Classification: Official

Non-Invasive Prenatal Testing (NIPT) R445: Offer for women with a previous pregnancy with Down's syndrome, Edwards' syndrome or Patau's syndrome (T21, T18 and T13)

Screening pathway and guidance for healthcare professionals

NHS England R445 Working Group

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Contents

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Abbreviations

A priori risk	The best assessment of risk before testing results are known.
CVS	Chorionic Villi Sampling
FASP	Fetal Anomaly Screening Programme
GeNotes	Genomic Notes – web-based resource developed by NHS Genomic Education Programme containing clinical information to support genomic testing.
IDPS	Infectious Diseases in Pregnancy Screening
KPI	Key performance indicators
NAD	Nothing abnormal detected
NGTD	National Genomic Test Directory
NICE	National Institute for Clinical Excellence
NIPT	Non-Invasive Prenatal Testing
PAPPA	Pregnancy associated plasma protein A
PND	Prenatal diagnosis
R445	Refers to code in the National Genomic Test Directory
SCT	Sickle cell and thalassaemia
T13	Trisomy (T13): Patau's syndrome
T18	Trisomy (T18): Edwards' syndrome
T21	Trisomy (T21): Down's syndrome
USS	Ultrasound scan

Forward

Non-invasive prenatal testing (NIPT) has revolutionised prenatal screening for the common trisomies T21 (Down's syndrome), T18 (Edwards' syndrome) and T13 (Patau's syndrome) and in recent years, this genomic test has been offered to women who have had a previous pregnancy with a trisomy in to assess the current pregnancy chance of recurrence. However, for this defined and small pregnant population, NIPT as a first line screening test for previous trisomy has not been publicly funded and was only available in the private sector.

In 2022/2023, NHS England provided funding for Central and South Genomic Medicine Service Alliance (GMS Alliance) to run a proof-of-concept project to assess the feasibility of mainstreaming a clinical testing pathway across several maternity sites outside of the West Midlands area for pregnant women with a previous trisomy. Given the benefit realisations of the project, a new test indicator was nationally commissioned as part of the National Genomic Test Directory (NGTD) – 'R445 – Common aneuploid testing - NIPT'.

The inclusion of R445, with testing criteria has garnered positive reception from pregnant women, midwives, and genetic counsellors. It is evident that pregnant women can benefit from an earlier opportunity to access and receive screening results that can provide information to help with reproductive decision-making.

Collectively, the development of the R445 pathway, operational guidance and accompanying resources has involved in collaboration among various organisations, groups, and individuals. These include the NHS England Genomics Unit, the NHS England Screening Sub-Directorate, the Central and South Genomic Medicine Service Alliance Local Transformation Project Group, the NHS England Midwives in Genetics and Genomics Network, the Clinical Scientist NIPT Laboratory Leads (covering Central and South, North Thames, and Southeast London), other specialists and a public and patient advisory group led by Antenatal Results and Choices (ARC).

In essence, the resulting document and supplementary resources are designed to be applicable to all maternity services in England. We are optimistic that these materials will contribute to the advancement of fair, secure, and high-quality care for pregnant women.

Background

The purpose of this document is to provide operational guidance for healthcare professionals offering non-invasive prenatal testing (NIPT) via the R445 test indicator. It should be read in conjunction with the R445 screening pathway (schema, page 8) and the R445 test indicator (Appendix 1) entry within National Genomics Test Directory (NGTD).

In this guidance, 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.

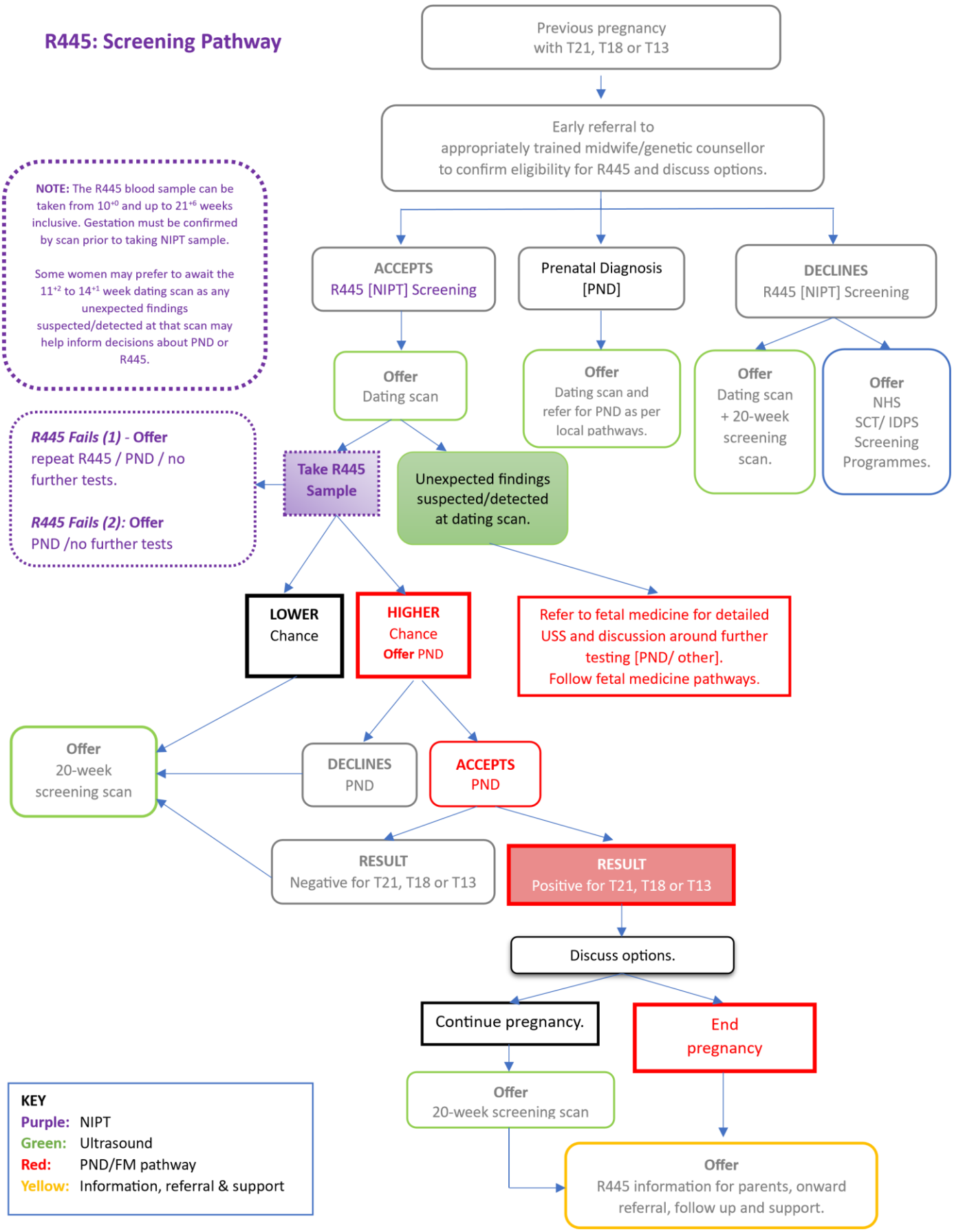
The R445 pathway offers non-invasive prenatal testing (NIPT) to pregnant women who have had any previous pregnancy with reported full trisomy T21, T18 or T13. This group of women are known to have an increased chance of recurrence of primary trisomy in any future pregnancy (*a priori* chance of around 1% **or** the chance related to maternal age, whichever is the greatest). Therefore, R445 offers these women the opportunity to proceed directly to the more sensitive screening test and at an earlier stage of pregnancy.

Process

NHS England Genomics Unit and the NHS England screening sub directorate established a working group with representation from other key stakeholder organisations, groups and experts to develop this comprehensive operational guidance as well as supporting resources. During a three-month period, several meetings were held along with task and finish groups to develop and synergise all outputs.

For midwives (or genetic counsellors), these documents will serve useful to aid to guide discussion with pregnant women during clinical consultations and to educate and train peers.

R445: Screening Pathway



R445 screening pathway

Eligibility for R445

Previous pregnancy
with T21, T18 or T13

Inclusion criteria

All women with history of pregnancy with a full trisomy of T21, T18 or T13 should be offered NIPT in any subsequent pregnancy.

R445 is offered from 10^{+0} to 21^{+6} weeks inclusive, confirmed by ultrasound scan (USS), to both singleton and twin pregnancies.

Eligibility for R445 should be established prior to offering the test. See the R445 test entry within the NGTD for latest eligibility and exclusion criteria.

It is recommended that the report from the previous affected pregnancy is reviewed to confirm full trisomy of T21, T18 or T13 prior to offering R445. However, R445 can still be offered even if the previous report is unavailable or obtaining it will cause a delay in screening. In such cases it should be explained to the woman that R445 is being performed on the basis that the previous pregnancy was a full trisomy T21, T18 or T13 and not another chromosomal anomaly, as these will not be detectable by NIPT.

Exclusion criteria

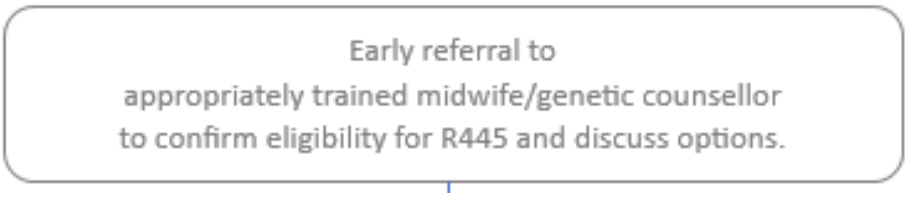
The standard exclusion criteria for NIPT applies (discuss with NIPT lab if unsure). In addition: R445 **is not to be offered** to women where:

- Previous pregnancy was a trisomy involving chromosomes other than T21, T18 or T13.
- Previous pregnancy was not a full trisomy: e.g., mosaicism, translocation or, partial trisomy of T21, T18 or T13.
- One of the parents has a Robertsonian translocation or balanced translocation involving chromosome T21, T18 or T13.
- Donor egg used in current pregnancy.

In these cases, referral to genetic counselling and / or fetal medicine should be offered.

Eligibility and exclusion criteria may change over time. Always refer to the latest version of the NGTD to confirm eligibility criteria prior to offering a test. Discuss with the local NIPT laboratory or Clinical Genetics Team if there is any uncertainty about eligibility.

Offer of R445



Women with a history of pregnancy with full T21, T18 or T13 should be referred for pretest discussion to a genetic counsellor or to an appropriately trained midwife (who is trained to discuss NIPT and pre-natal diagnosis: this might include a screening midwife, fetal medicine midwife or other specialist midwife practitioner).

Referral should be made at the earliest opportunity in pregnancy to allow adequate time for considering screening and testing options.

Women meeting eligibility criteria for R445 have the following three options:

- No screening or diagnostic tests
- Screening via R445 NIPT for T21, T18 or T13.
- Pre-natal diagnosis (CVS or amniocentesis)

It should be made clear to women considering R445 that:

- R445 NIPT is a screening test for T21, T18 or T13. It cannot tell you if your baby definitely has one of these conditions, but it can provide information that may lead to further decisions about your pregnancy.
- NIPT may not detect partial trisomies, translocations, or mosaicism,
- NIPT will not detect other chromosome conditions.

Note: *The offer of R445 replaces the offer of a combined/ quadruple screening test in the NHS Fetal Anomaly Screening Programme (NHS FASP) for this group of women. Therefore, these women* ***should NOT be offered*** *a combined or quadruple screening test as these tests have lower sensitivity for T21, T18 and T13 than R445.*

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

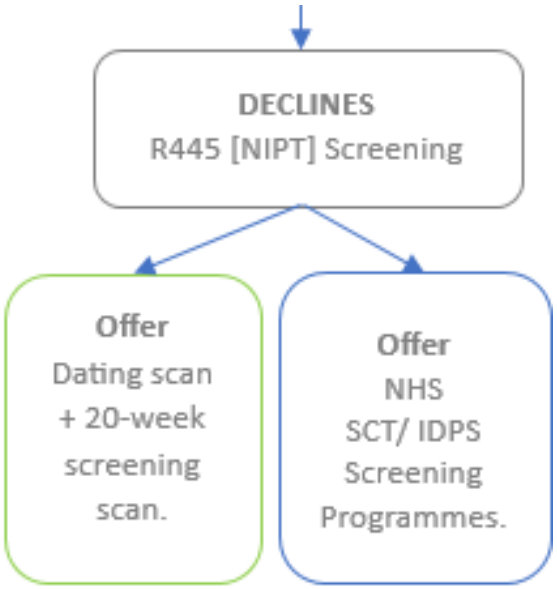
NIPT results must only be reported according to the woman's choice on the conditions screened for. For example, a lower or higher chance result for:

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

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



All discussions and decisions throughout the pathway should be documented in maternal records according to local policy.

Woman declines R445

If a woman initially declines R445 and prenatal diagnosis (PND) she should be advised who to contact should she change her mind, along with the latest time (upper gestational limit) for having these tests.

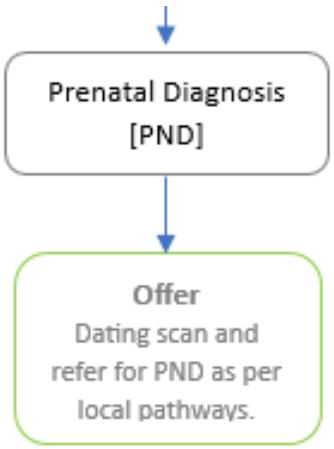
The woman should be returned to the routine antenatal care pathway and offered the following:

- Antenatal screening for sickle cell and thalassaemia (SCT), HIV, hepatitis B and syphilis (IDPS) and the 20-week screening scan as per national policy.

- a dating scan at 11^{+2}- 14^{+1} as per NICE Antenatal Care Guidelines

(NOTE: Where women have an early dating scan (to enable R445 to be taken at the earliest opportunity - 10^{+0} weeks), trusts should follow local ultrasound pathways regarding repeat dating scan at 11^{+2}- 14^{+1} weeks).

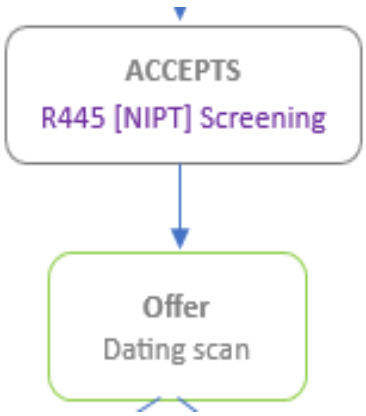
Woman declines screening and proceeds direct to PND



If a woman opts to proceed direct to PND, arrange a dating scan and refer for PND according to local pathways.

Arrange NHS Infectious Diseases Programme Screening (IDPS) and Sickle Cell and Thalassaemia (SCT) screening prior to PND as per local pathways.

Woman accepts R445: Offer dating scan



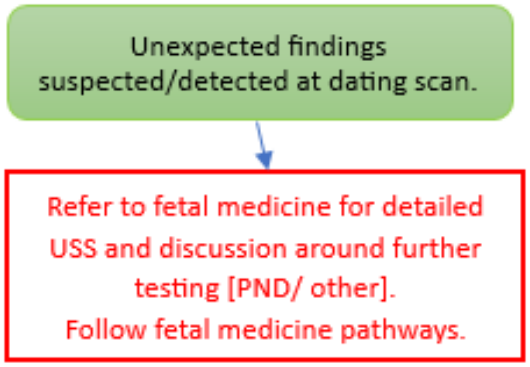
The R445 blood sample can be taken at any point from 10^{+0} up until 21^{+6} weeks of pregnancy inclusive.

Gestational age must be confirmed by ultrasound scan prior to taking the blood test.

Whilst some women may wish to access R445 at the earliest opportunity (10^{+0}), other women may prefer to await until the 11^{+2}-14^{+1} week dating scan as any unexpected findings suspected/ detected at that scan may help inform decisions about PND or R445.

NOTE: *Where women have an early dating scan (to enable R445 to be taken at the earliest opportunity - 10^{+0} weeks), trusts should follow local ultrasound pathways regarding repeat dating scan at 11^{+2}-14^{+1} weeks.*

Unexpected findings at dating scan



A blood sample for R445 **should not be taken** if unexpected findings are suspected/detected at the dating scan. Such findings might include raised nuchal translucency, higher order multiple pregnancy, structural defect, vanished twin, or other anomaly.

Refer woman to fetal medicine for a detailed USS and discussion about testing options.

Follow local fetal medicine referral pathways.

No unexpected findings at dating scan: Gestation 10^{+0} to 21^{+6} inclusive: Taking blood sample for R445.

Take R445 Sample

Refer to local NIPT laboratory guidance on sampling procedure to include using correct bottles, sample volume, form completion, sample storage and transport to laboratory.

Turnaround times for R445 will be the same as for NIPT taken on the NHS FASP pathway following higher chance combined or quadruple screening test.

R445 results process

The results will be reported in the same way as all other NIPT samples taken for screening on the NHS FASP pathway after a higher chance combined or quadruple screening test.

Results for R445 may be reported as higher chance, lower chance, or no result.

No numerical values are reported.

Samples with no result

Where the first R445 sample gives ‘no result’, the woman should be offered a choice of:

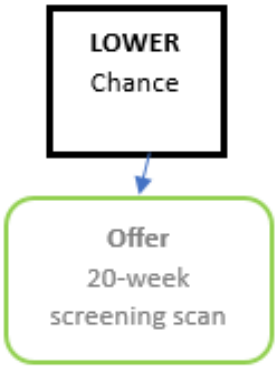
- No further tests
- One further repeat R445 NIPT
- PND (via CVS or amniocentesis)

Where a second R445 sample failed, the woman should be offered a choice of:

- No further tests
- PND (via CVS or amniocentesis)

In these cases, combined or quad should not be offered.

Lower chance result



Where the R445 NIPT result is lower chance, women should be advised that this is not diagnostic and does not exclude T21, T18 or T13. A lower-chance result means it is unlikely, though still possible, that your baby will have the condition.

Refer for USS at 20-week screening scan as per routine NHS FASP pathway.

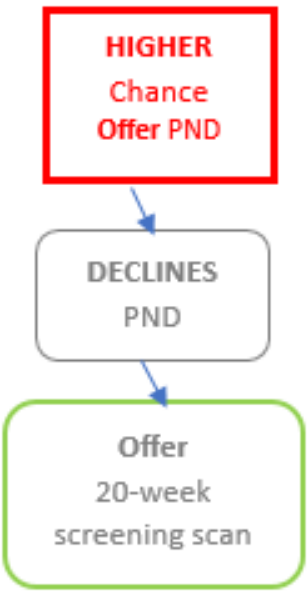
Higher chance results

Timeframes for reporting and actioning higher chance results should mirror those on the NHS FASP pathway.

If the NIPT result is a higher-chance result, women should be offered:

- Prenatal diagnostic testing to confirm the result.
- No further tests

Higher chance results where PND is declined



Where a woman declines PND after a higher chance R445 test, she should be offered the 20-week screening scan as per the NHS FASP pathway.

The woman should be advised that:

A baby with T21 may have no unexpected findings detectable on ultrasound or at the 20-week screening scan. This can also occasionally be the case for babies with T18 and T13, although other ultrasound findings are usually present.

Refer to fetal medicine and paediatric services to discuss on going antenatal care and postnatal assessment including options for confirmatory postnatal diagnostic testing.

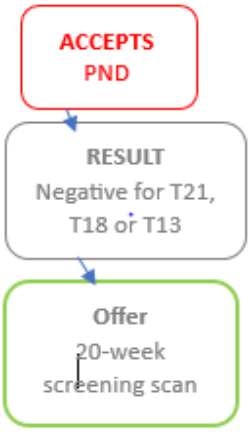
Signpost to support organisations as appropriate according to R445 result, for information and ongoing support.

Ensure the woman is aware that she may change her mind about PND later in her pregnancy, but that there may be gestational limits on which tests / options are available to her. Advise who to contact should she wish to revisit her decision.

Where PND is accepted

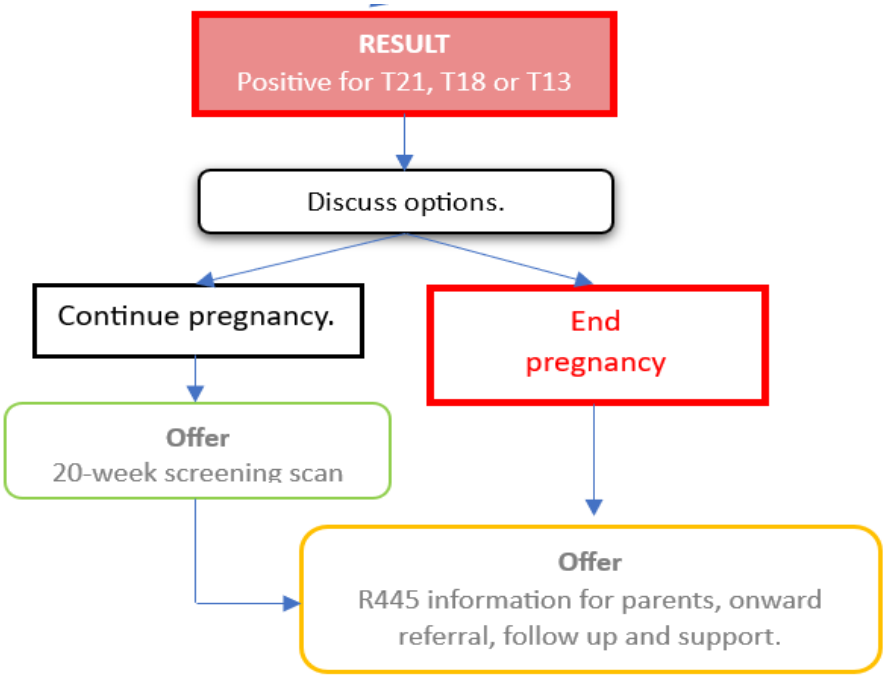
Refer to local fetal medicine department to arrange PND via invasive testing.

PND results: No evidence of T21, T18 or T13.



Refer for routine antenatal care including the offer of the 20-week screening scan.

PND result reports T21, T18 or T13



Follow local pathways for confirmed diagnosis of T21, T18 or T13

Offer – onward referral, follow up and support

Following the birth of a baby, a termination of pregnancy or pregnancy loss of a baby diagnosed with T21, T18 or T13, it is paramount that the woman is given a copy of the '*R445: Information for Parents'* by the midwife before discharge from hospital or the

community setting. Having this information ensures that the woman is aware that R445 is available, as an option, should she decide to know what the chance of trisomy if pregnant again.

Frequently asked questions

1. **Can a woman eligible for R445 also have combined screening?**

No. The offer of R445 replaces the offer of combined or the quadruple screening test. R445 has greater sensitivity than the combined screening test.

2. **Can a woman opt for combined screening [FASP pathway] instead of R445?**

Whilst this is possible, there would need to be a thorough discussion with the woman to explore her reasons for doing so, particularly given that combined screening is a less sensitive test than R445. If a woman opted for combined screening [NHS FASP pathway] and the result was lower chance, then NIPT would not be available to her.

3. **Can a woman eligible for R445 also have combined screening to assess PAPPA levels as a marker for fetal growth restriction?**

The combined test is a screening test for T21, T18 or T13. It is not a screening test for fetal growth restriction.

Women on the R445 pathway are not eligible for combined / quad screening tests.

Some trusts use PAPPA levels as part of an assessment pathway for fetal growth restriction, however this is not a national screening requirement. Therefore, women on the R445 pathway should be monitored for fetal growth restriction along the same local pathways in place for women who have declined combined screening or booked too late for combined screening (who also do not have a PAPP-A level measured).

4. **Are women on the R445 pathway missing out on the option for nuchal translucency measurement?**

Women who accept R445 will have a dating scan and any unexpected findings suspected/detected including an increased nuchal translucency (if visibly large between 11^{+2} and 14^{+1} weeks of pregnancy) on scan will be reported. Local pathways for unexpected findings should be followed.

See GeNotes for further information on raised nuchal translucency at: https://www.genomicseducation.hee.nhs.uk/genotes/in-the-clinic/presentation-fetus-with-raised-nuchal-translucency/

5. **A woman has received a lower chance R445 result but feels anxious and has now asked for PND. Can we offer PND?**

The R445 pathway stops after a lower chance NIPT result.

6. **Should R445 tests be reported along with the NHS FASP NIPT samples on the antenatal screening Key Performance Indicator (KPI) data returns?**

No. The NIPT samples taken as part of the NHS FASP programme are reported separately to NIPT samples taken on the R445 pathway.

The KPI returns only record data on NIPT samples taken for the evaluative roll out of NIPT as part of the NHS FASP pathway. NIPT samples taken as part of the R445 pathway should not be included. If unsure, please discuss with your local Screening and Immunisations Team or Screening Quality Assurance Service (SQAS) Lead.

7. **Can women who have already had combined screening subsequently be offered R445 in the following scenarios?**

i. *Women who had combined screening or quadruple test prior to R445 being added to the NGTD.*

If a woman had combined screening or quadruple test PRIOR to the implementation of R445, then it would be acceptable to offer R445 post implementation, assuming gestation is ≤ 21^{+6} weeks. If the combined screening test result was lower chance, R445 can still be offered but discussion must take place with the NIPT lab prior to taking and sending a sample so that they are fully aware of the reasons for offering R445 in this case. This scenario will only occur in the first few weeks following R445 implementation.

ii. *Where the previous pregnancy with T21, T18, or T13 was not initially disclosed at booking.*

If a woman initially did not disclose a previous pregnancy with T21, T18 or T13, and had combined or quadruple test screening, it would be acceptable to offer R445 later date [≤21^{+6} weeks] should this information subsequently become available. If the combined screening test result was lower chance, R445 can still be offered but discussion must take place with the NIPT lab prior to taking and sending a sample so that they are fully aware of the reasons for offering R445 in this case. Such cases are likely to be very unusual.

Appendix 1

R445 Common aneuploidy testing - NIPT

Testing Criteria

Any previous pregnancy with reported full trisomy of chromosomes 13, 18 or 21, meeting the following criteria:

Inclusion:

- From 10 weeks (gestational age confirmed by dating scan) and up to 21 weeks and 6 days (21+6) of pregnancy.
- Two attempts at NIPT per pregnancy can be offered.

Exclusion:

- Maternal cancer (unless in remission)
- Blood transfusion in the last 4 months (whole blood or plasma)
- Bone marrow or organ transplant recipient
- Vanished twin pregnancy (an empty second pregnancy sac or a second pregnancy sac containing non-viable fetus)
- Maternal T21
- Maternal balanced translocation or mosaicism of T21, T18 or T13
- Immunotherapy in the current pregnancy, excluding IVIg treatment.
- Stem cell therapy
- Previous pregnancy was not a full trisomy (reciprocal translocation or partial trisomy)
- Women who have used a donor egg for current pregnancy.

Overlapping indications

- R401 Common aneuploidy testing – prenatal should be used where amniocentesis or Chorionic villus sampling (CVS) taken.

Where in Pathway

Samples to be taken by trained midwife or Clinical Genetics Unit and sent directly to the testing laboratory using the same sample referral routes as per the Fetal Anomaly Screening Programme

Requesting Specialties

- Clinical Genetics
- Specialist Midwifery

Specialist Service Group

- Prenatal

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R445.1	Common aneuploidy testing NIPT	Singleton or duo	Aneuploidy	Genomewide	Genomewide	NIPT