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Cell-free fetal nucleic acids for non-invasive prenatal diagnosis

Report of the UK expert working group
Executive summary

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www.phgfoundation.org

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The PHG Foundation is the working name of the Foundation for Genomics and Population Health, an independent charitable organisation (registered in England and Wales, charity No. 1118664 company No. 5823194), which works with partners to achieve better health through the responsible and evidence-based application of biomedical science.

Disclaimer: the field of non-invasive prenatal diagnosis is extremely dynamic and technology is developing very rapidly; this report is accurate as of 7th January 2009.

Executive Summary

This report reviews the scientific and clinical status of the use of circulating cell-free fetal nucleic acid (cffNA) technology for non-invasive prenatal diagnosis (NIPD), a rapidly developing and dynamic field. 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 cffNA testing is to be implemented for different applications within the NHS. The report has been produced by a Working Group consisting of representative stakeholders, including relevant clinicians (GPs, obstetricians, midwives and geneticists), scientists, NHS commissioners, public health experts, ethicists and patient representatives.

The landmark discovery of cell-free fetal DNA (cffDNA) in maternal blood during pregnancy was made more than a decade ago. At the time it was recognised that, although cffDNA represents only a small fraction of the total cell-free DNA in the maternal circulation during pregnancy, the fact that it can be reliably detected from 7 weeks gestation, and is comprehensively cleared within a few hours of birth, could have important clinical consequences. The promise of that breakthrough is now being realised as the technology is translated into clinical practice for the non-invasive prenatal detection of specific fetal genetic traits.

In this report, we identify four distinct clinical applications of the technology: first, fetal sex determination in pregnancies at risk of a sex-linked disease, through detection of male Y chromosome DNA; second, diagnosis of certain single gene disorders, particularly through detection of a paternally inherited mutation; third, detection of fetal aneuploidy such as Down syndrome, in which there is a small but detectable change in the ratio between chromosomes; and fourth, diagnosis of fetal blood type in pregnancies at risk of incompatibility, particularly the Rhesus factor D (RhD) blood antigen. Although technical development is still ongoing, the diagnostic accuracy of the technique is expected to be very high in all applications.

To date, the translation of cffNA technology from research into clinical practice for each application has been somewhat fragmented, and influenced by the supporting infrastructure, relevant service provision and clinical setting. This report seeks to synthesise these different applications in order to provide a service-based overview of the implications for the NHS of implementing this technology. Hence, the potential applications have been divided into three categories in terms of their implications for antenatal care: specialist genetic services for high risk families, standard antenatal testing, and routine management of pregnancy. In the first two categories, cffNA testing could significantly reduce the use of invasive techniques for prenatal diagnosis (such as amniocentesis and chorionic villus sampling, which currently result in miscarriage in around 1% of cases), as well as allowing earlier prenatal diagnosis; the technology is also likely to be substantially cheaper than current invasive diagnostic testing. In the final category, testing could improve patient care through better targeting of anti-D therapy, which is currently given to all RhD negative women without testing to prevent a potentially fatal maternal immune response against a RhD positive fetus.

This service-based perspective raises a number of wider issues. Firstly, it highlights the ethical challenges to implementing cffNA testing within specific NHS services, including safeguarding patient autonomy, providing for informed consent, ensuring equity of access and avoiding adoption of the technology in new clinical areas without sufficient clinical consideration and ethical justification (a phenomenon known as specification creep). Secondly, in reviewing the implications of cffNA testing as a whole, it becomes apparent that there are a number of non-clinical applications of the technology, such as social sex selection and paternity testing. These tests are already available directly to the consumer over the internet, raising questions as to whether policy should be developed to regulate direct public access to these tests.

In the UK, tests based on the analysis of cffDNA have been available as a service to hospital trusts since 2001 to determine fetal RhD status in high risk sensitised women, and is also available in some NHS hospitals for fetal sex determination where there is clinical justification. In the US, the technology is currently being developed and tested by the diagnostics company Sequenom®, which expects to launch a commercial screening test for Down syndrome during 2009. Nonetheless, there are a number of key issues that need to be addressed before this technology can be widely implemented in the NHS.

The working group believes 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, and that the development of cell-free fetal nucleic acid technology for these purposes should be supported within the UK. The key findings and recommendations from the working group are as follows:

(1) NIPD using cell-free fetal DNA (and RNA) is likely to become increasingly available within the next 3-5 years, and the NHS should take steps now to ensure that it is able to respond in a timely and appropriate manner as the technology develops.

(2) Public engagement is urgently needed and should be pro-actively pursued with a clear, accurate and consistent message that recognises the limitations of cffNA testing.

(3) Professional education is urgently needed, particularly for key health care workers, and should be started immediately by relevant professional bodies.

(4) Formal evaluation of the use of cffNA testing for each application within a specified care pathway should be undertaken prior to implementation within the NHS.

(5) Formal audit and monitoring processes should be established for all non-invasive prenatal tests based on cffNA technology.

(6) National best practice guidelines should be developed by key clinical services to ensure that cffNA testing is only used within agreed clinical pathways.

(7) Standard protocols should be developed by expert laboratory services that include the whole care pathway, supplemented by quality assurance frameworks to ensure accuracy, reliability and comparability of results.

(8) Private NIPD services are already available on a direct-to-consumer basis, which will impact on NHS services; although the extent to which regulation can and should be applied to these services is debatable, development of a voluntary code of conduct should be supported to help ensure quality.

(9) Oversight from appropriate statutory authorities is needed to ensure responsible, effective and timely implementation of cffNA technology for NIPD within the NHS.

(10) Additional research is needed to investigate some of the broader implications of cffNA testing for NIPD.

The full report and recommendations are available from **www.phgfoundation.org**

Working Group Representation

The following professional bodies and advisory groups were represented on the working group; a full list of the members of the working group is given in Appendix I.

Patients

- Antenatal Results & Choices
- Genetic Interest Group

Physicians and scientists

- Antenatal & Child Health Screening Programme
- British Society of Fetal & Maternal Medicine
- British Society Human Genetics
- European SAFE Network of Excellence
- Joint Committee on Medical Genetics
- National Blood Service
- NHS Sickle Cell & Thalassaemia Screening Programme
- NHS Fetal Anomaly Screening Programme
- Royal College of General Practitioners
- Royal College of Midwives
- Royal College of Obstetricians & Gynaecologists
- Royal College of Pathologists
- Royal College Physicians
- UK National Screening Committee

Laboratories

- Great Ormond Street Hospital Regional Molecular Genetics Laboratory
- International Blood Group Reference Laboratory
- Manchester National Genetics Reference Laboratory
- National Haemoglobinopathy Reference Laboratory
- Wessex National Genetics Reference Laboratory

Commissioners and NHS Advisory bodies

- Human Genetics Commission
- UK Department of Health
- UK Genetic Testing Network

Steering Group

Dr Hilary Burton	Public Health Consultant, Programme Director, PHG Foundation, Cambridge
Dr Lyn Chitty	Reader in Clinical Genetics and Fetal Medicine, UCL Institute of Child Health
Dr Tessa Homfray	Consultant Clinical Geneticist, St Georges Hospital Medical School
Dr Ainsley Newson	Senior Lecturer in Biomedical Ethics, Centre for Ethics in Medicine, University of Bristol
Mrs Gail Norbury	Director, NE Thames Molecular Genetics Laboratory, Great Ormond Street Hospital
Professor Peter Soothill	Head of the Division of Obstetrics and Gynaecology, University of Bristol

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