Non-Invasive Prenatal Testing (NIPT) in Scotland

Evaluation Plan

Version history

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| Version | Date | Description |
| V1.0 | 04/05/2022 | Plan approved by Pregnancy & Newborn Screening Programme Monitoring & Evaluation Group |
| V1.1 | 22/07/2022 | Timescale for receipt of initial transfer of laboratory data extended from the end of September 2022 to the end of December 2022. Clarified that subsequent transfer of laboratory data expected annually rather than quarterly. |

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# Background

A series of [changes to the Scottish pregnancy screening programme](https://www.sehd.scot.nhs.uk/cmo/CMO(2020)20.pdf) were implemented from 28 September 2020. In summary these were:

* The expansion of the first trimester combined screening for Down’s syndrome (Trisomy 21) offered to women with a singleton pregnancy to include screening for Edwards’ syndrome (Trisomy 18) and Patau’s syndrome (Trisomy 13).
* The expansion of the screening programme offered to women with a twin pregnancy to include first trimester combined screening for Down’s syndrome, Edwards’ syndrome and Patau’s syndrome, and second trimester quadruple screening for Down’s syndrome.
* An evaluative roll out of Non-Invasive Prenatal Testing (NIPT) as a second line screening test for all pregnancies with a higher chance result of a fetal trisomy following first line screening in the first or second trimester.

This paper sets out the plan for evaluating the implementation of NIPT into the Scottish pregnancy screening programme.

This current plan is based on linkage and analysis of existing and new (currently in test phase) national data held by Public Health Scotland (PHS). This is a revised approach to the evaluation. Previously, an evaluation based on a combination of bespoke aggregate and patient level data returns from NHS Boards to PHS was planned. The revised approach has been formulated because:

* There were concerns about the completeness, consistency, and comparability of the bespoke aggregate and patient level data returns provided by NHS Boards to PHS for the evaluation as initially planned.
* Key national data developments have made evaluating NIPT through data linkage of existing and new national data returns feasible. These are:
* Data on antenatal bookings established as rapid response to COVID-19.
* Laboratory data on trisomy screening tests and antenatal/infant genetic diagnostic tests (currently in test phase).
* The [COVID-19 in Pregnancy in Scotland (COPS) study](https://publichealthscotland.scot/repository/cohort-profile-the-covid-19-in-pregnancy-in-scotland-cops-dynamic-cohort-of-pregnant-women-to-assess-effects-of-viral-and-vaccine-exposures-on-pregnancy/) developed the knowledge and methods to construct a dynamic pregnancy cohort identifying ongoing and completed pregnancies.

The revised approach brings advantages in the consistency and comparability of the data collected and removes the need for additional data collection requirements on NHS Boards. Crucially the new returns already include, or will include, retrospective data for a period prior to NIPT implementation to facilitate the evaluation of NIPT. The new approach was approved by the Pregnancy & Newborn Screening Programme Board and puts the evaluation of NIPT and monitoring of trisomy screening on a sustainable footing while acknowledging that some of the data required for the data linkage are still to be fully established.

# Overview

### Data sources

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| Data sources | Dates |
| Pregnancy cohort data  The knowledge and methods gathered by the [COVID-19 in Pregnancy in Scotland (COPS) study](https://publichealthscotland.scot/repository/cohort-profile-the-covid-19-in-pregnancy-in-scotland-cops-dynamic-cohort-of-pregnant-women-to-assess-effects-of-viral-and-vaccine-exposures-on-pregnancy/) will be used by PHS to construct pregnancy cohort data for the NIPT evaluation. The cohort will be constructed by interrogating population-level national datasets for records of events pertaining to pregnancy.  The COPS study creates a dynamic pregnancy cohort identifying ongoing and completed pregnancies. Ongoing pregnancies are identified from antenatal booking records. Completed pregnancies are identified from general and maternity hospital discharge records, general practitioner (GP) records, statutory termination of pregnancy records, NHS live birth notifications, and statutory live and stillbirth registrations. The bespoke data stream of general practitioner (GP) records to identify women with early miscarriage, molar pregnancy or ectopic pregnancy not admitted to hospital is currently available for the period and purpose of the COPS study only. While the GP data may not be available for the NIPT evaluation this is not a substantial issue as we are primarily interested in women with booked pregnancies and robust pregnancy cohort data for the evaluation can still be created.  Data used to identify:   * The cohort of pregnant women eligible for first line screening in the first trimester and second trimester * Pregnancy outcomes - miscarriage, termination of pregnancy, births, stillbirths | Cohort created for women booking from 1.4.2019  (Date the antenatal booking collection commenced) |
| First line trisomy screening programme laboratory data  National data on first line screening in the first trimester (Edinburgh laboratory) and second trimester (Bolton laboratory).  Data used to identify:   * Women taking up first line trisomy screening (first and second trimester) * Results from first line screening for identifying eligibility for NIPT   If CHI number is not available for some records CHI seeding will be applied. CHI seeding is a probability matching algorithm using patient information to derive a CHI number for the patient. | Data in test phase currently. Retrospective data from 1.1.2018 to be requested (laboratories extract data from their computer systems) |
| Second line trisomy screening programme laboratory data  National data on Non-Invasive Prenatal Testing (Dundee laboratory)  Data used to identify:   * Women taking up NIPT * Results from NIPT * NIPT test performance (when data used in conjunction with confirmatory genetic testing data) * NIPT laboratory performance, for example turnaround times | Data from 28.9.2020 (NIPT implementation date) |
| Antenatal and infant genetic diagnostic testing laboratory data  Antenatal and infant genetic diagnostic testing data for congenital conditions in fetuses and newborns that have a genetic basis from the four genetics laboratories in Scotland (Aberdeen, Dundee, Edinburgh, and Glasgow).  Data used to identify:   * Invasive Prenatal Diagnosis (IPD) procedures -amniocentesis/chorionic villus sampling (CVS) * Confirmation of trisomy (T13, T18, T21) following IPD or end of pregnancy (includes genetic tests following birth, stillbirth, termination of pregnancy, late miscarriage) * For apparent false positives from screening we may also look at the genetics data to see if another congenital condition was diagnosed   If CHI number is not available for some records CHI seeding will be applied.  The text descriptions of genetic test results on data returns from laboratories will require coding by PHS to identify T13, T18 and T21 diagnoses (and the subset of results that indicate mosaic trisomy, or trisomy due to a parental Robertsonian translocation). | Data in test phase currently. Retrospective data from 1.1.2018 to be requested (laboratories extract data from their computer systems) |
| Congenital conditions datasets  The existing national linked dataset on babies with congenital conditions (including trisomies) and the in-development national congenital condition register (CARDRISS) dataset which will supersede the linked dataset for pregnancies ending from January 2021 onwards. The existing linked dataset brings together the available national data to provide best estimates of the number of babies with a serious congenital condition such as a major structural or chromosomal condition. This includes live born babies diagnosed before their first birthday; miscarriages and stillbirths from 20 weeks of pregnancy onwards; and terminations of pregnancy at any stage of pregnancy. The CARDRISS register will work to the same inclusion criteria.  Data used to provide an indication of whether babies with a confirmed trisomy had co-occurring structural conditions such as a congenital heart defect, which may influence parental choices about continuing or terminating the pregnancy. | Linked dataset on congenital conditions currently has data available for pregnancies ending in 2000-2019 |

Through linking these data and applying a series of decision rules the eligible cohorts for screening and how women move through the pathway can be identified before and after the implementation of NIPT and concurrent changes in first line screening.

The linked dataset for the evaluation will not capture:

* Some of the more complex eligibility criteria for screening, for example, women presenting in the first trimester where it has not been possible to measure the nuchal translucency (NT), and women who moved from the screening pathway to a diagnostic pathway as a result of their initial booking scan (e.g. NT measurement ≥ 3.5mm). Although these will have some influence on the accuracy of the eligible cohorts for first line screening in the first and second trimester, affected numbers will be small and the available data are therefore expected to be sufficiently robust and consistent over time to provide a good understanding of uptake rates before and after the implementation of NIPT and the concurrent changes in first line screening.
* The mid-pregnancy ultrasound scan offered between 18 and 21 weeks of pregnancy to look for specific structural conditions. National data returns do not routinely capture data on mid-pregnancy scans.
* Screening or tests in the private sector. Results from these may influence women's decisions on further testing and whether to continue the pregnancy.
* Attempted Invasive Prenatal Diagnosis procedures which do not result in a sample sent to laboratory, although we may be able to identify some of these through SMR02 records generated if women were admitted for the procedure or if the procedure was carried out during a hospital stay.
* Outcomes for all pregnancies. We expect a small proportion of pregnancies to have an unknown outcome. This category will include who women may have had a miscarriage, or other pregnancy outcome, that we don't have a record for, or they may have emigrated.

Other points to note:

* Data for singleton and twin pregnancies will be reported separately however multiplicity is not recorded on the antenatal booking collection as it is not known at the time of initial booking. To derive separate singleton and twin cohorts we will assign multiplicity retrospectively from maternity hospital discharge records (SMR02), although not all pregnancies result in an SMR02 record. Our estimate is multiplicity will be assigned in around 90% of pregnancies from SMR02. Where there are gaps we may explore if it is possible to assign multiplicity from other data sources without introducing bias (for example screening data).
* The identification of how women move through the pathway will include setting some appropriate decision rule time parameters which specify how long at each particular stage of the pathway to search for the next pathway followed. For example following a higher chance first line screening result if an Invasive Prenatal Diagnostic procedure was done at a much later stage, then it's likely it was done for a reason other than the first line screening result, for example due to symptoms experienced in the pregnancy or findings on the mid-pregnancy scan.
* If we discover women in the screening data without booking data (due to data missing from the antenatal booking collection in error) we will explore if we can add their data to pregnancy cohort without introducing bias.

### Time periods covered

The screening pathway changes apply to women booking from 28 September 2020. We have identified that in practice a substantial proportion of women who had NIPT in the first few weeks of its implementation had a booking date in the month leading up to 28 September 2020. Therefore to ensure accurate separation of the pre-implementation and post-implementation cohorts:

* Pre-implementation data will cover women booking from 1 April 2019, the date when the antenatal booking collection started, to 28 August 2020.
* Post-implementation data will cover women booking from 28 September 2020 to 30 September 2023 (three years from implementation of the revised screening pathway).
* Women booking in the period 29 August to 27 September 2020 will be excluded from the analyses. In addition the small number of women booking prior to 28 August 2020 who were offered and chose NIPT will be excluded (from the pre-implementation cohort).

An appropriate follow-up period will be required for each cohort to capture outcomes for all pregnancies including final confirmation of trisomy status after the completion of pregnancy. We will search for trisomy diagnoses reported by laboratories up to six months after the completion of pregnancy and will examine how appropriate this cut-off is for obtaining confirmatory trisomy status, for example we are aware there will be some outlier later diagnoses of children with mosaic Down's syndrome. We may adjust the six-month cut-off up or down and will balance the completeness of capture of confirmatory trisomy diagnoses against the timeliness in which evaluation results can be produced.

Data for the post-implementation period will be split into annual cohorts and data analysed for each cohort as it becomes available. For example, monitoring uptake of first line screening can be split by annual cohorts of pregnant women booking as follows:

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| Women booking | Post-implementation cohort |
| 28 September 2020 to 30 September 2021 | Year 1 |
| 1 October 2021 to 30 September 2022 | Year 2 |
| 1 October 2022 to 30 September 2023 | Year 3 |

Based on assuming booking by 8+0 weeks gestation and allowing a six-month postnatal follow-up, women booking up to 30 September 2023 would be expected to have completed their pregnancies, their babies received any postnatal trisomy diagnoses, and associated genetic test data returned from the laboratories to PHS and prepared for analysis by 31 March 2025. The complete three-year final evaluation analyses and outputs will therefore be produced by PHS during the year ending 31 March 2026.

### Governance

From October 2021 to September 2025 there is a Medical Research Scotland PhD studentship on the impact of NIPT on pregnancy and postnatal outcomes of singleton babies affected by Down's syndrome in Scotland (MRS PhD). The MRS PhD is funded by Medical Research Scotland, with contribution from Public Health Scotland as the external partner organisation. The host organisation for the PhD is University of Aberdeen. Honorary PHS contracts are in place for the PhD student and principal University of Aberdeen supervisor to facilitate this work.

The NIPT evaluation and the PhD are interlinked, have similar data requirements, and are being taken forward as a combined programme of work within PHS. The evaluation covers trisomies T13, T18 and T21 and singleton and twin pregnancies. The PhD covers trisomy T21 and singleton pregnancies only, but includes other dimensions not covered by the evaluation such as examining outcomes for live born babies with T21 over time (hospitalisations and deaths) as well as predictive data modelling. Where analyses for the NIPT evaluation cross-over with the PhD (shown below) they will be developed as part of the PhD studentship. Data for the cohorts in the pre-implementation period and two years post-implementation will be available for analysis within the timescale of the PhD studentship.

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| Evaluation questions by section | Cross-over with PhD |
| 1. Uptake and behaviours - screening for T21 | PhD: singletons only |
| 2. Uptake and behaviours - screening for T13/T18 | Not applicable to PhD |
| 3. Invasive Prenatal Diagnosis | PhD: T21 in singletons only |
| 4. NIPT test failures | Not applicable to PhD |
| 5. NIPT test turnaround times | Not applicable to PhD |
| 6. NIPT test performance | PhD: T21 in singletons only |

The following joint governance for the NIPT evaluation and PhD will be undertaken prior to analysis commencing:

* Inform the PHS research office of this work
* Inform the PHS data protection team
* Inform the National Screening Oversight Board Research and Innovation Group
* Confirm with the University of Aberdeen and the North of Scotland research ethics committee whether ethical approval is required
* Secure NHS Scotland Public Benefit and Privacy Panel for Health and Social Care (HSC-PBPP) approval including completion of supporting Data Protection Impact Assessment (DPIA)

Oversight of the NIPT evaluation work in Scotland comes under the Pregnancy & Newborn (P&NB) Screening Programme Monitoring and Evaluation Group (MEG), and in turn through the governance structure to the P&NB Screening Programme Board, National Screening Oversight Board, and Scottish Screening Committee.

To ensure appropriate stakeholder input into the NIPT evaluation, PHS will convene a stakeholder group for the project. Representatives will be invited from Scottish Government, National Screening Oversight, NSS National Services Division, Public Health Scotland, territorial NHS Boards, the screening and genetics laboratories, and third sector organisations (specifically Down’s Syndrome Scotland, Support Organisation for Trisomy 13/18 [SOFT], the Don’t Screen Us Out campaign, and Antenatal Results and Choices). The stakeholder group will provide guidance and feedback to the PHS evaluation team, and support dissemination of evaluation findings.

For transparency, the initial agreed version of this evaluation plan, and any required post-hoc amendments, will be made publicly available through a suitable platform such as the PHS public GitHub site.

### Timescales and Reporting

Initial national returns from laboratories providing data on antenatal trisomy screening and antenatal/infant genetic diagnostic testing results reported in 2018 to 2021 inclusive should be received by PHS by the end of December 2022. Further annual data returns will then be received by PHS in the spring of each subsequent year (data for results reported in 2022 received by the end of March 2023; for 2023 by the end March of 2024; and for 2024 by the end of March 2025). As the evaluation progresses, there may be scope to move from annual to quarterly data submissions and/or to a more automated process for submission of laboratory data, depending on funding and laboratory capacity, however delivery of the evaluation is not dependent on this.

The annual official statistics publication on [Congenital Conditions in Scotland](https://www.publichealthscotland.scot/publications/congenital-anomalies-in-scotland/congenital-anomalies-in-scotland-2000-to-2019/) provides information on babies with confirmed congenital conditions including trisomies. Assuming that the laboratory data is received on time, the release in October 2023 (on pregnancies ending up to 31 December 2021) will for the first time include information on whether babies with confirmed Down's syndrome, Edwards' syndrome, or Patau's syndrome were detected through antenatal screening.

PHS will develop a complimentary official statistics publication on trisomy screening before the end of March 2024. This will cover the whole pregnant population (rather than just pregnancies/babies with a congenital condition). This will at least contain information on trisomy screening uptake and laboratory performance and will include data for the pre-implementation cohort and the year one post-implementation cohort. The publication content will be developed and published annually thereafter. After the first publication the release may be brought forward to before the end of each calendar year.

Following March 2025 when data for women booking in the full three-year period from the implementation of NIPT will be available for inclusion in the data linkage (including the required postnatal follow-up diagnostic data), PHS will produce an overarching three-year evaluation report during the year ending 31 March 2026. This will include any evaluation questions not previously addressed and will be submitted to an academic journal for peer-reviewed publication.

We will ensure that all published outputs from the evaluation take PHS's usual approach to statistical disclosure control into account, and do not include any information that could identify individuals.

Throughout the duration of the evaluation, we will ensure results are communicated to the UK National Screening Committee’s fetal, maternal and child health group.

### Evaluation of NIPT in rest of UK

NIPT was implemented in NHS Wales from 30 April 2018 and an initial evaluation based on data from the first 30 months following implementation has been completed, with the findings published in [Prenatal Diagnosis](https://obgyn.onlinelibrary.wiley.com/doi/10.1002/pd.6131).

NIPT was implemented in NHS England from 1 July 2021 and a three-year evaluation is planned by the English Department of Health and Social Care (DHSC) and NHS England. Given the later implementation date in England, our current assumption is that the English evaluation will report after the Scottish evaluation.

NIPT is not routinely available in the NHS in Northern Ireland.

Throughout the duration of the evaluation, we will liaise with colleagues in NHS England and NHS Wales to ensure that our plans are aligned to those in the other nations where appropriate. Each nation will retain responsibility for reporting their own evaluation. However, as the different evaluations complete, we will actively consider with the other nations the possibility of producing additional final results that draw on data from all three countries. This is likely to be particularly helpful when looking at NIPT test accuracy for T13/T18 in both singleton and twin pregnancies and for T21 in twin pregnancies, as the numbers of affected pregnancies in Scotland (and Wales) will be small, and hence results will be very imprecise/uncertain.

Due to some differences in the screening pathway across countries it will not be appropriate to produce combined results for all three countries for some of the evaluation questions. For example, in Wales first line screening in the first trimester is for all three trisomies: women can't opt for T21 or T13/T18 first line screening only as they can do in Scotland and England. This means that comparable measures of first line screening uptake cannot be produced for Wales and the other nations.

# Evaluation Questions

1. Uptake and behaviours - screening for T21

Results will be produced separately for singleton and twin pregnancies. Due to small numbers some of the data for twins may be descriptive only and/or will require several years of data to be combined. In general, throughout the evaluation, confidence intervals will be reported where feasible to indicate the level of uncertainty in results, and pre- and post- implementation results will be compared using statistical methods as appropriate.

We will demonstrate visually through over-arching flowcharts how women move through the screening, diagnostic, and outcomes pathways.

We will examine how uptake of screening for T21 varies across different groups, looking at maternal age, ethnicity, deprivation, and urban/rural residence status. We will examine whether the changes to the screening programme had a differential impact on the uptake across these different groups.

In general, throughout the evaluation, our focus will be on women following the standard NHS trisomy screening pathway. However, for completeness, we will also provide supplementary information on women who do not participate in NHS screening (those who have no NHS screening, and those who have NIPT testing in the NHS as a first line screening test for example due to a previous trisomy-affected pregnancy).

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| Question 1.1. | What is the uptake of first line screening (first and second trimester) for T21? |
| Definition | Proportion (%) of women who participate in first line combined or quadruple screening for T21. |
| Cohort(s) | Women booking in first or second trimester:   * Pre-implementation cohort =1.4.2019 to 28.8.2020\* * Post-implementation cohort = 28.9.2020 to 30.9.2023   \* Pre-implementation cohort not applicable to women with twin pregnancy booking in second trimester. |
| Notes | Time appropriate decision rules will be applied for identifying eligibility for first trimester/second trimester screening, including factoring in:   * Pregnancies ending between booking and first line screening (miscarriage, termination of pregnancy). * At the time of booking appointments, gestation is estimated based on last menstrual period and is recorded in complete weeks on the antenatal data booking collection. We may explore using gestation data from later in the pathway to override/correct the estimated gestation at booking (for example gestation recorded on screening and maternity hospital discharge records). |

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| Question 1.2 | What pathway did women follow after a higher chance first line screening result for T21? |
| Definition | What pathway did women follow (within timescale to be specified) after a higher chance first line screening result for T21?  Categories:   * No further tests * NIPT * Invasive Prenatal Diagnosis * Termination of pregnancy   Throughout the pathway we will take account of miscarriages. |
| Cohort(s) | Women with a higher chance result for T21 from first line screening from the:   * Pre-implementation cohort (NIPT option not available to this group) * Post-implementation cohort |

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| Question 1.3 | What pathway did women follow after a high chance second line screening result for T21? |
| Definition | What pathway did women follow (within timescale to be specified) after a high chance second line screening result for T21?  Categories:   * No further tests * Invasive Prenatal Diagnosis * Termination of pregnancy   Throughout the pathway we will take account of miscarriages. |
| Cohort(s) | Women from the post implementation cohort who have a high chance NIPT result for T21. |

1. Uptake and behaviours - screening for T13/T18

Results will be produced separately for singleton and twin pregnancies. Due to small numbers some of the data for T13/T18 may be descriptive only and/or will require several years of data to be combined.

We will demonstrate visually through over-arching flowcharts how women move through the screening, diagnostic, and outcomes pathways.

We will examine how uptake of screening for T13/T18 varies across different groups, looking at maternal age, ethnicity, deprivation and urban/rural residence status.

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| Question 2.1 | What is the uptake of first line screening for T13/T18 (first trimester only)? |
| Definition | Proportion (%) of women who participate in first line combined screening for T13/T18. |
| Cohort(s) | Post-implementation cohort only:  Women booking in first trimester 28.9.2020 to 30.9.2023 |
| Notes | See notes for question 1.1 |

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| Question 2.2 | What pathway did women follow after a higher chance first line screening result for T13/T18? |
| Definition | What pathway did women follow (within timescale to be specified) after a higher chance first line screening result for T13/T18?  Categories:   * No further tests * NIPT * Invasive Prenatal Diagnosis * Termination of pregnancy   Throughout the pathway we will take account of miscarriages. |
| Cohort(s) | Women from the post-implementation cohort with a higher chance result for T13/T18 from first line screening. |

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| Question 2.3 | What pathway did women follow after a high chance second line screening result for T13 or (separately) T18? |
| Definition | What pathway did women follow (within timescale to be specified) after a high chance second line screening result for T13 or (separately) T18?  Categories:   * No further tests * Invasive Prenatal Diagnosis * Termination of pregnancy   Throughout the pathway we will take account of miscarriages. |
| Cohort(s) | Women from the post implementation cohort who have a high chance NIPT result for T13 or (separately) T18. |

1. Invasive Prenatal Diagnosis

Results will be produced for each condition separately and for singleton and twin pregnancies separately. Due to small numbers some of the data may be descriptive only and/or will require several years of data to be combined, for example for T13/T18 in both singleton and twin pregnancies and for T21 in twin pregnancies.

We will demonstrate visually through over-arching flowcharts how women move through the pathway.

Where numbers allow, we will examine how women's choices following IPD vary across different groups, looking at maternal age, ethnicity, deprivation, and urban/rural residence status. We will examine whether the changes to the screening programme had a differential impact on these different groups.

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| Question 3.1 | What pathway did women follow after Invasive Prenatal Diagnosis? |
| Definition | What pathway did women follow (within timescale to be specified) after Invasive Prenatal Diagnosis (amniocentesis, CVS)?  Categories   * Continue pregnancy * Termination of pregnancy   By positive IPD results (separately for T13, T18 and T21), negative results and inconclusive IPD.  Some women may have more than one IPD which we will need to take account of. The linked dataset will not capture attempted Invasive Prenatal Diagnosis procedures which do not result in a sample sent to laboratory, although we may be able to identify some of these through SMR02 records generated if women were admitted for the procedure or the procedure was carried out during a hospital stay.  Throughout the pathway we will take account of miscarriages. |
| Cohort(s) | Women who came to IPD from the screening pathway:   * Pre-implementation cohort (T21 only) * Post-implementation cohort   Through the overarching pathway flowcharts we'll have the numbers of women who came straight to IPD following a higher chance first line screening result; women who had IPD after a high chance second line screening result; and those that didn’t come through screening. The evaluation will focus on women who came to IPD through the screening pathway, although we may comment on overall numbers of IPD for context. |

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| Question 3.2 | How many miscarriages occur after Invasive Prenatal Diagnosis? |
| Definition | How many miscarriages occur (within timescale to be specified) after Invasive Prenatal Diagnosis?  By positive IPD results (separately for T13, T18 and T21), negative results and inconclusive IPD.  Some women may have more than one IPD which we will need take account of. The linked dataset will not capture attempted Invasive Prenatal Diagnosis procedures which do not result in a sample sent to laboratory, although we may be able to identify some of these through SMR02 records generated if women were admitted for the procedure or the procedure was carried out during a hospital stay. |
| Cohort(s) | Women who came to IPD from the screening pathway:   * Pre-implementation cohort (T21 only) * Post-implementation cohort   Through the overarching pathway flowcharts we'll have the numbers of women who came straight to IPD following a higher chance first line screening result; women who had IPD after a high chance second line screening result; and those that didn’t come through screening. The evaluation will focus on women who came to IPD through the screening pathway, although we may comment on overall numbers of IPD for context. |

We will examine the overall total and live birth rates for the different fetal trisomies over time. These measures reflect the underlying prevalence of the trisomies, and the composite impact of the screening programme and women's reproductive choices.

1. NIPT test failures

Results will be produced separately for singleton and twin pregnancies. Due to small numbers some of the data may be descriptive only and/or will require several years of data to be combined, for example data for twins and data on test failure rates for final trisomy status of both T13 and T18.

We will demonstrate visually through over-arching flowcharts how women move through the screening pathway including how many women (pregnancies) do not obtain a result from NIPT.

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| Question 4.1 | What % of NIPT tests that are processed by the laboratory do not provide a result ('test failure rate')? |
| Definition | NIPT tests processed that do not give a result.  These are 'true' test failures from processed samples. If a test was not undertaken for some reason (for example sample dropped or sample delayed) or if the test was not completed due to equipment failure, then not included in denominator.  Split by first test and overall test result. |
| Cohort(s) | Post-implementation cohort who came to NIPT through the screening pathway |

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| Question 4.2 | What is the NIPT test failure rate by maternal BMI category? |
| Definition | NIPT test failures by BMI category.  BMI categories (to be confirmed)   * Underweight < 18.5 * Healthy weight 18.5 to < 25 * Overweight 25 to < 30 * Obese 30 to < 40 * Severely obese ≥ 40   These are 'true' test failures from processed samples. If a test was not undertaken for some reason (for example sample dropped or sample delayed) or if the test was not completed due to equipment failure, then not included in denominator.  Split by first test and overall test result. |
| Cohort(s) | Post-implementation cohort who came to NIPT through the screening pathway |

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| Question 4.3 | What is the NIPT test failure rate by gestation at sample collection category? |
| Definition | NIPT test failures by gestation at sample collection category (categories to be defined in consultation with the NIPT laboratory).  These are 'true' test failures from processed samples. If a test was not undertaken for some reason (for example sample dropped or sample delayed) or if the test was not completed due to equipment failure, then not included in denominator.  Split by first test and overall test result. |
| Cohort(s) | Post-implementation cohort who came to NIPT through the screening pathway |

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| Question 4.4 | What is the NIPT test failure rate by the final trisomy status for that pregnancy (i.e. T21 confirmed, T18 confirmed, T13 confirmed, T21/T13/T18 not confirmed)? |
| Definition | NIPT test failures by trisomy status based on confirmatory diagnostic genetic laboratory test.  These are 'true' test failures from processed samples. If a test was not undertaken for some reason (for example sample dropped or sample delayed) or if the test was not completed due to equipment failure, then not included in denominator.  Split by first test and overall test result.  Final trisomy status will be derived from genetic diagnostic testing data following end of pregnancy including post-mortem and post-natal diagnoses up to six months after birth (or result from IPD if all that's available). The six-month follow-up period will be explored to check it's appropriate and may be adjusted up or down. The absence of a genetic diagnostic test result during pregnancy or following the end of pregnancy will be assumed as indicating the trisomy of interest was not present. We will explore how appropriate this is through validation against CARDRISS. |
| Cohort(s) | Post-implementation cohort who came to NIPT through the screening pathway. |

Our primary analyses will focus on NIPT tests provided as part of the standard NHS trisomy screening pathway. However, we may also provide supplementary information on additional tests, for example those provided as a first line screening test to women with a previous trisomy-affected pregnancy.

In addition to the information on test failures above, we may also provide information on how often NIPT tests lead to unanticipated findings about the mother as appropriate.

1. Test turnaround times

Results will be provided for singleton and twin pregnancies combined.

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| Question  5.1 | What is the laboratory NIPT test turnaround time? |
| Definition | Number of days between date of receipt of sample in the laboratory and date the result was issued by the laboratory to the requesting NHS Board  Categories to be defined based on laboratory standards |
| Cohort(s) | Post-implementation cohort who came to NIPT through the screening pathway. |

Our primary analyses will focus on NIPT tests provided as part of the standard NHS trisomy screening pathway. However, we may also provide supplementary information on additional tests, for example those provided as a first line screening test to women with a previous trisomy-affected pregnancy as appropriate.

In addition to providing this specific information on test turnaround times, using data gathered to answer the previous questions, we will also provide summary information on the average gestation at which women in the pre- and post-implementation cohorts undergo IPD (and subsequent termination of pregnancy if relevant).

1. NIPT test performance

Results will be produced for each condition separately, and for singleton and twin pregnancies separately. Due to small numbers some of the data may be descriptive only and/or will require several years of data to be combined, for example for T13/T18 in both singleton and twin pregnancies and for T21 in twin pregnancies.

We will demonstrate visually through over-arching flowcharts how women move through the pathway.

Figure 1: Sensitivity, Specificity, Positive Predictive Value (PPV) and Negative Predictive Value (NPV) - for reference

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| --- | --- | --- |
| NIPT test result | T13/T18/T21  present\* | T13/T18/T21  not present\* |
| Positive | True Positive (A) | False Positive (B) |
| Negative | False Negative (C) | True Negative (D) |

\* Final trisomy status will be derived from genetic diagnostic testing data following end of pregnancy including post-mortem and post-natal diagnoses up to six months after birth (or result from IPD if all that's available). The six-month follow-up period will be explored to check it's appropriate and may be adjusted up or down. The absence of a genetic diagnostic test result during pregnancy or following the end of pregnancy will be assumed as indicating the trisomy of interest was not present. We will explore how appropriate this is through validation against the national congenital condition datasets.

For twin pregnancies with a high chance NIPT test result for T13, T18 or T21, if there is a confirmed diagnosis of the trisomy in at least one baby then this is a true indication of the presence of the condition.

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| Question 6.1 | What is the sensitivity of the NIPT test? For T13, T18 and for T21. |
| Definition | The proportion of pregnancies where the trisomy of interest was present that had a positive (high chance) NIPT test result for the trisomy. |
| Cohort(s) | Post-implementation cohort who came to NIPT through the screening pathway. |
| Notes | Numerator = True Positives (A)  Denominator = True Positives + False Negatives (A+C) |

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| --- | --- |
| Question 6.2 | What is the specificity of the NIPT test? For T13, T18 and for T21. |
| Definition | The proportion of pregnancies where the trisomy of interest was not present that had a negative (low chance) NIPT test result for the trisomy. |
| Cohort(s) | Post-implementation cohort who came to NIPT through the screening pathway. |
| Notes | Numerator = True Negatives (D)  Denominator = True Negatives + False Positives (D+B) |

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| --- | --- |
| Question 6.3 | What is the Positive Predictive Value (PPV)? For T13, T18 and for T21. |
| Definition | The proportion of pregnancies with a positive (high chance) NIPT test result for the trisomy of interest that have the trisomy present. |
| Cohort(s) | Post-implementation cohort who came to NIPT through the screening pathway. |
| Notes | Numerator = True Positives (A)  Denominator = Total high chance results (A+B) |

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| Question 6.4 | What is the Negative Predictive Value (NPV)? For T13, T18 and for T21. |
| Definition | The proportion of pregnancies with a negative (low chance) NIPT test result for the trisomy of interest that have the trisomy present. |
| Cohort(s) | Post-implementation cohort who came to NIPT through the screening pathway. |
| Notes | Numerator = True Negatives (D)  Denominator = Total low chance results (D+C) |

Our primary analyses will focus on NIPT tests provided as part of the standard NHS trisomy screening pathway. However, we may also provide supplementary information on additional tests, for example those provided as a first line screening test to women with a previous trisomy-affected pregnancy as appropriate.