

## Consumer Genetic Testing



DNA sequencing is getting faster and cheaper. This has paved the way for the development of genetic tests for predisposition to diseases. These are now being marketed directly to consumers over the internet. This POSTnote explores the scientific, regulatory, and ethical issues related to such tests.

### Background

In 2000, the International Human Genome Sequencing Consortium announced the first draft of the human genome sequence. The enterprise cost roughly \$3 billion, and took 13 years. Subsequent technological advances mean that:

- whole genomes can now be sequenced in a matter of days, at a cost of under \$1,000, although the costs of analysis and interpretation are much higher;
- genotyping, which takes a snapshot of up to a million snippets of sequence spread across the whole genome, is now a routine technique that costs around \$100.

### Genetic Tests

Until recently, genetic testing was a specialist service provided on referral, usually to individuals with a family history of a disease. A patient would be offered a diagnostic service for a single genetic condition, identified through patterns of family history and/or symptoms, and coupled with professional counselling. Several companies now offer genotyping services via Direct to Consumer (DTC) testing to provide some assessment of genetic risk of more common diseases. There is little hard information available about the size of this market<sup>1</sup>. Typically, such companies process a sample of a person's DNA, provide a report analysing the results, and set up an account where customers can compare their genome data with a regularly-maintained database of sequences and their associated traits. The traits tested for vary but typically include an individual's:

### Overview

- Technological and analytical advances are turning the analysis of genetic information into a consumer commodity.
- Companies are now offering predictive tests for a wide range of disease predispositions.
- Concerns have been raised about the accuracy and usefulness of such tests, and the interpretation of the results by consumers or health professionals.
- Specific regulatory challenges concern the handling of personal genetic data, possible non-consensual testing of third parties, and the value of the information supplied by companies offering these tests.

- propensity to a range of diseases by using predictive tests (see next section);
- reaction to a particular drug or compound (to inform medical treatment, so-called pharmacogenetics);
- responses to specific nutrients (nutrigenomics);
- origins and ancestry in population terms.

### Predictive vs Predisposition Genetic Tests

Of the various different types of genetic tests, it is the predictive and predisposition tests that have aroused most interest. These can be used to assess if an individual:

- Is affected by a **single gene disorder**. These are conditions such as Huntington's disease or cystic fibrosis, which are directly caused by mutations in a single gene. They are traceable through family lines and often have severe consequences for the individual. These tests, also known as pre-symptomatic, are highly predictive of the disease in question.
- Is at higher risk of being affected by a **complex disorder** such as cardiovascular heart disease or type 2 diabetes. These are caused by a complex (and often not fully understood) combination of multiple genetic and environmental influences. These so-called susceptibility or predisposition tests look at patterns of DNA sequences across many different genes and their usefulness (predictive value) relies on Genome Wide Association Studies (GWAS). These studies look for statistical associations between specific gene sequence patterns

and certain diseases. Their predictive value is limited, and has been the subject of recent debate (see Box 1).

#### **Box 1. Genome Wide Association Studies (GWAS)**

The basic building blocks of DNA are nucleotides, the four common bases (A,T,C and G) that build up the human genome. While all people share a similar version of the human genome, each individual has his/her own unique patterns of variations in the nucleotide sequence. These include variations in the sequence of single nucleotides called single nucleotide polymorphisms (SNPs). GWAS compare the SNP patterns of people diagnosed with a common disease against those of people not known to have the disease in question. The comparison can reveal statistical associations between certain sequence patterns and certain diseases. Such studies allow researchers to generate hypotheses about which genes may be implicated in which diseases. However, further studies are then required to test these hypotheses, and to investigate how the genes in question contribute to a disease.

#### **Usefulness of Predictive Genetic Tests**

Many of the DTC genetic tests currently offered to consumers are marketed as being predictive. However, tests for predisposition to complex disorders are only as good as the GWAS (Box 1) on which they are based and there are growing concerns about the validity of some such studies. For instance, the findings from GWAS account for only a small proportion of the predicted heritability in most diseases studied so far. Furthermore, GWAS simply detect statistical links between sequence variations in a particular gene and the likelihood of being diagnosed with a particular disease. This does not prove that the gene is somehow implicated in the disease, nor does it tell researchers anything about the function of the gene and how it might be involved in the condition in question.

Recent research has also shown variation between the predictions made when purchasing the same test from different DTC companies. For instance, the US General Accounting Office paid for the same individuals to be tested by four different companies. One individual was told that he was at below-average, average, and above-average risk for prostate cancer and hypertension<sup>2</sup>. This has led some to question whether tests that rely on GWAS associations are suitable for use as a predictive tool.<sup>3,4</sup>

#### **Interpretation of Test Results**

Another key issue raised by DTC genetic tests is the interpretation of the test results, which are delivered in terms of absolute and relative risks. Different business models are in operation, with some companies providing a detailed analysis of the results while others release raw data back to the consumer, who can subsequently analyse them through readily-accessible online software. In addition, some companies will have counsellors available to support their customers while others do not provide this service. DTC tests thus raise interpretation and counselling issues that potentially affect individual consumers, healthcare professionals and third parties.

#### *Individual Consumers*

Consumers may find interpretation of genetic test results difficult as it requires an ability to understand complex

patterns of probabilities of predisposition to a range of diseases. Results must also be considered in the context of consumers' hopes and fears, which might be driving the purchase of the tests in the first place. However, there is some evidence that increases in levels of anxiety triggered by access to genetic information might have been overstated.<sup>5,6</sup>

#### *Healthcare Providers*

In a recent survey of European clinical geneticists, 90% of respondents said that predictive DTC genetic testing should require direct medical supervision. However, this would place pressure on already stretched clinical genetics services in the UK. Another option would be for DTC companies to adopt existing guidelines for better communication of predictive results.<sup>7</sup>

Experience in the US suggests that an increasing number of the wealthy 'worried well' are active consumers of DTC tests and are seeking to discuss their test results with health professionals. There is no evidence to date of a similar trend occurring in the UK. However if it did, it is not clear whether GPs and other healthcare professionals within the NHS could meet the increase in demand. A recently published report by the UK Human Genomics Strategy Group includes specific recommendations for improved genomics training and education for healthcare professionals to meet some of these future needs.<sup>8</sup>

#### *Third Parties*

A feature of genetic testing is that it not only reveals information about the individual taking the test, but also information potentially relevant to other generations in the same family. The Nuffield Council on Bioethics and others suggest that DTC companies need to point this out to consumers prior to them buying genetic tests.

### **Legal and Ethical Framework**

Recent reports by the House of Lords Science & Technology Committee, the Nuffield Council on Bioethics, the Human Genetics Commission (HGC) and the Foundation for Genomics and Population Health have all highlighted areas of concern related to the current marketing of DTC genetic tests. Each has issued specific recommendations, or guiding principles for a review of the industry.<sup>9,10,11,12</sup> None of the organisations recommended an outright ban. Rather they focused more on the protection of the consumer in terms of validity of information, consent and data management, and access to qualified counselling if so required (depending on the nature of the test performed).

#### **Regulation of Genetic Tests**

Under EU law genetic tests are classified as medical diagnostics and regulated by the In Vitro Diagnostic (IVD) Medical Devices Directive (Box 2). This framework is enforced in the UK through the Medicines and Healthcare Products Regulatory Agency (MHRA). The regulations focus on assessing the safety and accuracy of a device rather than the benefits or indirect risks to the consumer.

**Box 2. Legal Framework for Test Regulation**

- The EU In Vitro Diagnostic (IVD) Medical Devices Directive, first proposed in 1998 and fully implemented since 2003, seeks to provide a unified European approach to the regulation of diagnostic tests, including genetic ones. The IVD Directive classifies devices according to the perceived level of risk, based on who the IVD user may be or the effect that the IVD may have if it fails to perform as intended. There is consensus that the current IVD Directive no longer effectively regulates a rapidly developing technological field. The Directive is currently under review and a new version is expected by 2015 following a public consultation in 2011.
- In the UK, the Human Tissue (2004) Act made non-consensual analysis of the DNA of a living person illegal in England. Similar legal provisions were made under the Human Tissue (Scotland) Act 2006. Different UK nations have also taken different approaches to legislative protection against genetic discrimination. Since 2001, the Association of British Insurers (ABI) has operated a voluntary moratorium on the use of genetic tests by insurance companies which has been extended until 2014.
- In the USA, under the Federal Food, Drug and Cosmetics Act, the Food and Drugs Administration (FDA) has authority to regulate medical devices. While this includes Laboratory Developed Tests (LDTs), including genetic tests, the FDA currently exercises this authority only to regulate test kits. However, it recently announced its intention to move towards implementing risk-based regulation of LDTs, reflecting developments in personalised medicine. This may require additional regulatory powers, or legislative changes. In 2008, the US Congress specifically passed the Genetic Information Non-discrimination Act (GINA), designed to prohibit the use of genetic information in health insurance and employment. However, it is unclear how this would apply specifically to the DTC genetic testing market. The US House of Representatives Committee on Energy and Commerce also recently launched an investigation into DTC genetic testing. Finally, the former Secretary's Advisory Committee on Genetics, Health, and Society published recommendations in 2008 to the US government regarding better protection for consumers of these products.

Under the terms of the IVD Directive:

- tests that are developed in-house by health institution laboratories – so called Laboratory Developed Tests (LDTs) – are exempt from pre-market assessment (PMA);
- test kits sold to laboratories must conform to the terms of the IVD Directive but do not require PMA;
- test kits sold to consumers who then conduct the test themselves do require PMA.

As outlined in Box 2, there have been several recent initiatives both in the US and the EU to introduce more stringent regulatory requirements for DTC genetic tests. The European Commission hopes that revised legal proposals will come into force as early as 2015. In the USA, where many of the DTC genetic companies are based, the FDA has the authority to regulate the tests but to date has chosen not to do so apart from tests marketed DTC as kits.

**Ethical Framework**

In 2007, the Council of Europe published Guidelines for Quality Assurance for Genetic Testing for Health Purposes, followed by an additional Protocol to the Convention on Human Rights and Biomedicine in 2008. Implementation of the protocol is informed by the European Society of Human Genetics on issues related to the accuracy and usefulness of the tests, and by the Organisation for Economic Co-

operation and Development guidelines on quality assurance in molecular genetic testing.

In regards to DTC, the key concerns relate to access to proper interpretation of test results and a guarantee of appropriate genetic counselling to understand their implications. However, the Protocol provides co-signature states with a degree of discretion when deciding which tests can be accessed without specified medical supervision.

**Accreditation of Tests and Testers**

UK tests developed in-house by NHS laboratories are classified as LDTs and thus exempt from pre-market approval but are part of wider accreditation networks. For instance, the UK Genetic Testing Network (UKGTN) was established in 2003, and provides a trusted and validated port of call for professionals wanting to corroborate the effectiveness of new genetic tests. The content of the UKGTN listings is focussed on the single gene disorders dealt with by the NHS and therefore does not cover the majority of products serviced by DTC companies.

Since its creation in 2005, the EU-funded EUROAGENTEST has been actively involved in quality management and harmonisation of standards and practice in relation to genetic testing. Further initiatives within the EU aim to create an additional system of voluntary accreditation for laboratories carrying out genetic tests, to exert quality control on those performing them rather than just the tests themselves. In the UK, laboratories performing genetic tests can be accredited through the Clinical Pathology Accreditation UK Ltd scheme. Accreditation ensures regular inspection of these laboratories. However, this does not apply to the clinical efficacy or interpretation of the results of the tests they provide.

The USA launched the Evaluation of Genomic Applications in Practice and Prevention programme in 2004. Its goal is to establish an evidence-based, systematic process of evaluation of genetic tests in transition from laboratory development to clinical practice. This was followed in 2008 with a recommendation from the US Secretary's Advisory Committee on Genetics, Health and Society, to create a public registry for genetic tests and the laboratories performing them. In 2010, the National Institutes of Health led the establishment of a Genetic Testing Registry in the USA, with the aim of becoming an accredited and trusted public database for researchers, healthcare providers, and consumers alike.

**Regulatory Barriers**

Concerns about the accuracy and validity of GWAS-based predictive testing have led to calls for stricter regulation of DTC genetic tests. For instance, a public consultation on the IVD Directive in February 2011 outlined clear support for a risk-based classification of tests using the specifications of the Global Harmonisation Task Force (GHTF) model (Box 3). Respondents also indicated support for the continued exemption of LDTs developed by health institution

laboratories (i.e. non-commercial) from PMA requirements, thus minimising the bureaucratic burden and enabling quick access to technological development. However, it was also outlined that DTCs posed specific concerns, and the Commission was keen to clarify the situation, emphasising public protection while also supporting innovation and enabling rapid adoption of useful tests. Critics have highlighted two main pitfalls that the current regulatory framework presents for an area of rapid technological advances, both within the EU as well as internationally.

- DTC genetic testing is predominantly an on-line, and thus international market that is difficult to regulate.
- The current lack of requirement for clinical evidence of the strength of the link between a particular gene sequence and a claimed clinical significance.

### Box 3. Global Harmonization Task Force (GHTF)

GHTF is a voluntary partnership of government and industry representatives from the US, Australia, Canada, the EU and Japan. It promotes international harmonisation of medical device regulation through the preparation and distribution of guidelines. The model advocates for classification of all genetic tests as medium risk, and the inclusion of Pre-Market Approval. Some suggest that this cannot be done, because of differential levels of risk between tests being provided as DTC. GHTF is currently preparing further guidance in regards to clinical evidence requirements for IVDs.

Alternative models for 'appropriate' regulation of this market will have to ensure adequate levels of protection, as well as the accuracy and usefulness of tests, while not stifling innovation and the potential benefits to consumers from accessing new technology.

A House of Lords Committee report has also identified risk as a critical parameter, and advocated for a change in the risk classification of genetic tests within the IVD Directive from low to medium risk.<sup>9</sup> It suggested that tests should be classified according to the degree of predictiveness of the test and the ability of the consumer to act upon the information.

### Consumer Protection

In 2006, the US Federal Trade Commission issued a specific alert, warning consumers of the limitations of the results provided by DTC genetic testing companies, and advising them to seek clarification from qualified health care professionals; a similar sentiment was expressed by the GAO in their 2010 report on DTC.<sup>2</sup> At the heart of any attempts to review existing regulation is the need to ensure "truth" in the way such tests are marketed and assess the evidence base for claims made about the predictive value of the tests supplied. This will require systematic monitoring and assessment of online service providers. The UK Advertising Standards Authority and the Committee for Advertising Practice work together to uphold "truth in labelling" of online advertised products and, through collaboration with the regulators including the MHRA, the enforcement of the consumer protection regulations.<sup>13</sup> The European Advertising Alliance also helps to report non-

compliant online sites to the respective national regulators.

## Data Management

### Consumers vs. Research Subjects

Under the current DTC model, consumers are buying information about their genome sequence and are thus in control of who can access that information. However, DTC companies are increasingly seeking consent from consumers to use sequence data for research purposes. A recent study has questioned whether sufficiently informed consent has been obtained from those purchasing the tests.<sup>14</sup> For example, details of a company's policies on data may be hidden in lengthy terms of service agreements or privacy policies making it difficult for consumers to make informed choices.

Concerns have also been raised about what happens to datasets when DTC companies merge or close.<sup>15</sup> The House of Lords Science and Technology Committee, the Nuffield Council on Bioethics and the HGC have all recommended that genetic testing firms should make information about their data policies prominently available to potential consumers in lay language.<sup>9,10,11</sup> The EU Data Protection Directive's definition of "sensitive data" currently excludes genetic data. However, the Directive is under review and this may have a substantial impact on how these datasets are managed in the future by DTC companies.<sup>16</sup>

### Healthcare Providers Model

As the cost of gene sequencing continues to fall, genomics may be offered more routinely by health care providers as part of a preventive medicine approach. However, implicit in such a model is that the healthcare provider would have access to gene sequence data to optimise its usefulness as a predictive and preventive tool. While the sharing of such data for research purposes is widespread throughout the world, such projects include safeguards such as consent and anonymisation of datasets as standard practice. Appropriate safeguards will have to be in place, to protect individuals.

### Endnotes

1 <http://www.nature.com/gim/journal/v12/n9/full/gim201097a.html>

2 <http://www.gao.gov/new.items/d10847t.pdf>

3 <http://goo.gl/Mh8gqa>

4 <http://www.nejm.org/doi/full/10.1056/NEJMop0810107>

5 Caulfield, 2011. *Human Genetics*, **130** (1), 23-25.

6 <http://www.ashg.org/cgi-bin/2010/showdetail.pl?absno=21043>

7 For example see: <https://www.eshg.org/eshgdocs.0.html>

8 Building on Our Inheritance; <http://goo.gl/krwSa>

9 Genomic Medicine; <http://goo.gl/tCXt8>

10 Medical Profiling and Online Medicine; <http://goo.gl/475Gk>

11 A Common Framework of Principles for direct-to-consumer genetic testing services; <http://goo.gl/830rq>

12 Wright *et al*, 2011. *Genet Med*; **13** (4):295-300.

13 Extending the Digital Remit of the CAP Code; <http://goo.gl/rkjpa>

14 Howard *et al*, 2010. *EMBO Reports*, **11** (8), 579-582.

15 Zawati *et al*, 2011. *Human Genet*, **130** (3), 425-32.

16 <http://goo.gl/Ulekq>