

GENETIC TESTING

Within the next few weeks, scientists will publish a 'working draft' of the human genome. One impact of this will be the development of genetic tests for a range of different purposes. Such tests will eventually change the way that diseases are classified, allow more accurate diagnosis, provide doctors with predictive tools, and allow drugs to be 'matched' with patients.

This briefing note examines recent developments in the field of genetic testing, and analyses the issues that arise.

GENES AND DISEASE

The first draft of the human genome will pave the way to understanding the mechanisms behind a range of diseases. This new understanding will not merely be confined to 'classic' inherited disorders; it will also extend to more common diseases where genetics is only one of the factors involved.

Rare Inherited Disorders

Diagnostic tests for relatively rare inherited disorders account for most of the genetic services currently offered through the NHS regional genetics centres. The majority of such conditions are 'single gene disorders' (SGDs), arising from a fault (mutation) in just one gene. Thousands of SGDs have been identified to date, ranging from conditions such as cystic fibrosis¹ (affecting around 1 in 2,500 UK births) and Huntington's disease (~1 in 3,000), to extremely rare disorders like Friedreich's ataxia (~1 in 54,000). Other genetic disorders include **chromosomal disorders** such as Down's syndrome² (affecting around 1 in 800 births).

Common Complex Disorders

Scientists have long known that many of the common 'killer' diseases (e.g. cancer, diabetes, neurodegenerative diseases and some types of heart disease) have a genetic component. Such conditions arise as a result of a complex interplay between genetic and environmental factors. Research (**Box 1**) is already starting to reveal some of the underlying genetic factors involved in these conditions. Expectation is high that future research linking genetic data with medical records, environmental exposure and family background will unravel the underlying causes of many such disorders. This raises the prospect of genetics-based diagnosis and classification of disease. It will also pave the way for predictive tests for assessing whether a person might develop a particular condition later in life.

¹ See Postnote 124, March 1999 on Cystic Fibrosis (CF) for more details.
² Down's individuals inherit extra chromosome 21 material.



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BOX 1 GENES AND SOME COMMON DISEASES

Alzheimer's disease (AD) – around 2% of cases in the UK are familial AD, characterised by early onset. Some 40% of such cases are associated with mutations in the presenilin-1 (PS1) gene. By far the most common form is late onset AD, which is genetically complex. To date, the only gene that has been unambiguously implicated is Apolipoprotein E (ApoE).

Cancer – cancer is now seen as being a genetic (but not necessarily an inherited) disease. Genes are involved in all stages of the development of tumours, from initiation, angiogenesis (growth of new blood vessels to supply the tumour), invasion, progression and eventual metastasis (spreading of the tumour); a variety of genetic factors involved in control of the cell cycle and processes such as apoptosis (cell suicide) have been implicated. Genes have also been linked with increasing risk of specific types of cancer:

- **breast cancer** – most cases of breast cancer are sporadic, and the genetic factors involved have yet to be identified. Mutations in the BRCA 1 and 2 genes are linked with increased risk of the rarer, familial form of the disease.
- **colorectal cancer** – around 20% of colorectal cancer cases are thought to be inherited. There are two distinct types of this form of the disease. One involves mutation(s) in a (cell adhesion) gene on chromosome 5, while the other mutation(s) in one or more of 4 genes involved in repairing mistakes in DNA copying.
- **ovarian cancer** – 5-10% of ovarian cancers are familial. Three hereditary patterns are known: ovarian cancer alone, ovarian and breast cancers, or ovarian and colon cancers. BRCA1 mutations are implicated in most families affected by the first two of these.
- **prostate cancer** – research has suggested the involvement of susceptibility genes, but predictive testing is not yet available.

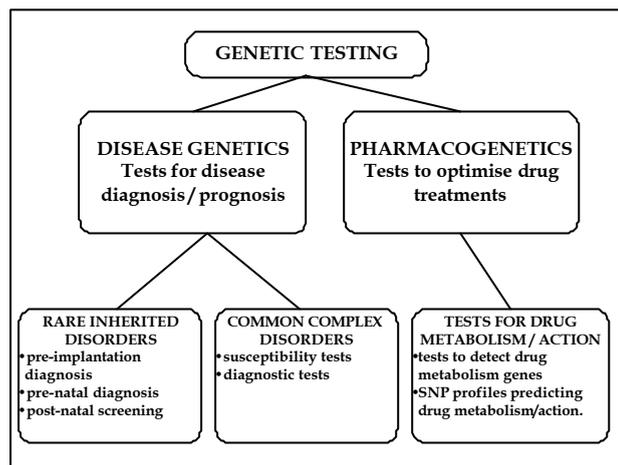
Diabetes – both major forms of diabetes tend to run in families. Several different genes have been implicated in increased risk of type 1 diabetes (which affects young people). Genetic studies have recently suggested a link between increased risk of type 2 (which mainly affects older people) and a gene or genes on chromosome 12 involved in insulin secretion.

Heart disease – ApoE is also thought to be implicated in the development of certain types of heart disease and conditions such as stroke through its effects on lipid (fat) metabolism. Other genes (e.g. angiotensin converting enzyme [ACE], angiotensinogen) have been implicated in predisposition to hypertension and heart disease. *Source: 'Genetic Tests and Future Need for Long Term Care in the UK', Report of the Continuing Care Conference, CCC, July 1999*

Other Diseases Involving Genetics

Genome research may reveal a larger role for genes in a number of other diseases than was hitherto thought likely. For instance, genetics may be a factor that determines a person's susceptibility to certain **infectious diseases**. Recent research suggests that susceptibility/resistance to diseases such as tuberculosis and malaria may be determined by small individual variations in gene sequences (e.g. single nucleotide polymorphisms, SNPs). Other studies have also suggested that **behavioural disorders** (e.g. manic depression, schizophrenia) have a small genetic component. Environmental factors play a very large role in such conditions, but understanding the genetic component may provide a basis for improved diagnosis and treatment.

FIGURE 1 DIFFERENT TYPES OF GENETIC TESTING



Source: Adapted from Roses AD, "Pharmacogenetics and Future Drug Development and Delivery", *The Lancet*, 355, 1358-61

GENES AND DRUG ACTION

Individual genetic variations also affect the way that drugs act and are broken down within the body (pharmacogenetics). Such variations mean that the same drug can affect different people in different ways. For instance, sequence variations in the genes coding for the cytochrome P450 family of enzymes are known to cause wide variation in the rate and manner in which drugs are broken down. Such variations can dictate whether the drug is efficacious or causes an adverse reaction, and influence the optimum dose required.

GENETIC TESTING

Most genetic tests conducted in the UK are diagnostic tests for inherited disorders, offered to families at high risk. But this situation is set to change as a result of rapid advances in science and technology. Research is identifying large numbers of new genes and sequence variations (e.g. SNPs³) involved in disease, drug action and drug metabolism. The technology for conducting genetic tests has also advanced: positioning short gene sequences onto tiny microarrays ('biochips') allows a single DNA sample to be simultaneously screened for tens of thousands of sequence variations. Such developments will place genetics – and genetic tests – at the heart of medicine. New tests will be developed for a range of different purposes (Figure 1) including:

- Diagnosis of rare disorders.
- Diagnosis of common disorders (classification of which will increasingly be based on gene tests).
- Susceptibility tests for common disorders. Tests

BOX 2 UK ADVISORY/REGULATORY FRAMEWORK

GOVERNMENT ADVISORY / REGULATORY BODIES

Human Genetics Commission (HGC) – a new strategic body which advises Ministers on developments in genetic technologies and their impacts on humans. It will involve stakeholders and the public through regular consultation exercises, and liaise with other regulatory and technical bodies. HGC replaces the **Human Genetics Advisory Commission (HGAC)**.

Advisory Committee on Genetic Testing (ACGT) – a non-statutory body which advises UK Health Ministers on developments in genetic testing. Its work is currently being transferred to HGC.

Advisory Group on Scientific Advances in Genetics (AGSAG) – an advisory body set up by the Department of Health (DH)/Medical Research Council (MRC) that has now been dissolved.

Genetics and Insurance Committee (GAIC) – a new non-statutory advisory body that will evaluate specific genetic tests and assess their application to particular conditions and their reliability and relevance to particular types of insurance.

NON-GOVERNMENT BODIES

British Society for Human Genetics (BSHG) – a professional society with members working in the field of medical genetics (i.e. in clinical, diagnostic and genetic counselling services) as well as those involved in genetic research.

UK Clinical Molecular Genetics Society (CMGS) – has members from within the NHS Regional Clinical Genetics Centres and is active in education, training, research and quality assurance.

Royal College of Physicians (RCP) and **Royal College of Pathologists (RCPath)** – are active in the formulation of guidelines, training, education, quality assurance, etc. and recently established a **Joint Committee on Medical Genetics (JCMG)** with BSHG.

Nuffield Council on Bioethics (NCB) – an independent body established in 1991, jointly funded by the Nuffield Foundation, Wellcome Trust and MRC.

Sources: www.medinfo.cam.ac.uk/phgu/info_database/Testing_etc/testing.asp and www.leeds.ac.uk/cmgs/.

for genetic 'risk factors' on healthy people may allow doctors to assess predisposition to disease.

- Pharmacogenetic tests to tailor drug treatments to individual genetic profiles. For instance, tests may be used to predict efficacy, adverse drug reactions or to optimise dose.

ISSUES

A 1998/99 review of the regulatory and advisory framework for biotechnology led to the setting up of the HGC (Box 2). This Commission is currently drawing up its work plan for the next 2-3 years. Among the main issues it has identified are the storage and use of genetic information, developments in genetic testing, the provision of genetic services, gene patenting and the consequences of genetic reproductive choices.

Organisation of Genetic Services

The predicted expansion in the range of genetic tests available raises the issue of how best to organise NHS testing. As far as testing for rare genetic disorders is concerned, the BSHG (Box 2) have identified three main problems:

- Rarity – total clinical demand across the UK for some tests is less than 100 per year.

3 The Wellcome Trust and 10 drug companies recently announced a consortium to construct a database of ~300,000 SNPs by April 2001.

- Discontinuity between research and establishing a service; this can lead to tests for a rare disorder being discontinued once research funding ends.
- Funding - inefficiencies and inconsistencies in the funding mechanism for such tests.

One possible option (suggested by the BSHG) is for the establishment of a UK Genetic Testing Network. Under this proposal, two regional centres will offer tests for any single rare disorder (a cost-effective way of ensuring reliability, quality assurance and patient access). This approach was endorsed in a recent ACGT Consultation on Pre-Natal Genetic Testing, which recommended organising testing services for such conditions on a supra-regional or national level, concluding that *"appropriate funding for such testing should be identified"*⁴.

Genetic tests for common complex disorders are more likely to be needed at GPs' surgeries (rather than regional centres). Groups such as the CMGS (Box 2) have called for a national strategy to address funding and organisational issues associated with the changing nature of genetic services offered by the NHS. The NHS Executive Board has set up an expert working group on laboratory services for genetics, that will report to the Board and the HGC by summer 2000. Its terms of reference include:

- assessing the current extent of genetic testing within the NHS;
- identifying those tests/technologies likely to become available in the next 5-20 years and considering the potential organisational and financial implications for the NHS;
- identifying potential barriers to testing (e.g. technical, organisational, or resource constraints, education/training needs);
- developing models of service delivery for genetic tests.

Education and Training

As genetic testing becomes integrated into mainstream medical practice, doctors will need education/training in medical genetics. Priorities identified by the Royal Colleges and patient groups (e.g. GIG - the Genetics Interest Group) include:

- **Education** - to improve medical genetics teaching for undergraduates and during nurses' training.
- **Continued training** - to improve qualified practitioners' knowledge of medical genetics.
- **Manpower issues** - a national strategy to assess future need for specialised medical geneticists and genetic counsellors, and to ensure sufficient

numbers of suitably qualified people are trained.

Assessing who to train to what level will be influenced by factors such as the type of tests developed, public demand for them, and the extent to which companies attempt to market tests direct to the public. The JCMG (Box 2) is considering how manpower planning for medical genetics could be co-ordinated on a national basis.

Counselling

Genetic counselling from clinical geneticists or genetic nurse specialists is offered to individuals and families affected by or at increased risk of a genetic disorder to allow them to make fully informed choices. Likely developments in genetic testing raise issues in two main areas. First are concerns that an increase in the number of diagnostic tests performed will increase demand for counselling. This will have resource and manpower implications and could affect the quality of the counselling offered, particularly if it leads to an increase in counselling by non-specialists. Second are the issues raised by the changing nature of the tests. Historically, genetic counselling has been associated with informing reproductive decisions. The development of predictive tests for common diseases means that counsellors will also need new areas of expertise (e.g. in risk assessment) to interpret the tests. Where such tests identify increased risk, counselling will also need to include medical or lifestyle advice to minimise the chance of a condition developing.

Patenting Issues

Genetic tests also raise issues concerning intellectual property rights. For instance, Myriad Genetics is a US company that owns patents on a highly specific and sensitive test for BRCA1 and 2 mutations and their use in the predisposition testing for breast and ovarian cancer. Its licensing agreements with US healthcare providers require all BRCA tests to be conducted in Myriad's own laboratory in Salt Lake City. The company has announced its intention to market its testing services in Europe and has recently signed an agreement with a UK company.

Groups such as GIG and CMGS have expressed concern about the possible adverse effects of a 'US-style' licensing agreement on the provision of BRCA-testing services by the NHS. The Department of Health is keeping this issue under active consideration in order to secure the optimal services for the NHS.

4 ACGT Report for Consultation on Prenatal Genetic Testing, DH, 2000.

Employment and Insurance Issues

Genetic testing also raises issues over whether third parties such as insurers or employers should have access to the results of tests. And if so, under what circumstances and for what purposes?

Insurance

As far as insurance is concerned, HGAC concluded in 1997, "*it is unlikely that actuarially important genetic predictions of common causes of adult death will be available and validated, for some time to come*". The Association of British Insurers published a 1997 code of practice on genetic testing establishing that:

- insurers **cannot** require applicants to undergo a genetic test to obtain insurance;
- but **can** require disclosure of existing test results under certain circumstances.

Specifically, insurers can require disclosure only where a genetic test shows an increased risk, and after a test has been validated. Validation requires showing the test is reliable and relevant to the insurance product in question. GAIC (Box 2) recently consulted interested parties on an application form for approval to use genetic test results for insurance risk assessment. The importance of validation is illustrated by the example of tests for mutations in the BRCA1 and 2 genes. These were widely available in the US *before* the results they yielded could be accurately interpreted. Only after further research did it become clear that BRCA tests were of value only to those (minority of) women with a family history of breast cancer.

Employment

From an employer's point of view, genetic test results might provide useful information on whether a current or prospective employee suffered from (or was predisposed to) a condition that might:

- lead to prolonged sick-leave;
- place them or other employees at risk;
- be particularly sensitive to a specific feature of a work environment.

Genetic tests are not currently widely used by employers. HGAC considered the issues concerning possible future uses in 1999, concluding that:

- Genetic tests are not yet reliable enough for current use for employment purposes.
- Individuals should not be required to take a genetic test for employment purposes, nor to disclose the results of genetic tests they have already taken (unless the test provided evidence to assess a person's ability to do a job safely or

their susceptibility to harm from doing a job).

- Employers should offer a genetic test if aspects of the workplace/work pose specific risks to individuals with certain genetic characteristics.
- All tests should be offered on a consensual basis, be accurate and reliable, and the results treated in accordance with data protection principles. Results should be interpreted carefully and communicated to the person tested; professional advice should be available.

Pharmacogenetics

Genetic tests can be used to identify sub-groups of patients most likely to benefit from a drug, as well as those likely to suffer an adverse reaction to it. This has implications for the design of clinical trials and for the evaluation of adverse drug reactions. For instance, companies may be able to design smaller, faster and cheaper trials by including only sub-groups of patients identified as being likely to benefit from a drug. Drugs tested in this way would only be authorised for use in particular genetic sub-groups of patients. Monitoring such sub-groups for rare adverse drug reactions might reveal further genetic variations relevant to the drug in question. In this way, the 'genetic definition' of the sub-group for each drug could be continually fine-tuned. The implications of such developments would require detailed consideration by regulatory bodies in the UK and elsewhere.

Other Issues

These and other issues raised by genetic testing are discussed in more detail in a forthcoming POST report on human genomics. These include:

- The use of genetic testing in pre-natal diagnosis (e.g. whether the increased availability of genetic tests might lead to a rise in the number of women opting for termination of pregnancy).
- Pre-implantation genetic diagnosis (PGD) - the use of genetic tests to select embryos prior to implantation during *in-vitro* fertilisation. A recent HFEA/ACGT consultation paper sought views on issues such as access to PGD and the seriousness of the conditions tested for.
- Wider ethical, legal and social issues involved with the collection, storage and use of genetic information (e.g. the MRC/Wellcome Trust project to collect genetic information on 500,000 UK people to assist the development of better diagnostics/treatments for genetic disease).