

IT'S ALL ABOUT THE MONEY? ISSUES FOR THE REGULATION OF GENETIC TESTING

By Rachit Buch

Whether talking about football or schools, in Britain or abroad, it has become commonplace to say, 'It's all about the money'. One area that has recently been attracting comment of this nature is healthcare, due to an increase in the influence of economic principles and analysis over policy decisions. This trend spans many countries, and with healthcare being such a crucial sector of society, this widespread development demands critical analysis. Research must address whether evidence exists to support such a trend. If it does, then is it having a positive or negative impact on healthcare governance? If negative, what directions can be taken in the coming years to improve on the current situation?

Genetic testing can be seen as a microcosm of the issues and forces affecting healthcare. It is clear that genetic testing is on the increase (Schmidtke et al. 2005, 80-84), and this presents pressing regulatory problems because of the need to avoid economic, social, political and public health damage from unchecked use of this powerful new technology. Indeed, with the number and nature of newspaper headlines generated, it would be hard to avoid the increasing impact of genetics. There is a wide range of tests available, concerning simple inherited diseases as well as complex disorders such as obesity. Furthermore, the approaches that various countries have taken to genetic testing mirrors their respective approaches to healthcare in general: the private and public sectors are variably deployed to use the new technologies with optimal efficiency. This makes a review of the literature on the regulation of genetic testing useful in assessing the impact of economic perspectives on such policies.

What is genetic testing?

Genetic testing is defined as 'the analysis of human DNA, RNA, chromosomes, proteins, and certain metabolites in order to detect heritable disease-related genotypes, mutations, phenotypes, or karyotypes for clinical purposes' (Holtzman N.A. and Watson M.S. 1997, executive summary). Although this definition from the National Human Genome Research Institute provides a good starting point, it is quite broad. Genetic testing can be further classified according to its aims. McPherson provides a succinct summary of the classification of genetic tests (McPherson 2006, 123-9), dividing the analysis of human biology based on whether the purpose of the analysis is diagnostic or predictive. Diagnostic testing is carried out to confirm or rule out a clinical diagnosis; an example would be the analysis of a person's gene sequence to confirm that they are suffering from a specific eye disorder out of a number of possible cases with the same clinical presentation.

Predictive testing falls into two categories: presymptomatic and predisposition testing. Presymptomatic testing involves testing a person with no clinical symptoms for a specific disease for which they may present a family history. A pertinent example would be to test a young adult with a family history of the late-onset neurodegenerative disease, Huntington's disease (HD), before symptoms have developed. A positive result here would mean that the person will definitely develop the disease, because the gene for HD is dominant and is always expressed by its carriers. Predisposition testing also involves testing a currently healthy person, but the test only provides information of a predisposition (or increased risk) of developing a particular disease. This contrasts with the certainty of, for example, having an HD allele. An example of this would be to test a person for a mutated version of the DNA repair gene *BRCA1*; a positive result here suggests an increased risk of developing breast cancer but does not mean that the person will definitely contract the disease.

Commercially, genetic testing incorporates a broad industry with a variety of products. Unfortunately, the science behind much of this is questionable, and in some cases, plainly wrong. For example, the company Sciona analyses individuals' DNA and offers personalised diet and

fitness programmes based on the results. According to their press release, it has been ‘proved’ that a ‘personalized diet based on genetics leads to significant advances in long-term weight management and blood glucose levels’ (Mycellf 2007). It is clear that weight loss needs to be sustained for years to be considered long-term, as this is the time scale over which the adverse effects of obesity are experienced. However, the study used as the source for this press release (Arkadianos et al. 2007, 29), considered anything more than 300 days to be a long-term period. It tested only 48 participants and crucially tested only the experimental groups’ DNA, and not that of the control groups. This makes it impossible to attribute observed difference to the diet alone. Baseline genetic differences between the control and experimental groups could explain the differences in weight loss between the groups, or it could simply be due to the psychological effect of being genetically tested and given a ‘personalised’ programme in the experimental group. Despite this, the study is the primary scientific source for the website and is used to market a test that apparently leads to a ‘scientific method’ of preventing obesity.

This is by no means the only example of dubious products or marketing in the world of genetic testing, and it is clear that the increased technical and economic viability of such testing has led to problems. From a legal point of view, genetic tests occupy a confused position. They are classified neither as drugs nor devices and indeed do not fall into any single legal class. Tests can be conducted in different ways and in various settings, such as by using laboratory-prepared reagents (called ‘home brew’ tests), or with company-manufactured ‘kits’, both of which can be put to use by a company, in a laboratory or at home (Gniady 2008, 2436-39). This has, in the absence of specific laws, led to a piecemeal legislative approach to genetic testing, characterised in the USA by tests being subject to regulation by the Food and Drugs Administration (FDA) only if they use a company-prepared kit.

The increase in ‘home brew’ tests has resulted in a large number of commercial products relevant to people’s healthcare being marketed with no regulation whatsoever. For example, the website ‘www.23andme.com’ offers personalised information on over 80 diseases (for a reasonable price of \$399), but there is no legal requirement that their tests or the advice they offer should be scientifically accurate. This has led to calls for a change in the law (Javitt and Hudson 2008, 59-66). But who or what should decide whether a specific genetic test is acceptable or not?

Ethics

The word ‘should’ sets ethical alarm bells ringing. There is a perception that while scientists should worry about matters such as the best way to use a pipette, the issue of what they should be allowed to pipette should be decided by social scientists and ethicists. However, to ignore scientists’ views on the ethics of science would be folly. A new educational strategy would not be introduced without consulting teachers; similarly, scientists should have an input in the debate about new technologies. It is also clear that ethical concerns, rather than strictly practical scientific issues, motivate much of the debate on genetic testing. This is evident in the numerous academic articles published on genetic testing that cite ethical dilemmas in the problem areas identified for genetic testing regulation (Hodge 2004, 66-70; Parker and Lucassen 2002, 1685-8), thus these issues deserve significant attention.

One of the primary ethical debates on this issue is the direct-to-consumer (DTC) marketing of genetic tests. Some authors believe that regulation should be implemented to a large degree to stop such advertising from taking place. For example, Gniady gives the example of the \$3000 test for *BRCA1* and *BRCA2* mutations predisposing carriers to breast and ovarian cancer (Gniady 2008, 2448-9). Though the test is mostly administered by licensed doctors to those judged to be most likely to carry these risk alleles, it is available to consumers directly - through the company DNA Direct. Of all breast cancer cases, only 5-10% are caused by a mutation in these genes; yet the company marketing this test does not mention such potentially profit-damaging information. The added effect of this is that the absence of such vital information can lead to anxiety and even panic about such disorders.

A linked ethical concern is the lack of counselling that accompanies many commercially available tests. Although research shows that genetic counselling only accounts for around 16% of the cost of genetic testing (Lawrence et al. 2001, 475-81), it is rarely offered as a part of commercially available packages (Giardiello et al. 1997, 823-7; Williams-Jones, 2003, 46-57). The benefits of genetic counselling include a reduction in psychological distress that may be caused by the test results, a better appreciation of these results (Berg and Fryer-Edwards 2008, 20-21) and a greater uptake of genetic tests by at-risk family members.

Additionally, the occurrence of genetic discrimination has been documented in a variety of studies. This includes discrimination of potential employees; unfair decisions are taken by employers and insurers, all based on genetic information (Billings and Beckwith 1992, 198-202). One US employer even gathered genetic information on susceptibility to carpal tunnel syndrome without the employees' consent, in order to avoid financial culpability in disability claims (Geppert and Roberts 2005, 518-24). Such cases provide bleak illustration of the harm that can be caused when ethical standards are not kept high in the use of genetic information.

Berg and Fryer-Edwards (2008) also note the impact that such testing, particularly when advertised direct-to-consumer, can have on a societal level. They note that it can lead to genetic determinism when the importance of genetic components in disease are overemphasised; the companies would thus be capitalising on people's fears (Berg and Fryer-Edwards 2008, 21-22). These researchers emphasise the ethical concerns of this developing group of technologies. Ethically-guided regulation should be implemented in order to protect the public. However, this is not the only view amongst scientists and other commentators on the subject. As is clear from the literature, an equally significant group of people prioritise scientific concerns.

Science

For genetic testing to develop at the pace that many researchers predict, a number of factors must take centre stage. Currently, most tests only detect a proportion of the mutations known to cause a specific disease. This must be improved so that tests can include as large a proportion of the known gene mutations for the conditions being tested as possible: the sensitivity of the tests must increase. Also, work must concentrate on strengthening the links between positive test results and phenotypic predictions (i.e. how these mutations will be expressed in people). Again, the current situation is that the predictive value of the tests (dependent on how the mutation affects expression of the gene) is not uniformly high. A rather obvious point is that earlier detection of conditions through the use of genetic tests is only beneficial if it leads to better treatment and survival or improvements in quality of life.

These points are almost without contention when being discussed as scientific goals. However, numerous scientists and other commentators also say that these scientific developments should form the regulatory basis of genetic testing. This belief is what leads Gniady to state that in order to protect consumers' right to make an informed decision (i.e. to regulate genetic tests fairly), 'there must be a scientifically valid [...] study that links the genetic markers being tested with the occurrence of a disease' (Gniady 2008, 2445-6). This primary concern should be reinforced by the validity and accuracy of the test. These are practical scientific issues, all achievable by work in the lab; Gniady is arguing that these issues, rather than ethical concerns about the misuse or effect of testing on society, should decide whether or not a test is acceptable.

Even when researching ostensibly non-scientific aspects of genetic testing, some researchers give scientific factors prominence. In their analysis of the costs and benefits (an economic measure) of diagnosing familial (as opposed to sporadic) breast cancer through genetic tests, Heimdal et al. (1999) concluded that it was the presence of founder mutations – mutations present in founder members of a population, that consequently appear in a high proportion of people from that population - that affected costs of testing more than other factors (Heimdal et

al. 1999, 167-73). Testing in a founder population (with origins in a small number of individuals) is significantly cheaper because the mutations that are high in frequency can be detected easily. Such scientific and anthropological factors can, according to such research, be seen as vital factors in testing a population for a certain disease. This emphasises the importance of scientific, rather than ethical, factors in the regulation and application of genetic tests. The view of scientific primacy is adopted by many scientists and other professionals, although their influence in policy-making is being significantly affected by the increased influence of another field: economics.

Economics

In recent years, a shift in the perception of science has taken place, one that is not visible from a superficial glance at scientific advances. There has been a cultural shift from viewing science as occupying its own cultural area, or vacuum, as many social scientists argue, to the view that science is a fully integrated component of society. This in itself is not a bad thing, as it is clear to everyone that scientists do not operate in a cultural vacuum. When the best scientists of an era work on how to prove the superiority of one race over another, as they did when eugenic science was at its peak in the early twentieth century, it is clear that cultural factors, not solely technical limitations, dictate the work of scientists.

This acceptance has, however, led to a further shift in the perception of science. As the importance of economics has increased in other sectors of society, such as politics and sports, this increase has spread to science. The result is that science is viewed in the context of economics, and economic justifications for pursuing scientific developments have become increasingly persuasive. When universities such as UCL receive huge financial compensation for the commercialisation of their research, or 'knowledge transfer' (UCL website, 2008), it is no surprise that arguments advocating research proposals based on financial grounds are highly effective. The idea applies to healthcare management as well as basic research: Javahera et al. illustrate this aptly by stating that, 'in recent years, economic evaluation has increased its prominence in healthcare decision-making' (Javahera et al. 2008,93).

A quick search of any literature search engine shows that the financial aspect of genetic testing is receiving a significant amount of academic attention.¹ Many of these papers tackle the subject of the cost-effectiveness of genetic testing. The analysis was traditionally a comparison of monetary cost and an outcome that is comparable between alternative processes or methods, but this analysis is now being modified for use in healthcare and genetics. The cost is compared against a health-related outcome such as mutations detected or year of life saved. This analysis was performed, for example, for the test for Long QT syndrome by Phillips et al. (Phillips et al. 2005, 1294-1300). They calculate that the test costs \$2500 per year of life saved, which is thankfully deemed more cost-effective than not performing the test at all.

Presumably, such authors would recommend the cost-effectiveness of a test to determine whether or not it is introduced on a large scale, regardless of the appropriateness of using measures such as the 'number of mutations detected' as an outcome measure. However, such analysis of genetic testing is not the only way in which economics can have an effect on the basis of regulation. Other forms of economic analysis have been performed on genetic technologies; financial factors affect uptake of genetic services, and guidelines for economic evaluation of healthcare are set at the highest governmental levels.

Javahera et al. (2008, 94) show that cost-minimisation analysis, another tool of economic analysis, has also been applied to genetics. An example they give is the comparison between genetic counselling given by genetic nurse counsellors and clinical geneticists (Torrance et al.

¹ The search terms 'genetic AND testing AND economics' generated 841 results on ISI Web of Knowledge; compared to 1,288 for the terms 'genetic AND testing AND ethics' http://apps.isiknowledge.com/UA_GeneralSearch_input.do?product=UA&search_mode=GeneralSearch&SID=X29@oJD4CJbdd4KMoD2&preferencesSaved (accessed 31 August 2008)

2006, 435-44). This form of analysis takes different methods for achieving the same goal (in this case, counselling a patient), and compares their relative costs in order to find the cheapest way of reaching a certain result. In the context of counselling, nurse counsellors cost less than clinical geneticists, and Torrance et al. state that, as anxiety levels were similar for both groups receiving counselling, the outcome is also similar.

However, it can be argued that just because the anxiety levels were similar for the participants of both types of counselling does not make the two counselling types analogous. If they do not have the same outcome then this comparison is irrelevant, as the difference in cost would reflect a difference in quality of counselling. For example, it may be established that receiving clinical geneticists' counselling significantly increases the understanding of a subject, whilst still leaving people anxious about their situation. In issues of healthcare, knowledge of risks may be extremely desirable, yet this type of analysis would not factor in the qualitative difference, as the outcome measure is anxiety. Therefore, even if other factors made the two types of counselling incomparable, these factors would not be detected by questionnaires designed just to measure anxiety.

The economic perspective is not only being put to use on the policy level. In countries with private insurance-based healthcare, there is strong evidence that financial factors affect uptake rates of genetic services at the individual level. An example is the research done by Kieran et al. into *BRCA1* and *BRCA2* testing for susceptibility to breast and ovarian cancer (Kieran et al. 2007, 101-110). They showed uptake of tests to be significantly lower in women who could not afford it, with women who took the test having better economic status and insurance coverage. This shows that economic factors affect individuals, and many would argue that this should be considered in any regulation of genetic testing.

The cost of testing at the individual level may seem less important in countries with public health systems, such as the UK. Here, however, a more fundamental shift has occurred. It is evident here that economic analysis has been prioritised in the provision of healthcare, at the governmental or advisory body level. For example, in the UK, the NHS has taken an active role in the increase in economic perspectives on healthcare. The NHS Economic Evaluation Database (EED) has been set up to gather economic evaluations of healthcare and to summarise their findings (Nixon et al. 2000, 32). These summaries take the form of abstracts that are compiled according to guidelines formed by health economists. Their acceptance in NHS programmes illustrates the importance of economics and healthcare at the highest level.

Another body, the National Institute for Clinical Excellence (NICE), gives advice to NHS professionals on healthcare standards and practices. These judgements are based on the expertise of the board members involved and also include judgements on the social value of treatments. Interestingly, an article on these value judgements was published in the *British Medical Journal* by the chairman of NICE, Sir Michael Rawlins, who is a professor of clinical pharmacology, and by a former member of the board, Anthony Culyer, a professor of economics (Rawlins and Culyer 2004, 224-7). They state that clinical effectiveness is not sufficient for a NICE value judgement and that economic evaluation must figure in these judgements.

It is not just in the UK where this economic influence can be seen. Leading American institutions are also recognising and contributing to the rise in economic involvement in healthcare. For example, the National Institutes of Health and the Department of Energy Special Task Force on Genetic Testing stated, as part of its final report, that 'Consumer involvement in policy making' was an overarching principle endorsed by the Group (Holtzman N.A. and Watson M.S. 1997, 15).

Is the increased role of economics good or bad?

The description of the value of economic evaluation in the development of NICE's guidelines is not intended to make this role seem negative. It serves to illustrate that economics does indeed

have a strong grip on the management of genetic testing – more so than on other healthcare issues in previous years. With this being acknowledged, and the role of ethics and science also reviewed, some concluding points on the effects of these trends are required.

It should be recognised that money has always been important in most aspects of life: healthcare is no exception. It would be ridiculous to wish for healthcare to operate in some sort of vacuum with infinite budgets. Due to this fact, economics is bound to play an important role in healthcare evaluation and, to some extent, always has. However, there are some crucial reasons to view the current change in the perception of healthcare as a negative one.

First, there are practical concerns. As Rawlins and Culyer note, healthcare professionals are not best placed to carry out economic analyses. Put simply, a medical doctor attempting to make the case for a treatment on economic grounds is more likely to get the economic reasoning itself wrong than would an economist. This point is reinforced by work showing that most papers that are supposed to be economic evaluations of genetics are deficient according to the guidelines set out by the NHS (Jarrett and Mugford 2006, 27-35).

A more fundamental point concerns whether healthcare professionals should be attempting to make economic cases at all. It can forcefully be argued that although economic factors can affect policy decisions, they should not *form* policy decisions. To clarify, this situation would involve just as much attention to economic factors, but only at a later stage in the decision-making process.

Adopting such an attitude would allow crucial scientific and ethical concerns to be given primacy in decision-making. Genetic tests could then be introduced, only if valid scientific studies back them up, as Gniady (2008) recommends. Assessments of their impact on society, and across socio-political boundaries, could then be used to assess their ethical viability. Scientific developments can be reflected in regulation. Only after these stringent scientific and ethical conditions have been met should an analysis of economic viability be completed. The priority of such analysis should be to assess the impact of healthcare on economic factors, rather than assessing healthcare through the prism of economics.

It is possible for this to occur in the context of science even if it does not happen across all sectors of society. Regulatory procedures that are in place make science a component of society that can simply be affected by social trends, rather than inevitably expressing them. An increasingly deterministic slant to economic evaluations of healthcare may affect public health negatively. Pål Møller, a Norwegian geneticist, argues that economic tools such as cost-benefit analyses are simply inadequate in analysing healthcare developments (Møller 2004, i55-i59). The evidence, to be collected over the coming years, may prove him right.

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BSc. Human Genetics
Faculty of Life Sciences

References

- Arkadianos, I., A. Valdes, E. Marinos, A. Florou, R. Gill, and K. Grimaldi, 'Improved weight management using genetic information to personalize a calorie controlled diet', *Nutrition Journal*, 6 (2007): 29.
- Berg, C. and K. Fryer-Edwards, 'The ethical challenges of direct-to-consumer genetic testing', *Journal of Business Ethics*, 77 (2008): 17-31.

- Billings, P. and J. Beckwith, 'Genetic testing in the workplace: a view from the USA', *Trends in Genetics*, 8 (1992): 198-202.
- Geppert, C. and L. Roberts, 'Ethical issues in the use of genetic information in the workplace: a review of recent developments', *Current Opinion in Psychiatry*, 18 (2005): 518-524.
- Giardiello, F.M., J.D. Brensinger, G.M. Petersen, M.C. Luce, L.M. Hyland, J.A. Bacon, S.V. Booker, R.D. Parker, and S.R. Hamilton, 'The Use and Interpretation of Commercial APC Gene Testing for Familial Adenomatous Polyposis', *New England Journal of Medicine*, 336 (1997): 823-827.
- Gniady, J., 'Regulating direct-to-consumer genetic testing: Protecting the consumer without quashing a medical revolution', *Fordham Law Review*, 76 (2008): 2429-2475.
- Heimdal, K., L. Maehle, and P. Moller, 'Costs and benefits of diagnosing familial breast cancer', *Disease Markers*, 15 (1999): 167-173.
- Hodge, J., 'Ethical issues concerning genetic testing and screening in public health', *American Journal of Medical Genetics*, 125 (2004): 66-70.
- Holtzman, N.A. and M.S. Watson, 'Final Report of the Task Force on Genetic Testing in the United States. Promoting Safe and Effective Genetic Testing in the United States', *The National Human Genome Research Institute*, (1997): 1-82.
- Jarrett, J. and M. Mugford, 'Genetic health technology and economic evaluation: a critical review', *Applied Health Economics and Health Policy*, 5 (2006): 27-35.
- Javahera, P., H. Kaariainen, U. Kristoffersson, I. Nippert, J. Sequeiros, R. Zirmern, and J. Schmidtke, 'EuroGentest: DNA-based testing for heritable disorders in Europe', *Community Genetics*, 11 (2008): 75-120.
- Javitt, G. and K. Hudson, 'Federal Neglect: Regulation of Genetic Testing', *The National Academies, Issues in Science and Technology*, 2008.
- Kieran, S., L. J. Loescher, and K.H. Lim, 'The role of financial factors in acceptance of clinical BRCA genetic testing', *Genetic Testing*, 11 (2007): 101-110.
- Lawrence, W.F., B.N. Peshkin, W. Liang, C. Isaacs, C. Lerman, and J.S. Mandelblatt, 'Cost of Genetic Counseling and Testing for BRCA1 and BRCA2 Breast Cancer Susceptibility Mutations', *Cancer Epidemiology, Biomarkers & Prevention*, 10 (2001): 475-481.
- McPherson, E., 'Genetic Diagnosis and Testing in Clinical Practice', *Clinical Medicine & Research*, 4 (2006): 123-129.
- Møller, P., 'Costs and benefits of diagnosing familial breast cancer', *Annals of Oncology*, 15 (2004): i55-i59.
- Mycelf, 'Press Releases: Groundbreaking Study Proves Personalized Diet Based on Genetics Leads to Significant Advances in Long Term Weight Management and Blood Glucose Levels', <<http://www.mycelf.com/news/press-releases/index.aspx>> (accessed 3 October 2008)
- Nixon, J., B. Stoykova, J. Christie, J. Glanville, J. Kleijnen, and M. Drummond, 'Infopoints: NHS Economic Evaluation Database for healthcare decision makers', *British Medical Journal*, 321 (2000): 32.

- Parker, M. and A. Lucassen, 'Working towards ethical management of genetic testing', *The Lancet*, 360 (2002): 1685-1688.
- Phillips, K.A., M. J. Ackerman, J. Sakowski, and C.I. Berul, 'Cost-effectiveness analysis of genetic testing for familial long QT syndrome in symptomatic index cases', *Heart Rhythm*, 2 (2005): 1294-1300.
- Rawlins, M.D. and A.J. Culyer, 'National Institute for Clinical Excellence and its value judgments', *British Medical Journal*, 329 (2004): 224-227.
- Schmidtke, J., B. Pabst, and I. Nippert, 'DNA-based Genetic Testing Is Rising Steeply in a National Health Care System with Open Access to Services: A Survey of Genetic Test Use in Germany, 1996-2002', *Genetic Testing*, 9 (2005): 80-84.
- Torrance, N., J. Mollison, S. Wordsworth, J. Gray, Z. Miedzybrodzka, N. Haites, A. Grant, M. Campbell, M.S. Watson, A. Clarke, and B. Wilson, 'Genetic nurse counsellors can be an acceptable and cost-effective alternative to clinical geneticists for breast cancer risk genetic counselling. Evidence from two parallel randomised controlled equivalence trials', *British Journal of Cancer*, 95 (2006): 435-444.
- UCL, '£5 million for UCL knowledge transfer', <<http://www.ucl.ac.uk/news/news-articles/08010/08100202>> (accessed 3 October 2008)
- Williams-Jones, B., 'Where There's a Web, There's a Way: Commercial Genetic Testing and the Internet', *Community Genetics*, 6 (2003): 46-57.