Non-Invasive Prenatal Testing (NIPT) for women with a previous pregnancy with trisomy (T21, T18 and T13):

Guidance for healthcare professionals on offering R445

R445 is a clinical indication code in the National Genomics Test Directory (NGTD) for a screening pathway which offers non-invasive prenatal testing (NIPT) to pregnant women who have had any previous pregnancy with reported full trisomy T21 (Down's syndrome), T18 (Edwards' syndrome) or T13 (Patau's syndrome) to assess the chance of recurrence in a current pregnancy.

This guidance aims to support healthcare professionals offering the R445 screening pathway. It should be read in conjunction with the R445 screening pathway (schema, page 4) and the R445 entry within the National Genomics Test Directory (NGTD).

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Contents

Foreword

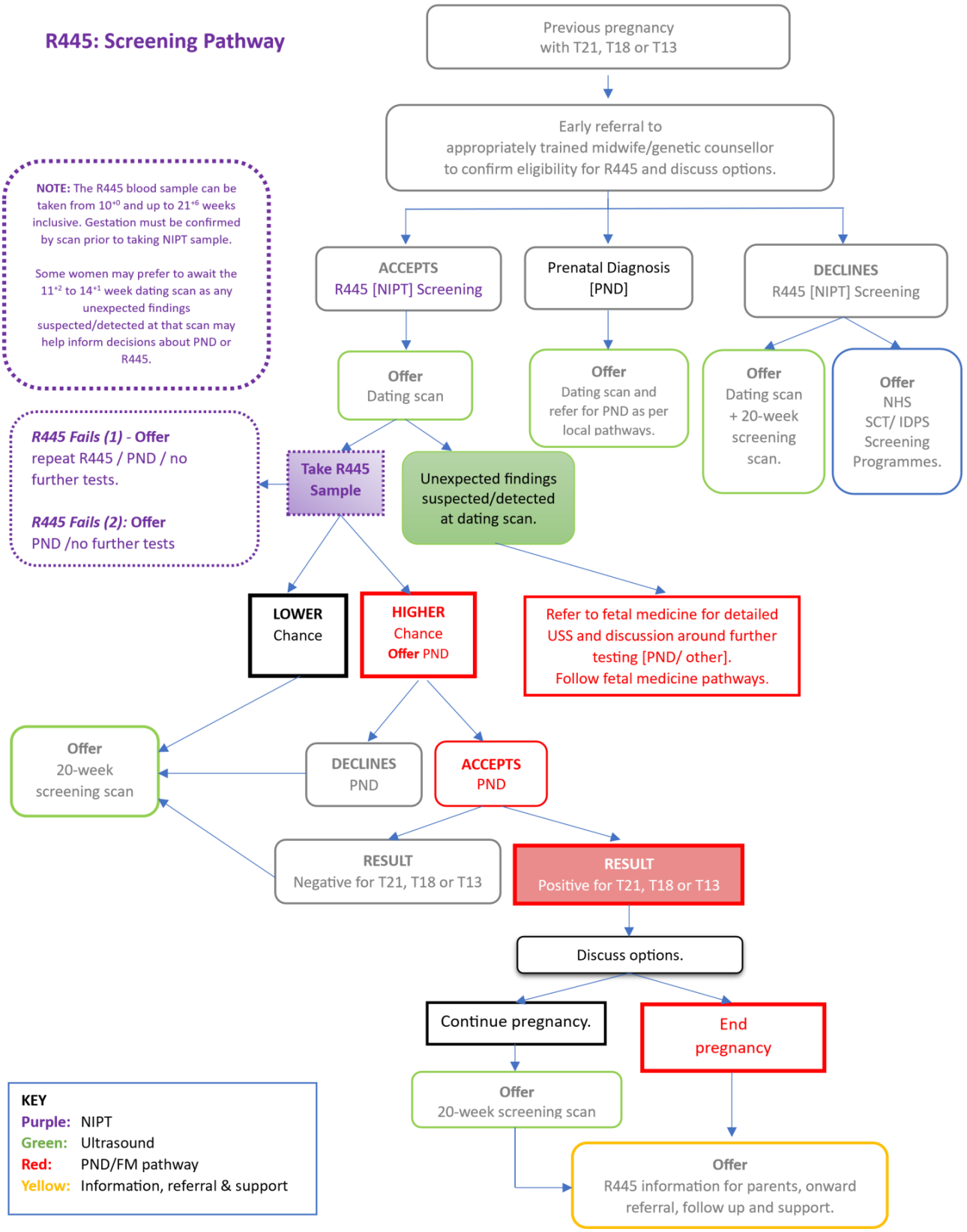
The purpose of this document is to provide operational guidance for healthcare professionals offering R445 non-invasive prenatal testing (R445/NIPT). It should be read in conjunction with the R445 screening pathway (schema, page 4) and the R445 clinical indicator entry within National Genomics Test Directory (NGTD).

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 full 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 option to proceed directly to the more sensitive screening test and at an earlier stage of pregnancy.

While most people using maternity and perinatal services are women, the CQC Maternity Survey (2022) found that 0.65% of respondents stated that their gender was not the same as their sex registered at birth (Three-Year Delivery Plan for Maternity and Neonatal Services. NHS England 2023). This information therefore also applies to intersex, transgender, and non-binary people experiencing pregnancy and birth and they should be offered all antenatal and newborn screening tests.

See Appendix 2 for background on development of the R445 pathway.

Schema: R445 screening pathway



The R445 screening pathway

Eligibility for the offer of R445

Inclusion criteria

Women with history of pregnancy with a reported full trisomy of chromosomes 21, 18 or 13 should be offered non-invasive prenatal testing (NIPT) in any subsequent pregnancy on the R445 screening pathway.

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

Eligibility for R445 should be established prior to offering the pathway. See the R445 clinical indicator within the national genomic test directory (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 (always discuss with the NIPT laboratory if you are unsure). In addition, R445 **is not to be offered** to women where:

- the previous pregnancy was a trisomy involving chromosomes other than T21, T18 or T13
- the previous pregnancy was not a full trisomy: for example, 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
- they have used a donor egg for the current pregnancy (**unless** the egg for this pregnancy is from the **same egg donor** used in a previous pregnancy with confirmed T21, T18 or T13)

If the woman's clinical history aligns with one of the categories listed above, consider referral to genetic counselling, fetal medicine or specialist midwife according to local

protocols.

Eligibility and exclusion criteria for the R445 pathway may change over time. Always refer to the latest version of the national genomic test directory (NGTD) to confirm eligibility criteria prior to offering NIPT. 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, fetal medicine consultant or to an appropriately trained midwife (who is trained to discuss NIPT and prenatal 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 testing for trisomy: T21, T18 or T13.
- prenatal diagnosis (chorionic villus sampling (CVS) or amniocentesis)
- screening via **R445 Common aneuploidy testing – NIPT:** For trisomy 21, 18 and 13

It should be explained to women considering R445 that:

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

The offer of R445 replaces the offer of a combined or 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

Women should be advised how the results of a NIPT test will be reported.

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

NIPT screening will screen for all three conditions and will **report individual chance results** for **T21, T18 and 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 NIPT screening and prenatal diagnosis

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

In these cases, the woman should be returned to the routine antenatal care pathway and offered:

- NHS Infectious Diseases Programme Screening (IDPS) for HIV, hepatitis B and syphilis
- NHS Sickle cell and Thalassaemia (SCT) screening
- 20-week screening scan as per NHS Fetal Anomaly Screening Programme
- a dating scan at 11^{+2}- 14^{+1} as per National Institute of Clinical Excellence (NICE) Antenatal Care Guidelines

Woman declines R445 NIPT screening and proceeds direct to prenatal diagnosis (PND)

If a woman opts to proceed directly 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

A blood sample for R445 testing 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 sample.

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 or detected at that scan may help inform decisions about prenatal diagnosis (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 or detected at the dating scan. Such findings might include raised nuchal translucency, higher order multiple pregnancy, structural defect, vanished twin, or other anomaly. In these cases, refer the woman to fetal medicine where appropriate, for a detailed ultrasound scan and discussion about testing options. Follow local fetal medicine or clinical referral pathways.

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

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 NIPT results from the R445 pathway will be reported in the same way as NIPT results received from the NHS FASP pathway (following 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
- prenatal diagnosis (via chorionic villus sampling (CVS) or amniocentesis)

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

- no further tests
- prenatal diagnosis (via chorionic villus sampling (CVS) or amniocentesis)

In these cases, the combined or quadruple screening tests should not be offered. No further NIPT testing can be carried out in this pregnancy, as per the NHS FASP pathway.

Lower chance results

Where the R445 NIPT result is lower chance, it should be re-iterated to women that this is a screening test, not a diagnostic test, and does not exclude T21, T18 or T13 in their baby.

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 result where prenatal diagnosis (PND) is declined

Where a woman declines PND after a higher chance R445 NIPT result, she should follow the NHS FASP screening pathway as per a higher chance NIPT result.

The woman should be advised that a baby with T21 may have no unexpected findings detectable on ultrasound at any gestation including 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 in these cases.

Refer to fetal medicine and paediatric services to discuss on going antenatal care and

postnatal assessment including options for confirmatory postnatal diagnostic testing.

Signpost women and their families to support organisations as appropriate according to the R445 result, for information and ongoing support.

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

Higher chance result where prenatal diagnosis (PND) is accepted

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

Prenatal diagnosis results: No evidence of T21, T18 or T13

Refer for routine antenatal care including the offer of the 20-week screening scan as per the NHSFASP Screening programme.

Prenatal diagnosis results: Reports diagnosis of T21, T18 or T13

Follow local clinical 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 a pregnancy loss (of a baby diagnosed with T21, T18 or T13), the midwife should give the woman a copy of the ‘R445: Information for Parents’ before she is discharged from the hospital or in the community setting. Providing this information ensures that the woman knows that R445 is an option, if she wants to find out the chance of trisomy in a future pregnancy.

The woman’s GP should also be informed that R445 is an option in future pregnancies.

Appendix 1: Frequently asked questions

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

No. The offer of R445 replaces the offer of the combined or quadruple screening tests. R445 has greater sensitivity than the combined or quadruple 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 who is eligible for R445 also have combined screening to assess the levels of pregnancy associated plasma protein A (PAPP-A) which is 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 or quad screening tests.

Some trusts use PAPP-A 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 an opportunity to have a nuchal translucency measurement?

Women who accept R445 will have a dating scan and any unexpected findings suspected or 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 prenatal diagnosis (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. Where the previous pregnancy with T21, T18, or T13 was not initially identified at booking.

If a previous pregnancy with T21, T18 or T13 was not identified during booking, and the woman had a combined or quadruple test, it would be acceptable to offer R445 at a later date ($\leq 21^{+6}$ 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.

ii. Where the current pregnancy is conceived using donor egg.

The increased chance of recurrent trisomy lies with the woman from whom the egg originated. Therefore the ‘a priori’ risk of trisomy is only increased in the current pregnancy if the egg originated from the same woman (same egg donor) as in a previous pregnancy diagnosed with trisomy. The following table considers different scenarios and whether R445 should be offered:

Origin of egg in a previous pregnancy with trisomy	Origin of egg in current pregnancy	Is the 'a priori' risk of trisomy in current pregnancy increased?	Can R445 be offered?
Pregnant woman's own egg	Pregnant woman's own egg	Yes	Yes: offer R445
Egg donor	Pregnant woman's own egg	No	No: Follow Fetal Anomaly Screening Programme (FASP) pathway
Pregnant woman's own egg	Egg donor	No	No: Follow FASP pathway
Egg donor	Egg donor: different donor to the one used in a previous pregnancy with trisomy	No	No: Follow FASP pathway
Egg donor	Egg donor: Same egg donor as used in a previous pregnancy with trisomy	Yes	Yes: Offer R445

iii. Where there is a previous history of mosaicism for T21, T18 or T13

In a mosaicism, only some of the individual's cells have the trisomy, hence there are two cell lines (some cells contain the usual number of chromosomes, and some contain the trisomy). If a previous pregnancy was a mosaic trisomy then R445 is not to be offered because NIPT is not validated to detect a mosaic trisomy. The evidence for this is constantly under review and guidance may change in the future.

Appendix 2: Developing the R445 pathway

Background

Non-invasive prenatal testing (NIPT) has revolutionised screening for trisomies T21, T18, and T13. However, women with a previous trisomy pregnancy have only been able to access NIPT in the private sector.

In 2022/2023, NHS England funded a proof-of-concept project to assess the feasibility of offering NIPT for this group of women and following a successful evaluation, the test was nationally commissioned as a clinical indicator. In the National Genomics Test Directory (NGTD) the clinical indicator code is 'R445' - Common Aneuploidy Testing – NIPT'.

Developed collaboratively, R445 now offers a fair and high-quality screening pathway available across all NHS maternity services in England.

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 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 as a useful guide for discussion with pregnant women during clinical consultations and to educate and train peers.

NHS England: R445 Working Group

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