


Towards safer, earlier prenatal diagnosis: expert recommendations



“We take calls every day on our national helpline from women agonizing over whether to have an invasive test and desperate to know when a safe alternative will be available”

- Jane Fisher, Director of the charity *Antenatal Results and Choices*.

Cell-free fetal nucleic acids - both DNA and the related molecule RNA - are present in the blood. More than ten years ago it was found that a small proportion of the cell-free DNA in the mother's blood during pregnancy actually comes from the fetus. Although it is difficult to identify, fetal DNA in maternal blood can be reliably detected from 7 weeks gestation and is lost within a few hours of birth. Now the technology to identify this fetal DNA is being used in clinical practice or developed for the non-invasive prenatal detection of specific fetal genetic traits. This new approach offers substantial advantages over current methods, being both safer and earlier, but potential application in UK health services raises various associated issues that require careful consideration.

Focus on PHG Foundation report
Cell-free nucleic acids for non-invasive prenatal diagnosis

What can testing be used for?

- **Fetal sex** can be deduced by the presence or absence of male-specific (Y-chromosome) sequences; this is important for rare sex-linked inherited diseases that affect only one sex.
- **Fetal RhD blood group status** can be determined by the presence or absence of the RHD gene; this is important for RhD-negative mothers at risk of dangerous incompatibility reactions caused by RhD-positive fetuses.
- **Mutations that cause certain inherited genetic diseases** can be identified by the presence (or absence) of corresponding sequences, especially those inherited from the father of the fetus.
- **Chromosomal aneuploidies such as Down's syndrome** can be identified by an abnormal ratio of different chromosomes.

Why is it important?

Non-invasive prenatal testing could affect both specialist and routine antenatal care. The capacity to detect these features via fetal DNA from the maternal blood is an important improvement over current, invasive methods of testing (amniocentesis or chorionic villus sampling / CVS) for two key reasons:

1. **It does not have any associated risk of miscarriage.**
Amniocentesis and CVS result in pregnancy loss in about 1% of cases. **This represents**

several hundred pregnancies lost each year in the UK - many of which would have been healthy fetuses. Many women at high risk of having a fetus affected by a genetic or chromosomal disorder who would like to know whether or not this is the case opt against invasive testing because of the risk to the fetus.

2. It is possible much earlier in pregnancy.

Currently, reliable testing can be performed from 7 weeks of pregnancy, compared with 11-16 weeks for invasive procedures.

Testing could also allow better pregnancy management in certain cases, such as improved targeting of anti-D therapy, a human blood-product currently given to all RhD-negative women to prevent a potentially fatal maternal immune response against a RhD-positive fetus; however, where the fetus is also RhD-negative, this treatment is unnecessary.

How advanced is this testing?

In the UK, the technique has been available to hospital trusts since 2001 to determine fetal RhD blood group status in high-risk women, and is also available in some NHS hospitals for fetal sex determination where there is clinical justification, such as a high risk of sex-linked genetic disease in the fetus. In the US, the technology is currently being developed and tested commercially, and there are plans to launch a screening test for Down's syndrome later this year.

Patient perspective

"I fully acknowledge that the first trimester of any normal pregnancy can be an anxious time, however, I feel strongly that the uncertainty of not knowing whether or not the mutation would be inherited plus concerns about the risks associated with invasive testing greatly exacerbated my level of stress during this period... I would sincerely love to see the service and support I experienced expanded as far as possible, so that others can benefit as I did"

- patient who has experienced both invasive and non-invasive fetal testing for a serious genetic disease during pregnancy.

What is this new report?

The new PHG Foundation report is the product of an expert Working Group, which included relevant clinicians (GPs, obstetricians, midwives and geneticists), scientists, NHS commissioners, public health experts, ethicists and patient representatives.

In addition to reviewing the current scientific and clinical status of the use of cell-free fetal nucleic acid technology for non-invasive prenatal diagnosis (NIPD), it also examines some of the major ethical, social and legal implications of the technology, and highlights some of the key issues that will need to be addressed if the technique is to be implemented for different applications within the NHS.

Experts behind the report

In addition to the PHG Foundation, key organisations represented on the Working Group include:

- Human Genetics Commission
- Department of Health
- British Society of Fetal and Maternal Medicine
- Royal College of Obstetricians and Gynaecologists
- Royal College of Midwives
- UK National Screening Committee
- NHS Sickle Cell and Thalassaemia Screening Programme
- NHS Fetal Anomaly Screening Programme
- NHS Antenatal and Child Health Screening Programme
- Antenatal Results and Choices
- National Genetics Reference Laboratories
- UK Genetic Testing Network
- Genetic Interest Group
- National Blood Service
- National Haemoglobinopathy Reference Lab.

Key ethical, legal and social challenges

Ethical challenges to implementing this form of testing within specific NHS services identified within the report include:

- **safeguarding patient autonomy**
- **providing for informed consent**
- **ensuring equity of access**
- **avoiding specification creep**
(*adoption for new purposes without sufficient justification*)

Non-clinical applications of the technology such as social sex selection and paternity testing raise questions as to whether policy should be developed to regulate direct public access to these tests, some of which are already available via the internet.

Geneticists' perspective

"...These technical advances provide challenges and hope for significant improvements in genetic prenatal diagnosis for couples in the UK and worldwide. The expert working group report however also stresses the vital importance of the full evaluation of the technical, social, ethical and healthcare delivery implications of these novel non-invasive prenatal techniques and as such provides the scientific and medical communities with sound guidelines for the introduction of these new technologies into NHS practice once full evaluations have been carried out"

- Dr John A. Crolla / Dr Helen White,
National Genetics Reference Laboratory
(Wessex)

Recommendations

The Working Group concluded that the **implementation of non-invasive prenatal diagnosis for clinically significant genetic disorders is desirable, both to improve the quality and management of antenatal care and to facilitate parental reproductive choice.** Technological development for these purposes should therefore be supported within the UK; however, a number of issues must be addressed before the technology could be widely introduced in the NHS.

The main findings of the group were:

- **Reliable non-invasive prenatal diagnosis using fetal DNA is already possible for some applications and likely to become available for others within the next 3-5 years.**
- **The NHS should take steps now to ensure that it is able to respond in a timely and appropriate manner as the technology develops. This includes formal evaluation of the test for different applications, development of specified care pathways and national best practice guidelines, and oversight from the appropriate authorities.**
- **Both public engagement efforts and health professional education are urgently needed regarding the potential of the technique and its limitations.**
- **The technique should only be used according to standardised protocols within agreed clinical pathways, with formal audit and monitoring processes, and quality assurance frameworks. This will ensure appropriate use and accurate, reliable results.**

- **Non-invasive prenatal diagnosis is already available privately on a direct-to-consumer basis, and may have an increasing impact on NHS primary care and antenatal services. A voluntary code of conduct should be supported to help ensure the quality of private services.**
- **Ethical and social issues associated with some of the broader implications of non-invasive prenatal diagnosis using fetal DNA warrant further consideration and research.**



The full report, executive summary and additional appendix, *Ethical, legal and social issues arising from cell-free fetal DNA technologies*, are available for free download from the PHG Foundation website:

www.phgfoundation.org

The PHG Foundation is an independent multidisciplinary policy research and development organisation working to achieve better health via the responsible and effective application of genomic science and technology in health services.