GENETIC TESTS AND HEALTH:

The Case for Regulation

GeneWatch UK

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The completion of the Human Genome Project has opened some new avenues for medical research. It has also led to the marketing of genetic tests which identify parts of the sequence of an individual's genome. Genetic tests are marketed over the internet; via alternative healthcare providers or private GPs; or via the health service. They have also been sold in High Street stores. Tests may be accompanied by health advice or products which are supposedly tailored to the customer's individual genetic make-up. One day, people may even be able to buy a scan of their whole genetic make-up[1]. This briefing considers the case for regulating these genetic tests.

Some important questions are:

- Will people taking genetic tests be given reliable and accurate information?
- Will the products and advice supplied with genetic tests be good for health?
- Are controls in place to prevent misleading marketing by commercial companies?

Types of genetic test

People taking genetic tests are not simply given a list of the chemical letters that make up part of the sequence of their DNA. They are normally given an interpretation of what this sequence means. This could be information about family relationships (usually paternity); their ancestry; or their current or future health. Health-related tests are usually accompanied by advice on lifestyle and/or medication.

"Germ-line genetic tests", considered in this briefing, measure the genetic make-up that people are born with - the DNA sequence that occurs in every cell of the body. Everybody has a slightly different sequence. Two other types of genetic test are not covered in this briefing. These are "somatic genetic tests" and biochemical tests. "Somatic genetic tests" look for changes to the DNA sequence that have occurred during a person's lifetime, often in a cancer cell. Biochemical tests are often used to diagnose genetic disorders - they do not directly measure the sequence of the DNA but other products in blood or sweat that are directly related to the function of the gene.

Genetic disorders are caused by rare changes in the sequence of the DNA called "mutations" that are often inherited but can also arise spontaneously at conception. Most people with genetic disorders have symptoms in early childhood. More common differences in genetic make-up are called "polymorphisms". Each polymorphism occurs in 1% to 50% of the population. This type of genetic difference does not necessarily cause an illness, but may be linked with an increased risk of illness in the future - tests for these genetic variations are "predictive" rather than "diagnostic".

A few predictive genetic tests are now being offered to some adults within the NHS and are beginning to be marketed and advertised more widely on the internet and over-the-counter. Because everyone has common genetic variations, predictive genetic tests may become available to a much larger number of people than those with genetic disorders.

When is a genetic test useful for health?

An expert committee in the US has identified four factors that influence whether or not a genetic test is of benefit to health[2]: analytical validity; clinical validity; clinical utility; and social consequences.

The analytical validity of a genetic test is the accuracy with which the test can identify a particular DNA sequence. This is a technical issue which depends on the reliability of the laboratory method and the interpretation of the test. Quality assurance in some labs is questionable: over half of the genetics laboratories included in a European survey did not undergo any form of inspection and almost none had external accreditation[3]. Establishing analytical validity is clearly important, but is not sufficient to ensure that the test results are not misleading.

The clinical validity of a genetic test depends on how accurately a particular genetic difference predicts the risk of a disease. This depends on the reliability of the statistical studies linking the genetic variation with an increased risk of the disease.

For genetic disorders, symptoms are often already present when a test is used. Even if the test is "pre-symptomatic" the predictive value is usually high, although age of onset and severity may still vary considerably. However, the same genetic disorder can often be caused by many different mutations in the same gene with varying severity[4, 5, 6].

For common diseases, the aim of genetic testing is usually to try to predict the risk that a healthy person will become ill in the future. Many common diseases have rare forms which are largely inherited. In this minority of 'familial' cases, the genetic test can have a relatively high predictive value, although the risk of having the gene may be uncertain and vary with other factors. The predictive value of genetic tests in most people is usually much lower because complex factors, including social, economic and environmental, biology and chance are involved. One test does not give a single answer and many people with a genetic variation will not get the disease and many people without it will. Trying to predict future health in this way is much more complicated than diagnosing an existing genetic disorder: it is more like trying to predict the weather. Studies have shown that most reported links between genes and common diseases later turn out to be exaggerated or wrong, so there is a real danger of misinformation if the clinical validity of the test has not been established (see Box 1). The same problems often apply to genetic tests intended to predict a person's response to different medicines (pharmacogenetic tests)[7].

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Box 1: Genetic research and common diseases

One study found that only 6 of 600 published links between genes and common diseases had been shown to be robust[8]. Another paper could confirm only 9 out of the 55 most studied links[9]. Strong associations between genes and diseases found in small, early studies were typically not confirmed by larger, later ones, which found either a weak association or none at all. For example, although some rare genetic forms of extreme obesity are known, so far none of the dozens of genetic factors that have been linked to 'normal' obesity have been confirmed[10, 11]. Studying genetic differences may help improve our understanding of disease. But predicting people's future risk may be impossible for most diseases, because they are so complex[12].

The clinical utility of a genetic test depends on how useful it is for making medical decisions. Even a valid test may not be very useful depending on whether interventions are available to reduce a person's risk (lifestyle advice, medication, surgery, screening, or a different choice of drug) and whether the test is a good way to decide who should have which interventions. For genetic disorders, the lack of effective treatments may be the most important problem. For common disorders, the European Society of Human Genetics has warned that testing for 'susceptibility' genes is likely to be of limited utility, because of the importance of environmental factors in these diseases[13]. Box 2 gives an example of an existing genetic test which is generally not useful in deciding who should get what advice or treatment.

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The most useful preventive measures (quitting smoking, eating healthily, exercising, living in a healthy environment) are of benefit to everyone. In many cases, genetic testing would only make these interventions less effective (by

restricting help to the 'genetically susceptible') and more expensive. More harmful interventions (such as surgery and some medications) may be rejected as too dangerous to use in healthy people, even if they are at high genetic risk, or they may be unacceptable to many patients. Therefore, genetic tests are often only useful in specific circumstances and often only when combined with other information (such as family history).

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Box 2: Factor V Leiden and venous thrombosis

Factor V Leiden is the name of the first "DNA-based" genetic test kit to be approved by the US Food and Drug Administration (FDA). The test kit, made by Roche Diagnostics, aims to identify people who have an increased inherited risk of developing blood clots in the veins of their legs and elsewhere (venous thrombosis)[14]. The link between Factor V Leiden mutations and venous thrombosis (its clinical validity) is relatively well established and this is now one of the most commonly performed genetic tests in US labs[15].

However, the clinical utility of the test is limited because it is not clear that people with mutations should be treated any differently from other people[16]. Because not everyone with venous thrombosis has mutations and not everyone with mutations gets venous thrombosis, the recommendations for treatment and prevention remain the same whatever a person's genetic test result. A possible exception is people with mutations who have a relative who already has thrombosis: some scientists argue that the test is useful for this much smaller group of people because they might benefit from preventive medication at an earlier age than is usually considered[17].

Factor V Leiden testing has been suggested in the past for certain groups of people at higher risk of blood clots such as women on the contraceptive pill and people taking long haul flights. However, even advocates of testing now accept that it is inappropriate for people with no family history of blood clots[17]. Because the predictive value of the test is poor, an estimated 10,000 women would have to be tested and 400 of them would have to stop taking the pill to prevent one case of venous thrombosis. Venous thrombosis is rarely fatal, so far more women (around 2 million) would need screening to prevent one death. On balance, this is likely to harm health by creating needless anxiety and large numbers of unwanted pregnancies.

Although Factor V Leiden mutations increase risk, most air passengers who develop deep vein thrombosis (DVT) do not have mutations. A 2001 study found that the risk of DVT could be reduced by wearing below knee fitted compression stockings, regardless of the passenger's genetic test results[18]. Consideration of age (people over 50 are more susceptible) seems to be more useful than a genetic test in helping to decide who should wear such stockings.

Broader social consequences are also important including the pros and cons of those at 'high genetic risk' taking preventive medication (potentially for life). Many people prefer alternatives, such as lifestyle changes[19, 20,]. Long-term medication may cause harmful side-effects, which may be hard to identify in advance. The benefits of preventive medication are also hard to assess, so scientists' view of benefit and harm may change as more research is done. For example, hormone replacement therapy was once thought to reduce women's risk of heart disease but it is now believed to *increase* risk of both heart disease and breast cancer[21].

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Marketing genetic tests and associated products

"*In the not-too-distant future, gene researchers envision that healthy persons will get a routine battery of genetic tests that predict their risk of heart disease, diabetes, and other ailments while they are still young and healthy. People could then adjust their lifestyle and diet, try preventive drugs, or take other action to reduce their risk of ever becoming sick*". Forbes.com, 11 Nov 2003[22].

Tests which identify common genetic variations have potentially staggering implications for the number of people who might be advised to take preventive drugs. For example, suppose a panel of 22 genetic tests each identified 5% of the population as 'at risk'. If the whole population took this panel of 22 tests, statistical analysis shows that two thirds of the population would have at least one 'at risk' test result[23]. In other words, most people would be told they had at least one 'bad gene'. If the predictive value of the tests is low, most of these people would not benefit, and might be harmed, by taking unnecessary medication.

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Given the massive marketing potential, it is not surprising that some biotech companies are already selling genetic tests combined with other products, mainly via the internet or alternative healthcare providers[24, 25] (Table 1). To have one of these tests, the customer takes a swab of DNA from inside their cheek which is posted to the company. A number of DNA-based laboratory tests are then made on the sample and a report sent back, sometimes via a health professional. One US company sells a skin cream, costing up to US$750 a jar, which it claims is "*customized based on each individual's DNA*"[26]. Another common approach is to recommend nutritional supplements based on test results.

Table 1: Genetic susceptibility tests currently on the market.

Company	Tests	Marketing strategy
DNA Direct (US) www.dnadirect.com	Predictive genetic tests include Alzheimer's disease, breast and colon cancer, heart disease and hearing loss.	Direct-to-consumer marketing planned to start in autumn 2004.
DocBlum (US) www.docbluminc.com	"Imagene" tests claimed to identify susceptibility to addictions.	Via the Internet.
Genova Diagnostics (US) www.genovations.com [Formerly Great Smokies Diagnostics Laboratory (GSDL).]	Four panels of "Genovations" tests claimed to relate to heart, bone, immune system and detoxification genes.	Via alternative healthcare providers[27] (with recommendations for supplements).
GeneLink (US) www.bankdna.com	"Nutragenetic" and "Dermagenetic" profiles with advice on vitamins and skin creams. Also profiles for genetic susceptibility to obesity and osteoporosis.	Via alliances with other companies, particularly those marketing nutritional supplements.
Interleukin Genetics www.ilgenetics.com	Tests for genetic susceptibility to gum disease.	Via dentists.
Market America (US) http://ezway.unfranchise.com	"NutriPhysical Gene SNP" with recommendations for supplements.	Via the internet.
MediChecks World Wide Ltd (UK) http://medichecks.com	A wide range of screening and diagnostic tests, including tests for genetic disorders and for Deep Vein Thrombosis (DVT).	Via the internet.

Myriad Genetics (US) www.myriad.com	Tests for hereditary ('familial' cancers).	Via health professionals but using advertising to the general public (see Box 3).
NuGenix (US). An alliance between GeneLink and Garden State Nutritionals. www.nugenix.com	Claims to help boost immune system and prevent cancer, heart disease, glaucoma and diabetes. Genetic tests marketed with supplements.	Via the internet and by phone.
One Person Health (Canada) www.onepersonhealth.com	"ONETest" includes genes claimed to cover: heart health; B vitamins; detoxification; bone health; inflammation; insulin sensitivity. Marketed with "customized vitamins".	Via the internet and by phone.
Sciona (UK) www.sciona.com	"Body Benefits" genetic screening kits combined with dietary advice, covering: nutrition; skincare; sport and fitness.	Marketed in Body Shop stores in Britain in 2001, but now withdrawn. Still available via some private GPs and alternative health clinics[28].

Professional bodies such as the American College of Medical Genetics (ACMG) oppose direct-to-consumer sales of genetic tests because they may harm health[29]. Many geneticists are concerned that these tests could do more harm than good and also damage trust in genetics in the future[30, 31]. They have criticised Sciona's tests as meaningless, unethical and irresponsible and the "Genovations" tests as "*bad science and a bad idea*"[32, 33].

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So far, the big pharmaceutical companies have not begun to market tests for common genetic variations, but this could soon change. The Swiss-based multinational, Roche, is the world leader in medical tests sales and plans to market genetic tests for 'predisposition' to common diseases along with lifestyle advice or medication[34, 35]. Roche has a licensing agreement with the Icelandic biotech company, DeCODE, to develop and commercialise these genetic tests. They plan to market a genetic test for risk of heart attack within 2 to 3 years[36, 37]. However, the published evidence for this test has been strongly criticised by other scientists[38] and the links between genes and diseases discovered by DeCODE in Iceland may be unreliable in other populations[39]. Roche has also been lobbying to weaken US regulation of genetic tests (see Box 4). Myriad is the first company to run a major advertising campaign for genetic tests in the US (Box 3).

Box 3: Myriad's advertising campaign

Rare mutations in the BRCA1 and 2 genes significantly increase a woman's risk of familial breast cancer, giving a lifetime risk of about 40-80%, and accounting for about 5% of cases. However, the risk associated with a BRCA1/2 mutation is better quantified in high risk families than in the general population, and the risk to an individual may vary due to other factors[40]. The clinical validity and utility of the test is therefore well established, but only for women who have a strong family history of breast or ovarian cancer. Some women from high-risk families choose to take the test and find it helpful. However, others prefer not to know because of the limited options for reducing risk (the main one is to have both breasts surgically removed).

The US company Myriad has a monopoly on BRCA1/2 testing in the US, although its patent applications in Europe have now been refused[41]. In 2003, Myriad ran an advertising campaign on US television, radio and in newspapers and magazines to try to get more women to take the tests. This was strongly criticised for giving women the misleading impression that everyone's risk of breast cancer can be quantified using genetic tests and reduced by 'known medical interventions[42, 43].

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Regulation

Although independent assessments of the clinical validity and utility of genetic tests and accompanying interventions are widely regarded as necessary, in most cases there is no such assessment. In Europe, genetic tests are regulated by the Medical Diagnostics Devices Directive, which is implemented in the UK by the Medical Devices Regulations. The Directive and the Regulations cover only analytical validity and there is no requirement for assessment of clinical validity or utility.

The Human Genetics Commission (HGC) has considered the issue of the sale of genetic tests direct to the public, without the involvement of medical geneticists or doctors[44]. It concluded that "*most genetic tests that provide predictive health information should not be offered as direct genetic tests*" and that companies wishing to sell genetic tests should have to "*convince a regulator that the test is suitable*". The HGC recommended that the Medicines and Healthcare Products Regulatory Agency (MHRA) should oversee clinical validity, clinical utility and the advice given to customers. However, the MHRA does not have the legal powers, remit or resources to undertake this task and the Government has still not responded to the HGC's report. The HGC did not consider how tests offered via private healthcare or in the NHS would be assessed.

In contrast, the US Federal Drugs Agency (FDA) already has the powers to assess the clinical validity of genetic tests. However, there are problems with the application of these powers and also with the way they might be changed in the near future (see Box 4).

Box 4: Regulating genetic tests in the USA

Current practice in the US is that tests that are packaged and sold as kits to multiple laboratories, or for use at home or in a doctor's surgery, require pre-market approval or clearance by the FDA including an assessment of the clinical validity of the test. However, in 2000 an expert committee recommended that the FDA should increase its oversight of genetic tests.[2] Problems with the US system include the fact that:

1. The FDA does not assess clinical *utility*, so tests of limited utility can still end up in widespread use (see Box 2).

2. Tests that are not supplied as kits but provided as 'clinical laboratory services' by individual labs receive no assessment. The FDA has the authority to regulate these so-called 'home brew' tests but chooses not to do so. Most 'direct-to-consumer' tests currently on sale are 'home brew' genetic tests.

3. Roche and other companies are lobbying to stop the FDA assessing the clinical validity of genetic test kits. If they succeed, misleading genetic test kits could be widely sold to a much bigger, worldwide market than the existing 'home brew' tests[45, 46, 47].

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In Britain, some mechanisms exist to assess the use of genetic tests within the NHS. However, there are some important gaps in these assessments (see Box

5), and, in practice, there is no open and transparent system for assessing clinical validity or clinical utility for most 'genetic susceptibility' tests.

Box 5: Assessing genetic tests within the NHS

The UK Genetic Testing Network (UKGTN)[48] will soon require all laboratories supplying genetic tests to the NHS to be accredited and will assess clinical validity and utility. However, its remit covers only tests for single gene disorders, not 'genetic susceptibility' to more complex diseases.

The National Institute for Clinical Excellence (NICE)[49] has recently assessed the evidence for testing for mutations in the BRCA1 and BRCA2 genes in women at risk of familial breast cancer. In contrast to the US, where these tests have been widely marketed (see Box 3), NICE concluded that the tests were only suitable for a minority of women from high-risk families. However, NICE is unlikely to assess the evidence for every genetic test that may be marketed in future.

The National Screening Committee (NSC)[50] assesses every genetic test that is proposed for use in an NHS screening programme. Screening involves seeking to test everybody in a certain population group. However, genetic tests may be widely used without any assessment if they are not part of a screening programme.

There are currently no regulatory controls to prevent misleading marketing or advertising of genetic tests

There are currently no regulatory controls to prevent misleading marketing or advertising of genetic tests, either 'direct to consumer' or via the medical profession. The sheer number of genetic variations, and the large number of published links between genes and diseases that later turn out to be wrong, means that it is virtually impossible for most medical professionals to make their own assessments of the clinical validity or utility of genetic tests.

Conclusions

Current regulation of genetic tests is inadequate to ensure that they are clinically valid, socially acceptable or useful for health. Marketing of genetic tests both via doctors and direct-to-consumers is growing in the USA, where the biotech and pharmaceutical industries are lobbying to weaken the regulation of genetic test kits. Companies have a powerful financial incentive to sell not only genetic tests but also associated advice and “individually tailored” products, including skin creams, supplements, medicines and foods. Most of these genetic tests will be misleading and the associated products and advice are, at best, a waste of money but, at worst, may harm health.

In Britain, companies are not required to supply any clinical data on the predictive value of genetic tests they sell, or their usefulness for health. Both direct-to-consumer sales and advertising are allowed. Neither customers nor GPs have the time, expertise or resources to make their own assessments of genetic tests. An independent regulator is urgently needed.

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