

Best practice guidelines for non-invasive prenatal diagnosis to determine fetal sex for known carriers of X-linked conditions excluding haemophilia.

Background

Fetal DNA is required for prenatal genetic testing. Traditionally invasive testing by amniocentesis or chorionic villus sampling has been required to obtain fetal DNA. These procedures carry a small but significant (around 1%) risk of miscarriage. In 1997 cell free fetal DNA (cffDNA) was identified in the maternal circulation. This is present from early pregnancy, is rapidly cleared from the circulation after delivery, but only constitutes a small proportion of cell free circulating DNA, the majority being from the mother (For review see RCOG 2009). cffDNA can be used as an alternative source of fetal DNA for prenatal testing for genes not present in the mother and has been used extensively in the UK and Europe for fetal sex determination (Finning and Chitty 2008, Hill et al 2010). Testing requires a simple blood test rather than an invasive procedure and thus avoids the risk of miscarriage.

This care pathway, describes an innovative method for fetal sex determination based on cffDNA which will massively improve equity of access and the quality of care offered to women whose pregnancy is at risk of a serious sex-linked condition by removing the need for invasive testing, and thus potential iatrogenic pregnancy loss for around 50%. An economic analysis has shown that there are no cost implications for service providers as testing in these circumstances has been shown to be cost-neutral (Hill et al. Manuscript submitted August 2010). There has been a thorough audit of this service as currently offered by NHS genetics service laboratories in the UK demonstrating a high sensitivity and specificity (Hill et al 2010). A pilot NEQAS scheme has been established (Schlecht et al 2010) and educational materials for health professionals, information and competencies are being developed by the National Genetics Education and Development Centre.

Additional care pathway information

1. Known carrier of X-linked disorder

- NIPD should be offered to known carriers of serious X-linked conditions. The majority of these women will already be under the care of the clinical genetics team and will have had a care plan for antenatal diagnosis discussed. Occasionally women who are known carriers of an X-linked metabolic or immunological disease will be under the care of the metabolic or immunological teams as practice varies with locality, but these women will also have a care plan for antenatal diagnosis in place.
- In the majority of cases the disease causing mutation will have been previously been characterised.

Red flag: Anyone presenting to obstetrics or GP without previous genetics or other relevant health professional care within the NHS should be given an urgent referral to the local regional genetics team.

2. Offer of fetal sexing by NIPD

- When a known carrier of a serious X-linked condition becomes pregnant contact is made with the genetics team, either directly or through their GP or obstetrician.
- The genetics team speak to the woman about NIPD at an appointment or by phone.
 - o Discuss how the woman would like to receive results (genetics appointment, phone call or letter)
 - o Discuss how NIPD performed, accuracy of NIPD and possible occurrence of inconclusive results.
 - o Describe need for dating scan and for confirmation of gender by ultrasound.
 - o Discuss option of amniocentesis/chorionic villus sampling if male identified.
- The woman will be referred to have a dating scan and the genetics team will organise for blood to be taken after 7 weeks gestation as confirmed by scan.

5. Dating scan

- Ultrasound scan performed at the woman's local maternity unit to establish gestation and confirm singleton pregnancy.

6. Discuss options with parents – when NIPD is declined

- Discuss options of invasive testing or standard antenatal care.

7. NIPD blood test

- Blood can be taken any time after 7 weeks (confirmed by dating scan). There is no upper limit of gestation for NIPD.
- A second blood sample may be required for testing for pregnancies below 9 weeks gestation. Please refer to the testing pathways of the specific laboratories providing this test.
- Blood can be taken wherever convenient for the woman - genetics appointment, GP or obstetrician/midwife appointment.
- Blood should arrive in the laboratory within 48 hours of sampling.
- The laboratory performing NIPD is notified to ensure rapid sample processing on arrival.
- Sexing test is performed with a target turnaround time of 3 days and report faxed to a named genetic counsellor or consultant.

9. Standard antenatal care

- Standard antenatal care should include the offer of Down syndrome screening according to local practise.

14. Confirm gender by ultrasound

- When NIPD indicates a female fetus an ultrasound scan performed at the woman's local maternity unit is used to confirm gender. Repeat scans may be needed.

15. Discuss options with parents - when the NIPD result is inconclusive

- When NIPD gives an inconclusive result parents should be offered the options of repeating the NIPD or having an invasive test.

16. Amniocentesis / chorionic villus sampling

- Discuss with the woman how she would like to receive results (genetics appointment, phone call or letter)
- Advise woman:
 - o to rest for a day or two after the procedure, avoiding lifting, bending or stretching where possible
 - o that she may experience discomfort in the lower abdomen after the procedure, which can be relieved with simple analgesics, eg. Paracetamol
 - o to contact her GP if she has a pyrexia (there is a slight risk of infection with invasive procedures), losing either fresh blood or water type loss (not urine) from the vagina, losing any discharge with an offensive odour from the vagina, severe lower abdominal pain, feeling generally unwell or decreased fetal movement (after amniocentesis only where some women have already experienced fetal movements)
 - o that she will not require Down syndrome screening if the pregnancy continues as the fetal cells obtained following the invasive test will also be sent for cytogenetic analysis.

Amniocentesis:

- procedure is suitable from 15+0 weeks of pregnancy
- is performed under continuous ultrasound guidance
- the procedure involves inserting a fine needle through the abdomen into the womb and then into the amniotic sac and aspirating a sample of amniotic fluid (fluid surrounding baby)
- at the laboratory, DNA testing is performed to identify the presence/absence of the mutation and in addition maternal cell contamination of the fetal sample is excluded. Fetal cells extracted from the amniotic fluid are examined; the number, arrangement and shape of the fetal chromosomes are checked

- about 1 in 100 samples proves to be inadequate
- the risk of miscarriage associated with amniocentesis is 1 fetal loss in 100 procedures

Chorionic villus sampling (CVS):

- procedure is usually performed from 11+0-12+6 weeks of pregnancy
- usually performed in a fetal medicine unit by a specialist trained in fetal medicine
- two types of CVS - Transcervical (TC) and Transabdominal (TA)
 - a) Transcervical (TC)** The procedure involves inserting a fine plastic catheter in the vagina, through the cervix and into the placenta (whilst simultaneously undertaking an abdominal scan). A small amount of placental tissue is then aspirated and sent for cytogenetic investigation. This is rarely performed
 - b) Transabdominal (TA)** Similar to an amniocentesis, this procedure is usually undertaken in up to 13+6 weeks but can be performed later in pregnancy. The procedure involves inserting a fine needle through the abdomen, into the womb and into the placenta and then aspirating a small amount of placental tissue for analysis
- at the laboratory, DNA testing is performed to identify the presence/absence of the mutation and in addition maternal cell contamination of the fetal sample is excluded. Fetal cells extracted from the CVS are examined; the number, arrangement and shape of the fetal chromosomes are checked
- about 2 in 100 samples prove to be inadequate
- the fetal loss rate associated with a TA CVS is 2 in 100 procedures. The risk associated with TC is slightly higher

18. Standard antenatal care

- Standard antenatal care should include the offer of Down syndrome screening according to local practise.

21. Standard antenatal care

- Standard antenatal care should include the offer of Down syndrome screening according to local practise.

25. Standard antenatal care

- Standard antenatal care does not include offer of Down syndrome screening at this point as karyotyping is done on chorionic villi or amniocytes.

26. Discuss options with parents – when an X-linked mutation is identified

- Provide information and support to the woman whose pregnancy is affected by the X-linked condition.

References

Amniocentesis test - information for parents. 2009. NHS Fetal Anomaly Screening Programme

Chorionic villus sampling (CVS) - information for parents. 2009. NHS Fetal Anomaly Screening Programme

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Hill M, Finning KM, Martin P, Hogg J, Meaney C, Norbury G, Daniels G and Chitty LS. Non-invasive prenatal determination of fetal sex: translating research into clinical practice. *Clin Gen.* 2010; *In press.*


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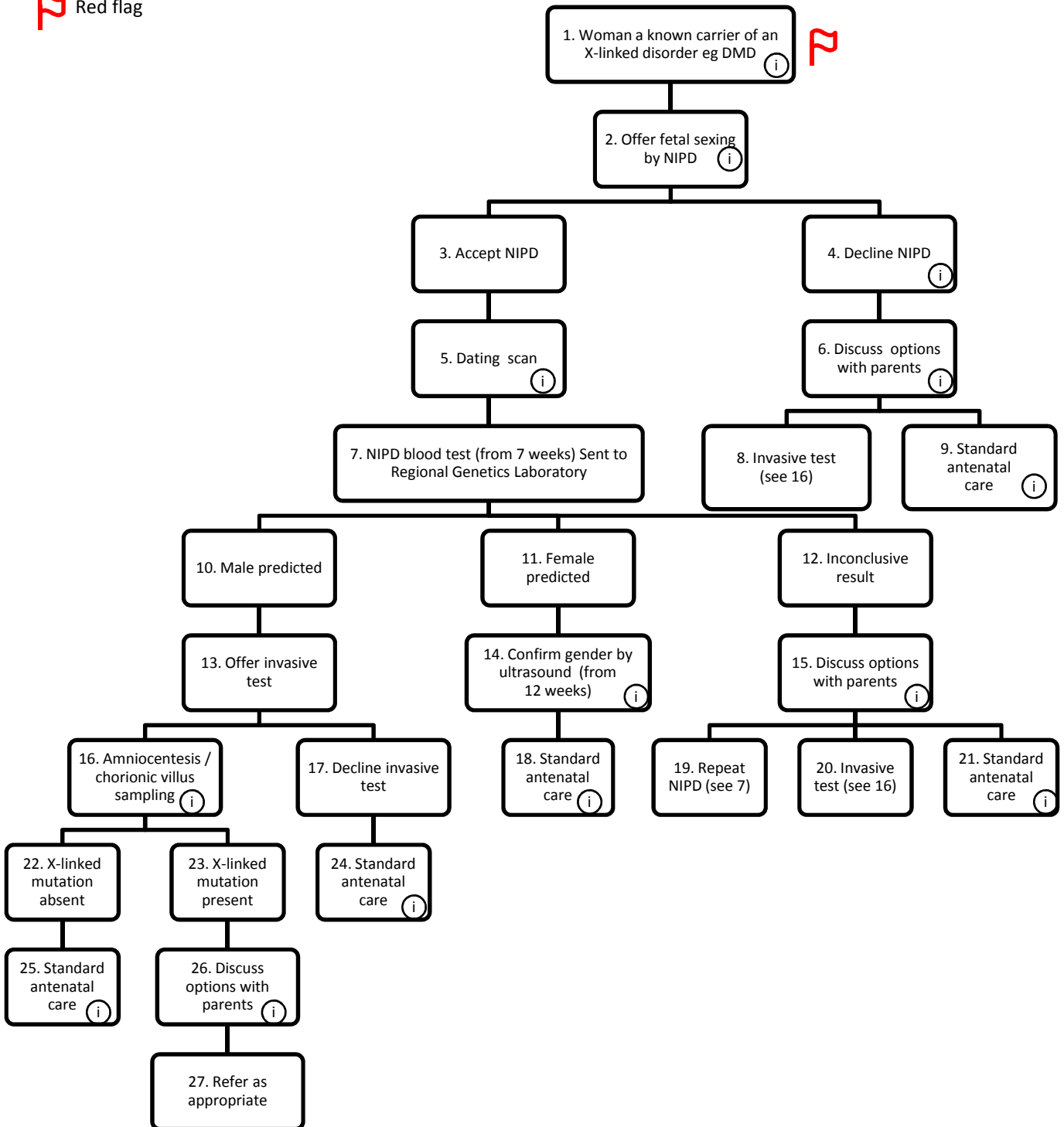
Schlecht HB, Charlesworth N, Ramsden SC, Elles RG and Deans Z. Non-invasive prenatal fetal sex determination – service experience and quality assurance. *J Med Genet* 2010; 47 Supplement 1 S72.

MANCHESTER CARE PATHWAY

Fetal sexing by non invasive prenatal diagnosis for serious X-linked conditions eg. Duchene muscular dystrophy (DMD) excluding haemophilia


 Additional information

 Red flag



BIRMINGHAM AND GREAT ORMOND STREET CARE PATHWAY

Fetal sexing by non invasive prenatal diagnosis for serious X-linked conditions eg. Duchene muscular dystrophy (DMD) excluding haemophilia

 Additional information

 Red flag

