



postnote

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NHS GENETIC TESTING

The sequencing of the human genome has generated large amounts of genetic data. Research is now focused on the difficult task of translating these raw data into clinically useful information and therapies. New genetic tests are considered by some as likely to be among the first applications. This POSTnote looks at the prospects for genetic tests and testing technology and examines a series of policy, organisational and ethical issues raised by current and possible applications.

Genetic testing

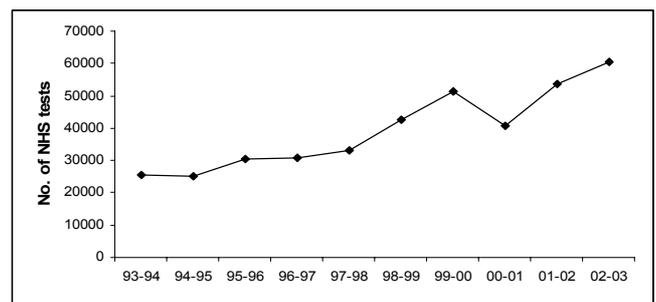
Genetic information can be inferred indirectly through observation of eye colour, family history and biochemical tests. Despite no agreed definition, genetic testing generally refers to more direct testing, such as analysis of the structure of DNA (cytogenetic testing) or changes within the DNA sequence itself (molecular testing).

Tests currently available

Genetic tests are used both before and after the appearance of disease symptoms. Tests to diagnose rare inherited disorders, such as cystic fibrosis and Huntington's disease, make up the vast majority of current services. Testing techniques can now also be used to examine non-inherited conditions, for example, analysing acquired changes in cancer tumours. Current uses of genetic tests include:

- diagnosing individuals with rare inherited disorders, where individuals inheriting a specific genetic change will nearly always develop the associated disorder;
- identifying individuals with an inherited genetic change making them at high risk of a small sub-type of some cancers, such as breast and bowel cancer;
- characterising leukaemias and tumours by analysing acquired genetic changes;
- prenatal / neonatal screening of a foetus or newborn baby for conditions such as Down's syndrome;
- examining whether genes are functional, as in tests for blood diseases such as sickle cell disease;
- carrier testing to test for the presence of a genetic

DNA molecular tests (England Regional Genetics Centres, 1993-2003).¹



change in healthy individuals (such as Fragile X, an inherited learning difficulty) which may have implications for children or their relatives.

Genetic testing can advance understanding of a condition, as well as providing diagnostic and prognostic information. In some cases, a genetic test may be cheaper and less intrusive than other methods. For example, a DNA test, as opposed to a muscle biopsy, can be used to confirm diagnosis of muscular dystrophy. For many rare genetic conditions interventions are unavailable, although receiving a diagnosis can enable an individual to understand their condition and retain control of their lives. While no treatment exists for Huntington's disease, a neurologic disorder with late onset typically from aged 45 onwards, diagnosis can inform future lifestyle and reproductive decisions.

At present, DNA molecular tests for around 300 rare single gene disorders are offered on the NHS. In total these disorders affect between 1-5% of the population and are estimated to cost health and social services £2 billion each year.² In the NHS in England, the bulk of genetic testing is performed in 20 Regional Genetics Centres, each serving a population of 2-6 million people. These centres offer clinical diagnoses, laboratory testing and counselling services for individuals and their families.

Possible future applications

Numerous forecasts have been made about the potential of genetic testing. However, common conditions such as heart disease arise from complex interactions between environmental (smoking, exercise, diet) as well as genetic factors. Therefore, tests would focus on genetic risk factors that predict disease, rather than providing definitive diagnoses. Predictive testing may be useful if early diagnosis allows inter-ventions or targeted care to reduce suffering or aid future decisions. For example, carriers of familial hyper-cholesterolaemia can be treated with cholesterol lowering drugs from a young age. Three future applications are discussed below.

'Common' diseases

- **potential:** identifying individuals with an increased genetic susceptibility to 'common' diseases to aid clinical management.
- **challenges:** clear evidence of the predictive strength of genetic factors for common conditions is needed. Identifying the many genes involved will be difficult and there is uncertainty about how to design research studies to ensure they give meaningful results.
- **prospects:** routine testing for common diseases would impact significantly on healthcare. However, much of the genomic data and testing technologies to predict common disease are currently "*more suited to research than to routine diagnostic activity*".³ Estimates for the emergence of useful clinical tests vary from 5-30 years. Large scale studies are needed to determine which genetic factors are clinically relevant. The UK Biobank, (POSTnote 180) "*will track participants health over the next 10,20,30 or more years*"⁴ to study the interaction between genes, lifestyle and environmental factors, offering one indication of the timescale involved.

Pharmacogenetics

- **potential:** pharmacogenetics examines the relationship between genetic variation and an individual's response to medicine. It potentially marks a departure from the "one size fits all" approach to prescribing, to one where the results of a pre-prescription genetic test guide subsequent drug selection and dosage levels.
- **challenges:** age, gender and drug interactions also influence the effect of medicines. Stratifying patient groups according to their genetic profile raises some clinical, regulatory and ethical questions.⁵ Pharmacogenetics will not impact on all drugs and early identification of relevant targets is needed.
- **prospects:** many clinical geneticists expect pharmacogenetics to drive the future expansion of genetic testing services. However, a better evidence base is needed and it remains uncertain how the interests of all relevant stakeholders (industry, clinicians, regulators and patients) can be met.

Molecular pathology

- **potential:** the rapid and simultaneous analysis of a number of genes offers the potential to obtain a molecular signature for diseases such as cancer, to guide subsequent prognosis and treatment.

- **challenges:** current IT capacity in the NHS is considered inadequate to meet predicted demands in this area (see below). Testing technology is expensive and changing legislation about the use of human tissue samples may raise hurdles for research.
- **prospects:** characterising disease at the genetic level offers benefits for diagnosis and management. The need to validate current studies on independent patient sets means such benefits are 5-10 years away.

Recent government policy

Genetic services in the UK are among the most comprehensive in Europe.⁶ However, the increased workload has placed strain on current services. The possible future expansion in genetic tests could push demand beyond existing capabilities. In response to these expectations, in 2001, the Secretary of State for Health announced an initial investment of £30 million, to:

- combat the shortage of staff specialising in genetics;
- create two National Genetics Reference Laboratories to assess new advances and methods of service delivery;
- create six Genetic Knowledge Parks (GKPs), to build a knowledge base on all aspects of human genetics (jointly funded by Department of Trade & Industry);
- establish a UK Genetic Testing Network (UKGTN), to co-ordinate the evaluation, commissioning, funding and prioritisation of services for genetic disorders.

In 2003, the Department of Health published the Genetics White Paper, outlining an additional £50 million for further investment (see box 1).

Box 1: 'The Genetics White Paper'²

The White Paper focused on a series of objectives:

- Strengthening specialised services – upgrading laboratory facilities and expanding specialist staff. Six areas have received £18 million to modernise.
- Building genetics in mainstream services – fund pilot schemes to examine benefits of genetics in mainstream clinical areas, such as cancer and heart disease.
- Spreading knowledge across the NHS – training commissioners and setting up a NHS Genetics Education and Development Centre in Birmingham.
- Generating new knowledge and applications – funding GKPs and a range of research projects, continuing to develop an appropriate regulatory framework and promoting public understanding of genetics.

Given the research required before early associations between genes and common disease can be turned into real health benefits, some critics have claimed that the White Paper raises unrealistic expectations. Opponents have called for caution in prioritising genetic 'solutions' to disease and the need for greater consideration of the long term economic and clinical effectiveness of genetics in the NHS (see box 3).

However, despite descriptions of the £50 million as a 'drop in the ocean', the signal sent out by the White Paper has been widely praised by patient groups and those working in human genetics. Such groups support the Government's recognition of the importance of genetics and the need to improve awareness and strengthen existing services.

Issues

Evaluation of new tests and services

There are over 1,500 clinical disorders with associated genetic mutations, although not all of these form the basis of clinically useful tests. An evaluation of the use and accuracy of emerging tests is needed.

Establishing clinical usefulness

To date, tests have moved into clinical use in an ad hoc way, depending on local expertise and funding. The UKGTN has begun to formalise the assessment process for rare inherited disorders. Associations between genetic variations and common diseases are being reported with increasing regularity. The evidence base for genetics is expanding but there are uncertainties around the most appropriate use of some tests (see box 2).

Oversight of tests

Legal requirements for medical tests do not cover the predictive value of the test, nor its usefulness for clinical decisions. The extent to which the regulation of genetic tests needs to be distinct from other medical tests is contentious. While some genetic tests provide information that is similar to other testing methods, other genetic tests yield sensitive personal genetic information.

The Medical Devices Regulations are intended to harmonise the regulation of all medical testing kits sold over the counter in the UK. However, there are fears that these may prohibit transfer of samples between laboratories, a practice that is fundamental to the rare disease testing network. The newly formed Medicines and Healthcare Products Regulatory Agency (MHRA) is currently seeking legal clarification on this issue.

As illustrated above, genetic testing has a series of distinct applications. The Human Genetics Commission (HGC) recommended that all genetic tests should be subject to some sort of oversight.⁷ Other groups have called for a national independent body to be set up to oversee all aspects of genetic testing. However, the governance and policy issues raised by each application vary and an alternative view is that improving clinical governance and education would be sufficient to ensure the appropriate use of most tests.

Quality Assurance

As testing expands, there is an increased need to establish best practice and quality assurance policies. A survey across European laboratories revealed a high number of technical errors and evidence of poor result interpretation and reporting.⁸ In the UK, external quality assessment schemes are in place for some diseases and the majority of genetic laboratories offering clinical testing have official accreditation. This will be compulsory by 2005. Many accept that the creation of best practice guidelines will be particularly important if testing services expand beyond specialist laboratories. It is also seen as one way of maintaining public trust in testing services

Box 2: Case Studies

Haemochromatosis.

Hereditary haemochromatosis is a disorder characterised by inappropriate iron absorption which, without treatment, can cause death. In 1996, the 'haemochromatosis gene' (HFE) was identified and testing followed shortly after. However, only a minority of individuals with a positive genetic test result go on to develop the disease, creating doubts over the clinical utility of the test. Monitoring iron levels may be more cost effective and accurate than a DNA-based test. Despite these concerns, testing for HFE gene mutations is the third most common test in the NHS (2002-3). Assessments to clarify appropriate use of this test are currently in progress.

Breast Cancer

Breast cancer involves lifestyle and environmental factors. However, current studies suggest 3-5% of cases are largely caused by inherited genetic variations. Genetic tests for these highly predictive changes in the BRCA 1 & 2 genes became available in the mid 1990s and now account for the highest workload of all postnatal genetic tests (2002-3).

However, there has been uncertainty regarding the appropriate use of such tests. In June 2004, partly in response to regional variation in testing policies, the National Institute for Clinical Excellence (NICE) clarified that testing was suitable only in a minority of cases. The NICE guidelines will standardise practice and aid the identification of women for whom testing is appropriate. In the short-term the guidelines will result in an increase in women receiving genetic testing, but will also lead to improved selection of patients recommended for testing.

Organisation of Genetic Services

Existing services provide low volume testing and counselling to small, widely dispersed patient groups. The White Paper did not establish a national blueprint for future organisation, instead allowing individual NHS Specialised Services Commissioning Groups to reappraise local organisation. However, future testing possibilities raise issues that the government will need to continue considering on a national level, including:

- *New single gene disorders* – there is already a gap in service provision for rare genetic diseases. Additional centralised funding may be needed to fund rare tests.
- *Familial risk of inherited cancers* – existing services are concentrated at a small number of laboratories. Despite recent investment (see Box 1), novel tests in this category would prompt further capacity concerns.
- *Predictive testing for common diseases* – these tests would put large demands on the service because of higher patient numbers. Sophisticated result interpretation would also be required.
- *Molecular pathology* – the routine use of genetic testing techniques in molecular pathology would require high volume testing of tissue samples. The most effective division of labour between clinical genetic and pathology laboratories is unclear.
- *Pharmacogenetic testing* – most pre-prescription testing would require rapid turnaround of results or even point of care testing (currently unavailable) and suitably trained on-site staff.

Research is also needed to examine the delivery and outcomes of services (see box 3).

Box 3: Impact of genetic testing

The importance of research examining the commissioning, organisation, and impact of genetic testing is reflected both in the work of the Genetic Knowledge Parks and in the £1.5 million White Paper investment into research into genetics based health services. This money will accompany existing social science research focusing on issues including:

- communication and response to genetic information;
- equity of access for all patient groups;
- public engagement and confidence in genetics;
- national and international policy for genetics;
- the ethics and regulation of developments in genetics;
- the economic and clinical effectiveness of genetics.

The recommendations from such work need to be widely disseminated and fed into future policy and clinical practice. The importance of developing strong links between science and social sciences is recognised by the Department of Health; academic initiatives like the Innovative Health Technologies programme aim to promote this.⁹

Genetic Profiling & Screening

The White Paper raised the prospect of screening babies and storing information about their genetic profile. It stated, "*although its possible introduction is some years away.. it is important to think through (the benefits and risks of) such possibilities now..*" All existing screening programmes must meet criteria set out by the National Screening Committee (NSC). The aim of genome profiling is to tailor healthcare to the individual. However, it raises ethical concerns over data security, confidentiality, and consent. A public forum run by the Royal Society in 2003 found that people were concerned by these issues and suggested that a clear legislative framework be set up to maintain confidentiality of information. The HGC and NSC will report on this issue at the end of 2004.

Patient Confidentiality and Consent

More tests will mean more genetic data on more people. The storage of genetic data raises questions about confidentiality of information and consent to its use. The Human Tissue Bill and the Data Protection Act are designed to protect patients. A HGC survey of 'Public Attitudes to Genetic Information'¹⁰ found concerns that employers and insurance companies may gain access to personal genetic information. Since 2001, a moratorium has prohibited insurance companies from using genetic data. The Genetics and Insurance Committee monitors compliance with the moratorium. A longer-term policy solution will be needed when it ends in November 2006. The HGC has also called for legislation making it an offence to test people's DNA without their consent.

Genetics and IT

Information systems are vital to:

- look for genetic features in disease;
- aid GPs in increasingly complex referral decisions;
- track samples through the testing network;
- support and validate data for laboratory management
- improve the efficiency of reporting patient results.

However, a recent review concluded: "*There is no coherent approach to the implementation of IT systems in genetic laboratories...the majority of systems are bespoke, developed in-house, and not integrated with*

pathology or other hospital IT systems."¹¹ IT advances in genetics must be closely aligned with the National Programme for IT (POSTnote 214). The White Paper outlined £1million over three years to improve this situation although it is currently unclear whether this money will be sufficient and how it will be spent.

Impact on staff and patients

The Regional Genetics Centres provide a vital service for individuals with rare genetic disorders and the UKGTN is currently working to ensure equitable access to genetic services and support. To date, genetic services have depended on a relatively small, specialised workforce. However, the expanding role of genetics is in contrast to the limited number of genetic counsellors, where planned increases will take time to impact. With test referrals increasingly originating from non-genetics specialists, staff across the NHS may need to be trained to identify patients for whom testing is appropriate and to communicate information about genetic risk. Well trained counsellors are particularly important given the reactions (guilt, anxiety) that some people experience on learning genetic information. The Genetics and Education Centre (see Box 1) has the role of catalysing education and training in genetics. Nurses & midwives, undergraduates and postgraduates, and pharmacists have been identified as early priorities.

Overview

- The range of genetic testing services is increasing. The pace and scale of growth will depend on whether proposed applications prove feasible and useful.
- The Government has invested in expanding existing services in anticipation of such a rise.
- Tests need to be safe, accurate, useful, and cost effective before their introduction into clinical services.
- Continued growth will have implications for the organisation of testing services and already strained IT.
- Staff need to be suitably trained and patients need access to equitable services and support.

Endnotes

- 1 Source: Clinical Molecular Genetics Society
- 2 *Our Inheritance, Our Future*. Department of Health, June 2003
- 3 Bell, J. Predicting disease using genetics. *Nature*, 429: 453-455
- 4 www.biobank.ac.uk
- 5 Webster et al, *Nature Reviews Genetics*, 5, No. 9 (in Press)
- 6 Harris R. Genetic Services in Europe. *Eur. J. Hum. Genet*, 5 suppl 2, 1997: 1-220
- 7 *Genes Direct*. Human Genetics Commission. March 2003
- 8 *Towards QA and harmonisation of genetic testing services in the EU*. Report EUR 20977 EN. Sept 2003
- 9 www.york.ac.uk/res/iht
- 10 *Public Attitudes to Genetic Information*. Human Genetics Commission. March 2003.
- 11 *A review of information services in English Regional Genetics Centres*. Commissioned by Manchester NGRL. April 2004.

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