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Genetics, genomics and society

Introduction

This chapter will explore some of the challenging issues surrounding clinical care, with particular reference to genomics. The latter issue, of which mention has already been made, is of course one of the most important in the field. Our genomes are our genetic make-up – now potentially identifiable down to the last nucleotide base pair. When we know what our genomes are, and the effect that they can have on ourselves and our illnesses, our lives may change in very many different ways. Some of those changes will be examined below.

Genetics and society

Genetics and legal process

One of the effects of having individual genetic profiles is that the individual with the profile can be traced, followed or associated with events that leave a genetic marker. Put differently, anywhere that we leave our DNA can betray where we have been. In recent years, criminal investigation has been revolutionised by this technology – individuals have been convicted of rape simply by associating DNA found on a victim with DNA in a suspect. This ability hinges on the singularity of a person's DNA make-up.

As a consequence of this kind of technology, a database of DNA profiles is being built up in the UK and elsewhere. It is estimated that 5% of all adults in the UK now have their DNA profile held on this database, and the figure is growing all the time. The implications for criminal investigation are obvious – where a DNA sample is recoverable at a crime scene, the police may be able to recall a profile that gives an immediate match to a suspect on the database.

However, this area is fraught with argument. What should be the entry criteria for the database? To what extent should health care professionals involve themselves in the collection of samples?¹

There are UK government policies that address these areas.² They tend to argue that the larger the database, the better the rate of detection of crime, although these arguments have not gone unchallenged.³

Primary care professionals are unlikely to be involved directly in the forensic investigation of crime, but may be approached by other legal authorities to take samples of tissue in order to confirm family relationships. These are now generally buccal scrape specimens, rather than the blood tests that were previously required. The drivers for these investigations emerge from contested paternity

or child protection procedures. In cases where court-ordered paternity confirmation tests are required, health care professionals are not in a position to refuse to participate.

If the paternity testing is requested by patients, or more usually by their parents, it is very important to establish that it is actually in the best interests of the child that such testing should proceed. This requires careful consideration of what those interests may mean, and how they might be served by the confirmation, or otherwise, of biological parentage.⁴ For example, will the determination result in concrete benefits to the child? Do those benefits depend on the age of the child involved? Will the child be able to contribute to the decision at all?

Health care professionals will no doubt want to add up all the factors before participating in such a process.

Over-the-counter testing

This issue is analogous to others in health care currently in the public domain. Should there be direct advertising of prescription medicines to the public? How much access should individuals have directly to specialists or allied health care professionals? Similarly, should people have direct access to genetic tests on an 'over-the-counter' basis? Precisely which counter is not particularly important, although pharmacies' counters, for obvious reasons, are often quoted.

One of the roles of health care professionals is the translation of their esoteric language into everyday vernacular. In that sense the skill of communication, already referred to in this book in the context of communication of genetic risk, is of great importance. If the public were to have direct access to genetic testing, then inevitably those interpretive skills would be of considerable use.

Some pathology tests are already available in the UK (e.g. pregnancy testing kits, ovulation detection kits). It has been argued that genetic tests are significantly different in their complexity, their interpretability and their impact on individuals other than those tested.⁵ Although we would not disagree with the last point, the idea that 'ordinary' tests are simple and easy to discuss with patients is not necessarily true. For example, consider the complexities of interpreting the significance of a blood lipids test, or even a blood pressure result.

In any event, 'over-the-counter' genetic testing is not currently available in the UK, and this position is supported (with one important qualification that will be dealt with below) by the Human Genetics Commission (HGC).⁶

Such testing is available in other parts of the world. For example, in the USA, commercial companies will process ordinary buccal cell samples (taken by simple mouth swabbing) and produce a genetic profile of risk for certain diseases, particularly ischaemic heart disease. This is claimed to be done by genomic analysis, and is described as the new science of *nutrigenomics*. Given the uncertainty of the results in defining (as yet) real risk, and the difficulty of interpreting risk even without unconfirmed genetic testing, such tests cannot be recommended as being necessarily in patients' best interests. Also available in the USA are over-the-counter tests for carrier status (e.g. for thalassaemia or sickle-cell trait).

The qualification referred to above is important for primary care. The UK HGC does not proscribe all such 'over-the-counter' tests, but suggests that those

which are made available rely on the agency of primary care as a 'genetically literate workforce' to 'manage and allow access.'⁷ Although we would argue for the former description, the latter is self-evidently more problematic.⁸ It is in the nature of 'over-the-counter' activity to be outside professionals' control, so quite how access is controlled is unclear. As ever, it is likely that the role of the health care professionals is to interpret the results of patients' self-discovered knowledge, requiring these professionals to be 'genetically literate' in those areas.

Genetics at work

A scenario that the primary care professional might encounter is a patient asking for advice as to whether they should undergo a genetic test, at their employer's request, as a condition prior to employment. So far, genetic testing has not been used systematically by employers in the UK. In the USA, a well-publicised case was highlighted in which an employer used genetic testing of a marker that has been associated with hereditary neuropathy (which gives rise to pressure palsies) as a way of predicting whether the employees would be susceptible to carpal tunnel syndrome.⁹ The US congress is considering the Genetic Information Non-Discrimination Act of 2005, which aims to protect citizens against unwarranted genetic testing.¹⁰

This case highlights a number of reasons why an employer may want to consider a genetic test. The first is that an employer may consider that the nature of the job may predispose and expose susceptible people, with a genetic predisposition, to occupational hazards, which in turn may increase the likelihood of their developing an illness or their health being adversely affected. In effect, the employer is screening for any potential disease, and may use an adverse result to look for early signs of disease as a consequence of exposure to occupational hazards.⁸ The factors that would counter this reason for testing, apart from the legal and ethical aspects, would be that the predictive test or clinical utility of genetic testing might be very low, that other issues such as environmental factors may be important, and that improving workplace safety procedures and protocols may be more effective. If an employee were to develop a disease (and be known to have a genetic predisposition), proving a causal link between the disease and the occupation may well be a scientific conundrum.

However, there are instances where a genetic test may be required or requested in the interest of public safety. The classic example that is cited is the pilot with a family history of sudden cardiac death syndrome. Clearly, the ethical and legal ramifications need to be considered carefully in the use of predictive genetic testing.

The Human Genetics Commission (HGC) has clearly stated that 'No person shall be unfairly discriminated against on the basis of his or her genetic characteristics.' Clearly, the UK Disability Discrimination Act 1995¹¹ as well as human rights declarations would support the notion that anyone who is suffering from a genetic condition should not be precluded from obtaining gainful employment.

The key recommendations made by the HGC in 2002¹² include the following:

- a statement on the use of information that an employer may have on an employee relating to a genetic condition; recognition of the fact that an employer may use the information in a number of different ways, including

risk assessment in the workplace, workforce planning, and occupational pensions and insurance

- employers must not demand a pre-employment genetic test as a precondition for employment
- the recognition that predictive personal genetic information is not being used systematically in the UK, and that employers should inform the HGC voluntarily if there are any plans to do so
- further consultation with interested parties and groups should take place.

A recent House of Lords debate¹³ highlighted the concern that some felt about genetics in the workplace, and it is likely that a Green Paper for consultation will be published with the HGC's recommendations.

Eubionics and euphenics

In Chapter 3 we considered the reproductive issues that are relevant to genetics, with some reference to the challenging ethical dilemmas contained therein. There are additional areas of interest that are essentially societal. The term 'eubionics' was coined by McNally in 2004, to describe a quest for bodily perfection via the genetic or non-genetic route.¹⁴ McNally suggests that 'eugenics' as generally rendered is an unfortunate and effete term used to describe, among other things, the fact of abortion following an adverse genetic diagnosis. It may have the purpose of collectively making a people different to what they were before – a kind of human 'tidying up.' As such, eugenics is vulnerable to the perversions of the process, as practised by the Nazis.

To be eubionic is to seek bodily improvement, or even perfection, in ourselves and our children by whatever route. Thus this theoretical position tends to subvert any notion of genetic exceptionalism (i.e. that there is anything special about genetic information or decision making). This seems to be congruent with the general aims and objectives of primary care in general.

An earlier author adds to the word salad by coining the term 'euphenics', which is generally taken to mean an improvement in phenotype, and thus overlaps with the meaning of eubionics as above.¹⁵ The difference probably takes account of the concept of the genome, which was not fully acknowledged in 1963.

It is the genome, or our knowledge of it, that gives rise to the possibility of euphenic or eubionic change. If we endorse it, as clinicians our motives may change 'from caring for people to fixing them.'¹⁶ This is a very important aspect of clinical practice, taking in the whole of medical ethics in one way or another. In short, the change captured by this rather snappy phrase is one of primary clinical intent. Should clinicians aim to counteract human suffering as their main professional purpose, or should they be partners in a eubionic enterprise of self-improvement? Perhaps the latter is the role of the scientist, or the salesman.

Pharmacogenetics

To clarify the terminology, *pharmacogenetics* is a term that describes the fact that genetic factors can modify drug action, whereas *pharmacogenomics* involves the

analysis of DNA, in particular looking for genomic variations that might be used to predict the response to administered drugs, and to predict adverse drug reactions.¹⁷ This personalisation of pharmacology helps to predict the possible outcomes of therapy, particularly in cancer treatment. The variation in the genome that might give rise to varying drug responses may be accounted for by single nucleotide polymorphisms (SNPs). This can be used to make a genetic map of the variation between individuals, helping to predict variations in drug handling and metabolism. The haplotype refers to groups of SNPs on the same gene, and current research is focusing on developing the Hap Map,¹⁸ a haplotype map that will describe patterns of human DNA variation.

Pharmaceutical companies have been developing technology to make diagnostic tools to try to determine these genetic variations. For example, Roche Diagnostics have developed an AmpliChip technology which uses the microarray technique, a powerful tool that can rapidly analyse literally thousands of genes. Their aim is to characterise individuals who may have the genotype for and perhaps need treatment for depression, cancer or leukaemia.

An example of this is the CYP2D6 enzyme, which is part of the cytochrome P450 enzyme system, and is involved in the metabolism of antidepressant drugs. Variation in the CYP2D6 gene has been associated with variation in drug metabolism, with some patients being poor metabolisers and others being ultra-rapid metabolisers of tricyclic antidepressants and antipsychotic drugs.

Important policy documents have aided the debate in describing the ethical and social aspects of pharmacogenetics,¹⁹ as well as its potential uses.²⁰ There does appear to be a consensus that the scenario of pharmacogenetically personalised drug administration in routine clinical practice may not occur for another two decades. The complexity of the necessary genetic studies and other factors, such as environmental interactions, ethnic differences in drug metabolism, drug interactions and disease (e.g. renal disease) makes for a rich vein of potential research. It also highlights the difficulty involved in translating research into clinical practice.

However, the primary care physician may already have seen examples of situations where drug treatment can be tailored to a knowledge of the individual's genetic make-up. For example, there are women with breast cancer who express a gene for a tumour growth factor receptor called HER2, and when the gene responsible is over-expressed can respond to treatment with trastuzumab (Herceptin). This drug has been shown to reduce 'time to disease progression' in women with breast cancer, and the drug is only prescribed if multiple copies of the gene that expresses HER2 are present.

In patients who require immunosuppression (e.g. in the treatment of inflammatory bowel disease) and might need to be given azathioprine, it is useful to measure thiopurine methyl transferase (TPMT). This is an important enzyme that is necessary for the metabolism of thiopurine drugs. Mutations in the gene that codes for this enzyme can lead to life-threatening bone-marrow suppression after administration of azathioprine.

Classic examples of the way in which genetic variation may affect drug dosing are the cough associated with ACE inhibitors, which has been linked to bradykinin levels, and the fact that individuals with a deficiency of the enzyme glucose-6-phosphate dehydrogenase are at risk of anaemia following the administration of antimalarial drugs.

With regard to the administration of warfarin, anything that reduces the risk of bleeding should be welcomed, but it is clear that further research will be necessary to achieve this. Two common variant alleles of the cytochrome enzyme CYP2C9 have been associated with reduced warfarin metabolism and hence an increased risk of bleeding. However, the authors of a systematic review and meta-analysis on CYP2C9 and its relationship with warfarin administration have called for further evidence of the cost-effectiveness and clinical utility of routine testing, before recommending it.²¹

Based on the public consultation organised by the Royal Society, it is clear that a wide range of research needs to be undertaken to reassure the public, particularly in the field of pharmacogenetics research.²² Box 7.1 summarises the range of current and future research.

Box 7.1 Pharmacogenetics: themes of current and future research

Sample storage
Regulation
Privacy and confidentiality
Racial group differences
Genetic stratification – differences based on genotype
Information transfer to health care professionals
Insurance issues

Genetics and free will

How much, it might be asked, are we the prisoners of our genomes? In everyday thoughts and actions, how much is unchangeable by virtue of genetic ‘programming’, and how much is the product of real free will?²³ This question is of relevance to those who might wish for or advise a change in behaviour – which, after all, is something that primary care clinicians are often doing as they work in the best interests of their patients.

Case study

G is a 40-year-old car dealer who drinks too much by his own admission. His alcohol consumption is generally around 60 units per week, and has been so for some time. His responses to the CAGE questionnaire are positive, and his work is suffering. Investigations have revealed a high Gamma Glutamyl Transferase (GGT) blood level. His father was an alcoholic who died of oesophageal varices.

This case differs from others that have been considered so far in that it involves the psychology and behaviour of the patient to a far greater extent. There is a hint of a genetic loading to G’s problem drinking, in his family history,²⁴ but, most importantly, the solution to the impending health problem is in his own hands. No doubt clinicians will wish to support him in his efforts to curtail his drinking in whatever way is appropriate, but in the end the prognosis is self-determined.

Herein lies the genetic angle. Does G's family history mean that he is much less able to control his drinking by sheer effort of will? Alternatively, does it mean that G is fated to become an alcoholic because of his genetic loading? These questions of heritability are more difficult to answer in the area of behavioural genetics. We have seen that gene penetrance is variable in the context of physical disease – that is, the degree to which genotype is expressed into phenotype. It is immeasurably more difficult to assess genetic expression in the field of behaviour.²⁵

Philosophers have one perspective on this issue, which they term *determinism*. A deterministic view of G would be that he is the prisoner of his genome, and that events could not turn out other than in his alcoholism. His free will is irrelevant or unavailable, and there is no role for his personal experiences in the modification of his fate. Nature will triumph over nurture. The term *genetic determinism* has been used to express this kind of view – that we are in fact the prisoners of our genes and cannot do other than that which they 'require' us to do. However, it is unlikely that this is so.

First, there is little empirical evidence that in the area of human behaviour, genes code for proteins which inevitably, and ultimately, determine actions.

Secondly, it makes little psychological sense that, given the wide range of possible contexts in which behaviours can occur, only one will actually happen. In the case of G, if this is so, whatever the life events he encounters, he will always be alcohol dependent.

Thirdly, it is important to acknowledge that there are situations in which genetic determinism is true. In the case of phenylketonuria,²⁶ those individuals who have the relevant genotype will turn out to have the phenotype as governed by the protein coding that follows. This analogy is not relevant to those less defined, polygenic traits that are involved in behaviours.

However, there is an interesting coda to this discussion of alcohol-related behaviour, and it is essentially monogenic and racial. The adverse effects of alcohol intoxication are associated with the breakdown product, acetaldehyde, which causes nausea, flushing and headache, among other things. The breakdown requires the alcohol dehydrogenase (ALDH) gene (or variants thereof) to code for the relevant enzymes. In South East Asia, the ALDH2*2 variant, which codes for a slow-metabolising form of the enzyme, is common, and the possession of this slow-ALDH allele seems to protect against alcoholism. This is a rare instance of a monogenic variation having a marked behavioural effect.

The wider issue of how behaviour might have a genetic basis has been explored in increasing depth in recent years. The details of this research are beyond the scope of this book, but some useful summary points should be made.

The more that connections are made between genotype and behaviour, the more danger there is of 'medicalising' behaviour, or characterising behaviours under various disease models. This has already happened in the case of alcoholism, and this has a clear empirical advantage, but it is less clear in other areas. The illusory nature of the 'gay gene'²⁷ substantiates this view. There is also the possibility that pre-implantation genetic diagnosis might be extended from its current application in serious disease, to traits such as intelligence or personality attributes. This is generally to be deplored.²⁸

Future trends and developments

In the last section of this chapter, we shall take the liberty of indulging in some prognostication, perhaps even speculation, on the interaction between genetics and the primary care clinician in the years to come.

We consider that genetics will form more of the core work of primary care. There will be more conversations between clinicians and patients about what is 'bred in the bone.'²⁹ Some patients, informed by modern means of access to information, will seek to know more about their genetic risks, and how these may be moderated by environmental factors or behaviour. This inevitably will involve clinicians in complicated conversations, requiring relevant knowledge, about the interpretation of those risks. It will also require the traditional skills of good communication and *caritas*.³⁰ To this should be added, in view of the complexity of genetic knowledge, as revealed in this book, the skills of information searching and evaluation.

In this sense, the primary care clinician is not simply a traditional healer, but also an interface with the wider world of genetics – the more modern genetic knowledge that has become available in the last 20 years or so.

In 2007, the *British Medical Journal* offered the following list as summarising the key medical advances that have been made since 1840:³¹

- 1 anaesthesia
- 2 antibiotics
- 3 chlorpromazine
- 4 information technology
- 5 discovery of DNA
- 6 evidence-based medicine
- 7 microbiology
- 8 medical imaging
- 9 immunology
- 10 oral rehydration
- 11 oral contraception
- 12 knowing the risks of smoking
- 13 sanitation
- 14 tissue culture
- 15 vaccination.

Readers will no doubt have their own lists to offer, and as the *BMJ* notes, the list was initially informed by their readers' choices. Items 5 and 14 have clear genetic connections. Without tissue culture, we would not have *in-vitro* fertilisation, modern vaccines or karyotyping. Without DNA analysis, we would have no modern biology at all. It is a persuasive argument that this one advance holds the key to the future of medicine, which initially will be in the research environment, but will eventually trickle down to primary care. How might the primary care practitioner change his or her practice as a result in, say, 50 years' time?

It is our suspicion that patients will know much more about their individualised risks. The interrelationship between their genetic endowment and external risk factors should be better understood. Thus, as well as assessing patients' coronary artery disease risk simply in terms of lipids, smoking and the other risk factors considered in Chapter 4, clinicians will have more precise details

about the overall risk. It will be personalised in the sense that where there is a family history, the genetic analysis of that risk should be more complete. The genes that code for the risk will be better understood, and their presence or absence in individuals will be known. Thus the internal risks of genetic loading can be evaluated with the external risks of, for example, smoking or alcohol.

Of itself, that individual knowledge might be considered valuable, but it may also cause patients to think, perhaps in a more fatalistic way, about their own lifespan. Already an issue for patients with monogenic disorders, it will thus become an issue for those with polygenic factors, too.

There are a number of research-level issues that are discussed in the public domain, but which are as yet of limited relevance to the primary care practitioner. Nonetheless, awareness of their future application may be useful in terms of general interest.

Cloning

Clones are genetically identical human beings, or indeed genetically identical animals or plants. Identical twins, for example, are naturally occurring clones. Cloning has been brought about already in lower animals, and famously in sheep. No human clones have been reported or confirmed yet. To clone a person would inevitably have enormous ethical implications, but technically it may become possible fairly soon. The clinical implications are hard to see, and cloning in humans is generally represented as the whim of strange, rich people who wish to reinvent themselves.

Stem-cell therapy

Stem cells are pluripotent cells that are found in early development. As they are capable of developing into virtually any kind of cell, they have the opportunity to be used as a source of replacement cells for diseased or abnormal cells. They can be sourced from human embryonic tissue or cadaveric fetal tissue, and therein lies the ethical difficulty. Those who would object to the use of this kind of tissue from embryo research or abortuses would resist research in the field.³² Nonetheless, research is ongoing, and treatments are beginning to be offered in some areas (e.g. after bone-marrow ablation in leukaemia). Future therapies may be developed for severe neurological disease, including Parkinson's disease.

Germ-line manipulation

The term 'genetic engineering' loosely describes situations where the genome is manipulated, by insertion or deletion of DNA segments. If such a process is performed on differentiated cells, it is referred to as somatic cell manipulation. If it is performed on sperm or eggs before fertilisation, it is termed germ-line manipulation. Clearly in the latter case the change will be passed on to future generations. The procedure is not yet performed in humans, but if it was, it could have the capacity to alter 'adverse' genes and eradicate congenital disease. Germ-line manipulation is also fraught with ethical complications.

Chimaeras and hybrids

Chimaeras are entities that possess genetic material from two separate individuals. Thus body tissues are endowed with two separate genetic complements, usually as a result of embryo fusion. Hybrids are formed similarly, but are simply the result of genetic combination. The area is of importance in the research field because this kind of technology might be useful for redressing a shortage of stem-cell lines. At the time of writing, the UK Government is consulting on redrafting the law to include reference to these processes, as the hybridising of human and animal genes in research obviously has enormous implications. So far, the legislative drive is to allow hybrids for research, but to prohibit implantation in a woman.³³

A new Lamarckism?

The final future trend we shall describe here is a fascinating recent finding from a European research team, who have observed that acquired change to humans may indeed cross the generations.³⁴ In their study populations, those boys who started smoking early were found to have sons with a higher body mass index (BMI). Furthermore, grandparental nutrition seemed to affect the mortality of grandsons. They concluded that these environmental factors have an effect that is trans-generational, and may reflect the classic Lamarckian inheritance of acquired change, no longer part of Darwinian biology. Clearly further research is required, but if this is a true finding, it may have implications for the advice that primary care clinicians can give their patients, as the impact on future generations suddenly becomes pertinent.

After this diversion into higher research, let us return to the theme mentioned at the beginning of this section. The traditional skills of primary care are based on caring for individuals, and will be more useful than ever in the age of genetic medicine. Although health care professionals might become more knowledgeable and skilled in the genetic area (and we hope that they do), it is their traditional skills which will be the building blocks for working in the 'genetically literate' age.

There are likely to be many challenges ahead for primary care. These will range from genetic risk assessment, and the diagnosis and understanding of the clinical utility of genetic testing, through to the coordination of care of people with genetic conditions. The challenges will include dealing with the ethical dilemmas that might be faced by individual patients, their families or society as a whole.

The important principle is that there is a basic understanding of the potential impact of clinical genetics within primary care. As Dr Frances Collins of the US National Human Genome Research Institute has stated,³⁵ 'the foundation stone of the genomic era, the Human Genome Project, has been laid.' Collins and colleagues suggest that the translation from genomics to biology, health and society will lead to scientific advances through the resources, technology development and the power of computational biology. However, if healthcare professionals are to rise to this new world of genomic medicine, they will need to be trained, educated and able to deal with the ethical, legal and social issues and dilemmas that will undoubtedly arise.

References

1. Nelkin D, Andrews L. DNA identification and surveillance creep. In: Conrad P, Gabe J, editors. *Social Perspectives on the New Genetics*. Oxford: Blackwell Publishers; 1999. This chapter deals with the larger questions about DNA testing, mainly from the American perspective.
2. www.parliament.uk/documents/upload/postpn258.pdf (accessed 2 January 2007).
3. For a discussion of this aspect, as well as most other areas of general genetic interest, see www.genewatch.org
4. The prevailing moral climate seems to support a child's right to know their biological parentage. If this is true, it is not the same thing as a parental right to know.
5. Human Genetics Commission. *Genes Direct: ensuring the oversight of genetic tests supplied directly to the public*. London: Human Genetics Commission; 2003. p. 23; www.hgc.gov.uk/UploadDocs/DocPub/Document/genesdirect_full.pdf
6. Ibid.
7. Ibid.
8. Kumar S, Gantley M. Tensions between policy makers and general practitioners in implementing the new genetics. *BMJ*. 1999; **319**: 140–3.
9. McCunney RJ. Genetic testing: ethical implications in the workplace. *Occup Med*. 2002; **17**: 665–72.
10. For US Congress details, see http://olpa.od.nih.gov/tracking/109/house_bills/session1/hr-1227.asp (accessed 1 March 2007).
11. For full text, see www.opsi.gov.uk/acts/acts1995/1995050.htm (accessed 1 March 2007).
12. Human Genetics Commission. *Inside Information: balancing interests in the use of personal genetic data*. London: Human Genetics Commission; 2002.
13. Hansard. House of Lords debate. *Genetic Testing: employment and insurance*, 15 March 2006.
14. McNally R. *Post-eugenics, 'eubionics' and the 'handicap ground' for abortion*; <http://genome.wellcome.ac.uk/doc%5Fwtd020978.html> (accessed 2 February 2007).
15. Lederberg J. Molecular biology, eugenics and euphenics. *Nature*. 1963; **198**: 428–9.
16. Moore P. *Babel's Shadow*. London: Lion; 2000. A very readable science journalist's perspective on all aspects of modern genetics.
17. Roses A. Pharmacogenetics' place in modern medical science and practice. *Life Sci*. 2002; **70**: 1471–80.
18. www.wellcome.ac.uk/doc_WTD003500.html 2.12.06.
19. Nuffield Council on Bioethics. *Pharmacogenetics: ethical issues*. London: Nuffield Council on Bioethics; 2002.
20. Royal Society. *Personalised Medicines: hopes and realities*. London: Royal Society; 2005.
21. Sanderson S, Emery J, Higgins J. CYP2CP gene variants, drug dose and bleeding risk in warfarin-treated patients: a HuGenet systematic review and meta-analysis. *Genet Med*. 2005; **7**: 97–104.
22. Royal Society. *Pharmacogenetics Dialogue*. London: Royal Society; 2005.

23. Greenspan PS. Free will and the genome project. In: Nelson JL, Nelson HL, editors. *Meaning and Medicine: a reader in the philosophy of health care*. London: Routledge; 1999. A very engaging series of essays on various medico-philosophical subjects.
24. Cooper B. Nature, nurture and mental disorder: old concepts in the new millennium. *Br J Psychiatry*. 2001; **178 (Suppl. 40)**: S91–101. A comprehensive and accessible review of genetic influences on psychiatric disorder.
25. Song R. In: *Human Genetics: fabricating the future*. London: Darton, Longman and Todd; 2002. An interesting development and background to this area, with a Christian perspective, that may be of relevance to some readers.
26. In PKU, there is a recessive allele on chromosome 12 coding for phenylalanine hydroxylase.
27. Manson C. Presenting behavioural genetics: spin, ideology and our narrative interests. *J Med Ethics*. 2004; **30**: 601–4. A review of the Nuffield Council's report on behavioural genetics,²⁸ with reference to the distortions of publicity about behavioural genetics.
28. Nuffield Council on Bioethics. *Genetics and Human Behaviour: the ethical context*. London: Nuffield Council on Bioethics; 2002. A full examination of the area of behavioural genetics.
29. An old saying, but also the title of one component of *The Cornish Trilogy*, a wonderful series of books by the Canadian author Robertson Davies, who had much to say about doctors. Penguin; 1991, ISBN 0140144463.
30. *Caritas*, part of the motto of the Royal College of General Practitioners in the UK, denotes the quality of caring for the patient.
31. *Medical Milestones*. *BMJ*. 2007; **334 (Suppl. 1)**.
32. Singer P. Creating embryos. In: Mappes TA, DeGrazia D, editors. *Biomedical Ethics*. 4th ed. McGraw-Hill; 1996, ISBN 0-07-040141-1.
33. For a summary of current recommendations, see www.dh.gov.uk/PolicyAndGuidance/HealthAndSocialCareTopics/StemCell/StemCellGeneralInformation/StemCellGeneralArticle/fs/en?CONTENT_ID=4124082&chk=5mbZjS. 2.12.06.
34. Pembrey M, Bygren LO *et al*. Sex-specific, male-line transgenerational responses in humans. *Eur J Hum Genet*. 2006; **14**: 159–66.
35. Collins FS *et al*. A vision for the future of genomics research. *Nature*. 2003; **422**: 1–13.