Evaluation of molecular tests for prenatal diagnosis of chromosome abnormalities

GM Grimshaw1*
A Szczepura1
M Hultén2
F MacDonald3
NC Nevin4
F Sutton5
S Dhanjal2

1 Centre for Health Services Studies, University of Warwick, Coventry, UK
2 Biological Sciences, University of Warwick, Coventry, UK
3 West Midlands Regional Genetic Laboratory and Consultancy Services, Birmingham Womens Health Care Trust, Birmingham, UK
4 University of Belfast, Belfast, Northern Ireland
5 Statistician, Learning and Skills Council, Coventry, UK

* Corresponding author

Executive summary

Health Technology Assessment 2003; Vol. 7: No. 10
How to obtain copies of this and other HTA Programme reports

An electronic version of this publication, in Adobe Acrobat format, is available for downloading free of charge for personal use from the HTA website (http://www.ncchta.org).

Also, a fully searchable CD-ROM containing the full text of all HTA monographs is available from the NCCHTA offices or via the HTA website. The CD-ROM is updated with the most recently published monographs every 6 months and is available free of charge to postal addresses in the UK.

In addition, printed paper copies of this report may be obtained by writing to:

The National Coordinating Centre for Health Technology Assessment, Mailpoint 728, Boldrewood, University of Southampton, Southampton, SO16 7PX, UK.

Or by faxing us at: +44 (0) 23 8059 5639
Or by emailing us at: hta@soton.ac.uk
Or by ordering from our website: http://www.ncchta.org

The website also provides information about the HTA Programme and lists the membership of the various committees.
Executive summary

**Background**

Many women undergo prenatal tests for chromosome abnormalities in their baby, usually following identification of an increased risk of the baby having Down syndrome. One test that can show up abnormalities likely to lead to mental or physical handicap is done by sampling the amniotic fluid that surrounds the baby, usually around 14 weeks of pregnancy. There is a very small risk of miscarriage with this procedure and parents are warned of this. If the test shows there is chromosome abnormality, parents may want to discuss whether to continue with the pregnancy.

Until now parents have had to wait for up to 3 weeks for the results of this test (karyotyping), which is based on culturing the cells sampled from the amniotic fluid. Karyotyping allows examination of all the baby’s chromosomes. New DNA tests have been developed that can give results in 2–3 days. These new molecular tests, using fluorescence in situ hybridisation (FISH) or the quantitative polymerase chain reaction (Q-PCR), search for abnormalities in specific chromosomes. Errors in chromosomes other than in those tested will not be disclosed. The abnormalities not tested for are much more rare. For example, only 4 in every 1000 babies tested will have one of these rarer abnormalities and some of these may be identified during other examinations, for example during routine ultrasound examinations.

Many parents will welcome the quicker result from a more focused test but some may be prepared to wait for the result of a test that examines all the chromosomes.

**Objectives**

The objectives of this study were to:

- assess the cost-effectiveness of molecular tests, and consider possible changes in current testing protocols.

**Design**

Two-stage trial; technical performance assessed through a blinded comparison of molecular tests against the accepted gold standard (karyotyping) in a laboratory setting in the first stage; effectiveness and cost-effectiveness measured in a service setting in the second stage. Measurement of anxiety and health status of women; willingness to pay (WTP) for four stakeholder groups; and survey of UK obstetricians and midwives.

**Setting**

Two study sites – the catchment areas for the West Midlands Regional Genetic Laboratory and the Northern Ireland Regional Genetics Centre, Belfast.

**Participants**

**Blinded samples:** 2376 Down only molecular tests; 1576 multiplex/5-probe tests; 3952 karyotyping.

**Trial:** 194 women (141 intervention group; 53 control group).

**WTP:** 1000 general public; 141 women; 84 partners; 105 health commissioners.

**Interventions (diagnostic tests)**

- Molecular tests for the five most common chromosome abnormalities.
- Molecular tests for Down syndrome only.
- Karyotyping.

**Main outcome measures**

Technical capacity, diagnostic accuracy, diagnostic impact, patient outcome and cost-effectiveness.
Results

Technical capacity – does the test perform reliably and deliver accurate (i.e. precise) information?

FISH and Q-PCR test results are as reliable and precise as karyotyping for the five most common chromosome abnormalities.

Diagnostic accuracy – does the test contribute to an accurate diagnosis (of chromosome abnormalities)?

The ability to detect the five most common chromosome abnormalities, absolute sensitivity and specificity, are 1.00 and 1.00 for FISH and 0.9565 and 0.9997 for Q-PCR, respectively.

The ability to detect all clinically significant chromosome abnormalities, relative sensitivity and relative specificity, are 0.8605 and 0.9999 for FISH and 0.8234 and 0.9996 for Q-PCR, respectively.

Diagnostic impact – will the test replace other diagnostic tests or procedures?

Preferences of clinicians, women and other stakeholders will influence diagnostic impact.

Fifty-seven per cent of obstetricians expressed a preference for molecular tests for most patients and karyotyping for a minority; only 15% would choose both tests. The views of midwives were similar.

Most women (67%) and 54% of partners expressed a pre-test preference for molecular tests. Health commissioners were undecided.

Patient outcome – does the test contribute to improved health/reduced anxiety for the patient?

Quality of life measure (EuroQol EQ-5D) demonstrated significantly increased health status linked to more rapid test results. Anxiety measure (Speilberger) exhibited similar impact.

Cost-effectiveness – does the test use improve cost-effectiveness compared to alternative interventions?

Molecular tests are less expensive than karyotyping. As a replacement within larger laboratories (> 1100 specimens per annum), Q-PCR is preferred; for smaller laboratories (< 450), FISH is preferred. Five testing regimes were assessed in terms of cost-effectiveness:

1. Molecular test and karyotyping for all women.
2. Molecular test as a replacement for karyotyping

Simple cost-effectiveness analysis based on the cost per case detected (all cases) demonstrates that regimes 2, 3 and 5 are more cost-effective than karyotyping and 1 and 4 are not. This pattern does not change if cost-effectiveness analysis is limited to clinically significant cases only.

Cost–utility analysis estimates a cost per quality-adjusted life-year gained of £23,542–£41,939 for regime 1; it was not possible to assess regimes 2–5 using this technique.

Regimes 2, 3 and 5 will not detect some rare chromosome abnormalities (approximately 2–4, 1–2 and 1 per 1000 women tested, respectively).

Introduction of regime 1 could increase annual UK test costs by up to £2.8 million. Regimes 2 and 3 should result in savings of up to £1.76 million per annum, and regime 5 approximately two-thirds of these savings. Regime 4 would be largely cost neutral.

Conclusions

Implications for healthcare

In the current climate, the use of prenatal testing is determined by individual clinicians, laboratories and hospitals. There is evidence of a lack of equity of provision, and of regional and local variations with regard to primary risk assessment. This may well be replicated with regard to final diagnosis if molecular tests are introduced without discussion of appropriate implementation protocols based on this report.

Debate and consensus will be necessary to develop clinical protocols for introduction of molecular tests and prevent continuation of inequities and variations. Important ethical issues must not be overlooked and crucial to this debate will be the needs and wishes of parents as well as the views of other stakeholders such as scientists, obstetricians and midwives.
Recommendations for future research
It was not possible to assess the impact on quality of life and anxiety of replacing karyotyping with molecular tests for all women or selected groups of women within this study. This could be addressed ethically as tests are introduced into service and should form part of the implementation. Alternative mechanisms for delivery of test results should also be explored to optimise the advantage of faster results. There is currently little evidence of the potential impact of false-negative results on parents and on the healthcare system. If molecular tests are to replace some karyotyping tests, further research in this area is needed.

Publication
The NHS R&D Health Technology Assessment (HTA) Programme was set up in 1993 to ensure that high-quality research information on the costs, effectiveness and broader impact of health technologies is produced in the most efficient way for those who use, manage and provide care in the NHS.

Initially, six HTA panels (pharmaceuticals, acute sector, primary and community care, diagnostics and imaging, population screening, methodology) helped to set the research priorities for the HTA Programme. However, during the past few years there have been a number of changes in and around NHS R&D, such as the establishment of the National Institute for Clinical Excellence (NICE) and the creation of three new research programmes: Service Delivery and Organisation (SDO); New and Emerging Applications of Technology (NEAT); and the Methodology Programme.

This has meant that the HTA panels can now focus more explicitly on health technologies (‘health technologies’ are broadly defined to include all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care) rather than settings of care. Therefore the panel structure has been redefined and replaced by three new panels: Pharmaceuticals; Therapeutic Procedures (including devices and operations); and Diagnostic Technologies and Screening.

The HTA Programme continues to commission both primary and secondary research. The HTA Commissioning Board, supported by the National Coordinating Centre for Health Technology Assessment (NCCHTA), will consider and advise the Programme Director on the best research projects to pursue in order to address the research priorities identified by the three HTA panels.

The research reported in this monograph was funded as project number 94/43/04.

The views expressed in this publication are those of the authors and not necessarily those of the HTA Programme or the Department of Health. The editors wish to emphasise that funding and publication of this research by the NHS should not be taken as implicit support for any recommendations made by the authors.

Criteria for inclusion in the HTA monograph series
Reports are published in the HTA monograph series if (1) they have resulted from work commissioned for the HTA Programme, and (2) they are of a sufficiently high scientific quality as assessed by the referees and editors.

Reviews in Health Technology Assessment are termed ‘systematic’ when the account of the search, appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

HTA Programme Director: Professor Kent Woods
Series Editors: Professor Andrew Stevens, Dr Ken Stein, Professor John Gabbay, Dr Ruairidh Milne and Dr Chris Hyde
Managing Editors: Sally Bailey and Sarah Llewellyn Lloyd

The editors and publisher have tried to ensure the accuracy of this report but do not accept liability for damages or losses arising from material published in this report. They would like to thank the referees for their constructive comments on the draft document.