to generate a result at any point of the analytical or reporting process.

In cases where 'no result' is obtained from the initial NIPT sample, providers must offer:

- one further NIPT sample
- PND
- no further testing

NIPT may fail again on the second sample.

A woman must be ≤ 21^{+6} weeks of pregnancy when the first NIPT sample is taken.

A second NIPT sample can be offered and taken even if the woman is more than 21^{+6} weeks, in the following cases when a:

- sample is rejected
- 'no result' report is issued

FASP NIPT-S03 (https://www.gov.uk/government/publications/screening-for-downs-syndrome-edwards-syndrome-and-pataus-syndrome-non-invasive-prenatal-testing-nipt/experimental-fasp-nipt-metrics#fasp-nipt-s03-test-turnaround-time-nipt) outlines expected turnaround times for NIPT results to maternity services.

All NIPT results will be reported and sent to providers by the individual laboratories as outlined below.

Central and South GLH (Birmingham)

Report will be sent electronically.

South East Thames GLH (St. George's)

Report will be issued on the online portal and providers notified by email that the report is available.

North Thames GLH (HSL)

Report will be sent by encrypted email.

3.1 NIPT results

NIPT results are reported as either lower chance or higher chance. A numerical value is not reported.

NIPT results must only be reported according to the woman's choice on the conditions screened for. For example, a lower or higher chance result at term for:

- T21, T18 and T13
- T21 only
- T18 and T13 only

NIPT screening will report individual chance results for T18 and T13. This is unlike the combined test which reports a joint chance result for these conditions. For example, when a woman chooses NIPT screening for T18 and T13 she will receive both:

- a lower or higher chance result for T18
- a lower or higher chance result for T13

In twin pregnancies, the higher chance result report should state that one or both babies may have the condition screened for.

Women should expect their NIPT results around 2 weeks from sample collection.

3.2 NIPT result report contents

Only results and comments relating to the conditions screened for as part of the NHS FASP screening pathway should be included on the NIPT result report, for example T21, T18 and T13.

The NIPT result report should include all the information listed below as a minimum.

Patient ID

The report should include:

- surname
- forename(s)
- NHS number (or equivalent)
- hospital number
- DOB

Sample information

The report should include:

- sample type (please specify NIPT screening)
- date of NIPT sampling
- is this a repeat sample? Yes or No
- date of sample receipt in the laboratory
- details of requestor

Clinical information

The report should include:

- gestational age (in weeks and days) by ultrasound at time of NIPT sampling
- singleton or twin pregnancy
- chorionicity in twin pregnancy (please include one of these options: monochorionic, dichorionic or unknown)

Reporting information

The report should:

- include the date that the report was authorised in the laboratory

- include the date the report was communicated to maternity services
- include the title of the report (for example, NHS FASP NIPT screening result report)
- clearly state, for prenatal samples, that the result is for screening the fetal genotype, and not the woman
- in the case of a higher chance result report, include the following statement: 'It is recommended that prenatal diagnosis is offered to confirm this result to support personal informed choice about ongoing care and pregnancy options'
- in the case of a higher chance result report for a twin pregnancy, include a statement that one or both babies may have the condition screened for
- in the case of 'no result' reports, include:
    - 'first NIPT screening sample – no result obtained' (please provide reason and state that 'The provider should offer one of the following (one further NIPT sampling, PND or no further testing) and inform the laboratory of the woman's decision'
    - 'second NIPT screening sample – no result obtained' (please provide reason and state 'Discuss further options with the woman including no further testing or PND')

Reporting terminology (must use NHS FASP terminology)

The summary statement must be clear on the report, for example:

- 'lower chance result for Down's syndrome'
- 'higher chance result for Down's syndrome – offer of prenatal diagnosis recommended'

Do not use the terms 'normal', 'abnormal', 'positive' or 'negative'.

A numerical value must not be reported.

Summary of laboratory processes and properties

The summary should include:

- testing methodology
- limitations of the test (for example, test does not detect other chromosomal or genetic conditions)
- sensitivity/specificity based on the laboratory methodology

3.3 Managing NIPT results

Women receiving a higher chance or 'no result' NIPT result should attend an appointment in ≤ 3 working days of maternity services receiving the result (FASP NIPT-S04 (https://www.gov.uk/government/publications/screening-for-downs-syndrome-edwards-syndrome-and-pataus-syndrome-non-invasive-prenatal-testing-nipt/experimental-fasp-nipt-metrics#fasp-nipt-s04-referral-timeliness-of-information-and-support).

This appointment should be face to face or virtual, depending on the woman's choice, and discuss the option of:

- no further testing

- having PND, which should be completed in ≤ 3 working days of the woman receiving the NIPT result (FASP NIPT-S05 (https://www.gov.uk/government/publications/screening-for-downs-syndrome-edwards-syndrome-and-pataus-syndrome-non-invasive-prenatal-testing-nipt/experimental-fasp-nipt-metrics#fasp-nipt-s05-diagnosis-and-intervention-timeliness-of-prenatal-diagnosis-pnd))

The result should be given by a healthcare professional with knowledge of NIPT and the NHS FASP pathway. Healthcare professionals should provide clear and accurate documentation in line with local guidelines.

4. Prenatal diagnosis (PND)

Information on PND can be found in the NHS FASP handbook (https://www.gov.uk/government/publications/fetal-anomaly-screening-programme-handbook) and chorionic villus sampling (CVS) or amniocentesis (https://www.gov.uk/government/publications/cvs-and-amniocentesis-diagnostic-tests-description-in-brief) parent information.

PND results should be reported in ≤ 3 calendar days of sample receipt (FASP NIPT-S06 (https://www.gov.uk/government/publications/screening-for-downs-syndrome-edwards-syndrome-and-pataus-syndrome-non-invasive-prenatal-testing-nipt/experimental-fasp-nipt-metrics#fasp-nipt-s06-diagnosis-and-intervention-test-turnaround-time-quantitative-fluorescence-polymerase-chain-reaction-qf-pcr)).

5. Education and training

NHS FASP recommends all healthcare professionals who are involved in the offer of screening for T21, T18 and T13 in England, complete the 'NIPT – evaluative rollout' e-learning resource.

This resource includes:

- a full version, which should be completed by healthcare professionals who have not completed the old NIPT cascade training
- a short summary and update version, which should be completed by healthcare professionals who completed the old NIPT cascade training

NHS FASP also recommends that all NIPT laboratory staff undertake the following e-learning modules prior to the service starting:

- introduction to population screening
- screening for Down's syndrome, Edwards' syndrome and Patau's syndrome (recommended every 24 months)

These resources are available on e-learning for Healthcare (e-LfH) (https://www.e-lfh.org.uk/).

All providers are responsible for making sure staff receive sufficient time to complete minimum training requirements. This is to maintain an effective screening workforce and includes continuing professional development (CPD) (https://www.gov.uk/guidance/nhs-population-screening-education-and-training).

All providers should maintain a record of training.

Further information on education and training can be found in the NHS FASP handbook (https://www.gov.uk/government/publications/fetal-anomaly-screening-programme-handbook).

6. Data requirements and monitoring

As this is an evaluative rollout, PHE Screening will be collecting data and monitoring how the pathway is working to learn and make improvements where necessary.

Maternity services, screening and genomic laboratories providing NIPT screening and prenatal diagnostics are required to submit data to enable the ongoing evaluation of the national rollout of NIPT in England.

Data is required to answer specific evaluation questions. This data will be collected either directly from:

- maternity services
- genomic laboratories
- National Congenital Anomaly and Rare Disease Registration Service (https://www.gov.uk/guidance/the-national-congenital-anomaly-and-rare-disease-registration-service-ncardrs) (NCARDRS)
- Down's syndrome screening quality assurance support service (https://www.gov.uk/guidance/downs-syndrome-screening-quality-assurance-support-service) (DQASS)

Data should be submitted at regular intervals (each month or every 3 months).

PHE Screening will collect this data (https://www.gov.uk/government/publications/screening-for-downs-syndrome-edwards-syndrome-and-pataus-syndrome-non-invasive-prenatal-testing-nipt/experimental-fasp-nipt-metrics) to enable reporting of:

- coverage (FASP NIPT-S01 (https://www.gov.uk/government/publications/screening-for-downs-syndrome-edwards-syndrome-and-pataus-syndrome-non-invasive-prenatal-testing-nipt/experimental-fasp-nipt-metrics#fasp-nipt-s01-coverage-nipt))
- the choices women make at each stage of the screening pathway
- timely receipt of NIPT sample (FASP NIPT-S02 (https://www.gov.uk/government/publications/screening-for-downs-syndrome-edwards-syndrome-and-pataus-syndrome-non-invasive-prenatal-testing-nipt/experimental-fasp-nipt-metrics#fasp-nipt-s02-test-timely-receipt-of-nipt-sample))
- NIPT test turnaround times (FASP NIPT-S03 (https://www.gov.uk/government/publications/screening-for-downs-syndrome-edwards-syndrome-and-pataus-syndrome-non-invasive-prenatal-testing-nipt/experimental-fasp-nipt-metrics#fasp-nipt-s03-test-turnaround-time-nipt))
- timeliness of information and support to women (FASP NIPT-S04 (https://www.gov.uk/government/publications/screening-for-downs-syndrome-edwards-syndrome-and-pataus-syndrome-non-invasive-prenatal-testing-nipt/experimental-fasp-nipt-metrics#fasp-nipt-s04-referral-timeliness-of-information-and-support))
- timeliness of PND (FASP NIPT-S05 (https://www.gov.uk/government/publications/screening-for-downs-syndrome-edwards-syndrome-and-pataus-syndrome-non-invasive-prenatal-testing-nipt/experimental-fasp-nipt-metrics#fasp-nipt-s05-diagnosis-and-intervention-timeliness-of-prenatal-diagnosis-pnd))

- PND test turnaround times (FASP NIPT-S06 (https://www.gov.uk/government/publications/screening-for-downs-syndrome-edwards-syndrome-and-pataus-syndrome-non-invasive-prenatal-testing-nipt/experimental-fasp-nipt-metrics#fasp-nipt-s06-diagnosis-and-intervention-test-turnaround-time-quantitative-fluorescence-polymerase-chain-reaction-qf-pcr))
- rate of NIPT 'no results'
- performance of NIPT in singleton and twin pregnancies
- performance of NIPT in detecting T21, T18 and T13

7. NIPT evaluative rollout

The UK National Screening Committee (https://www.gov.uk/government/groups/uk-national-screening-committee-uk-nsc) (NSC) recommended the introduction of non-invasive prenatal testing (NIPT) as part of the NHS FASP screening pathway (https://www.gov.uk/government/publications/fetal-anomaly-screening-care-pathways). This is an evaluative rollout so that any necessary changes to the pathway can be made.

NIPT is a technique that is used to screen for T21, T18 and T13 during pregnancy. It involves taking a sample of blood from the woman.

The maternal blood contains a mixture of maternal DNA and placental DNA. This is known as the total cell free DNA (cfDNA). In most cases, the placental DNA will be the same as the baby's DNA. The contribution of DNA from the placenta is called cell free fetal DNA (cffDNA).

cffDNA can be detected in the maternal blood as early as 5 weeks of pregnancy. cffDNA remains in the maternal blood for only a few hours after each pregnancy, making it suitable for pregnancy-specific testing.

Cells in the human body typically contain 46 chromosomes – 23 from the mother and 23 from the father. Each chromosome has sequences of DNA that are specific to that chromosome. NIPT uses cffDNA in the maternal blood to assess the chance of the baby having T21, T18 or T13.

The majority of cfDNA comes from the woman, usually consisting of approximately 90% DNA from the woman's cells and 10% DNA from the placenta. If the baby has T21, there should be slightly more chromosome 21 than expected from the placental DNA (cffDNA) in the maternal blood. The same will apply for chromosomes 18 and 13.

The 2 testing methodologies eligible for assessment in the evaluative roll-out (https://legacyscreening.phe.org.uk/downs) are:

- next generation sequencing technologies – for example, massively parallel shotgun sequencing (MPSS)
- microarray

NIPT does not analyse the DNA and does not detect any specific gene disorders, for example cystic fibrosis.

8. NIPT performance

NIPT is a screening test and is not 100% accurate. This is because the cffDNA is derived from the placenta, not the baby itself.

Some women who receive a higher chance NIPT result will have a baby that does not have one of the conditions screened for.

Some women who receive a lower chance NIPT result will have a baby with one of the conditions screened for. This is rare but can happen, in particular, when a woman has a very high chance result from the combined or quadruple test, for example 1 in 2 to 1 in 10.

There is uncertainty around the performance of NIPT, particularly in T18 and T13. It is suggested this happens because babies with T18 and T13 have smaller placentas, but the reasons are not fully understood.

Current literature review and data modelling suggest that of the NIPT screening results:

- about 90% will be lower chance
- about 8% will be higher chance
- fewer than 5% will give no result

Current literature review and data modelling also suggest that:

- over 90% of women (9 out of 10) with higher chance NIPT results for T21 will be pregnant with a baby who has the condition
- over 80% of women (8 out of 10) with higher chance NIPT results for either T18 or T13 will be pregnant with a baby who has the condition
- there will be some women with higher chance NIPT results who will be pregnant with a baby who does not have any of the conditions screened for

9. Screening safety incidents

A screening safety incident is any unintended or unexpected incident or incidents that could have or did lead to harm to one or more persons who are eligible for NHS screening. This also applies to staff working in the screening programmes.

A screening safety incident can affect populations as well as individuals. It is an actual or possible failure in the screening pathway.

Providers will comply with the national guidance for the management of safety concerns and incidents in screening programmes and NHS England's guidance for managing safety incidents in NHS screening programmes (https://www.gov.uk/government/publications/managing-safety-incidents-in-nhs-screening-programmes).

Laboratory services are expected to inform the Medicines and Healthcare Products Regulatory Agency (MHRA) (https://www.gov.uk/government/organisations/medicines-and-healthcare-products-regulatory-agency) of any adverse incidents.

Shared learning from screening incidents is published via the PHE Screening blog (https://phescreening.blog.gov.uk/).

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