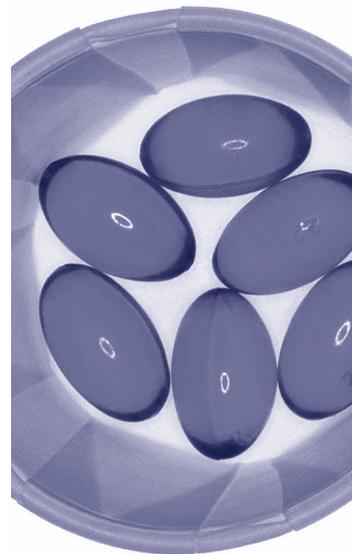
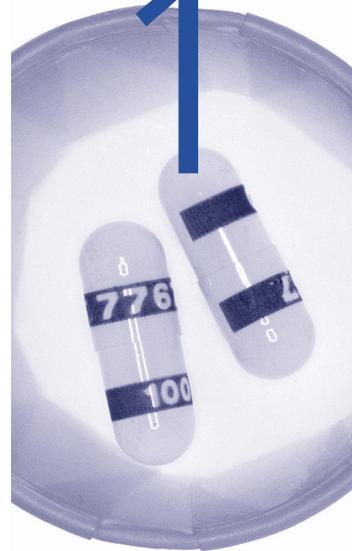


Chapter

Introduction



Introduction

- 1.1 People vary in their response to the same medicine. Few medicines are effective for everyone; all may cause adverse reactions or, occasionally, death. Some of the variation between individuals in response to medicines is due to differences in their genetic make-up. There are many different reasons why medicines may be dangerous or ineffective, such as inaccurate prescribing, poor compliance by the patient, and interaction between a particular medicine and other substances, including other medication. However, advances in genetic knowledge may enable us to take better account of differences between individuals. Pharmacogenetics is the study of genetic variation that affects response to medicines. It has the potential to play an important role in improving the safety and efficacy of medicines. (See Box 1.1 for definitions of terminology used in this Report).
- 1.2 The relevance of pharmacogenetics for the development and administration of medicines was first recognised in the 1950s. In parallel with the significant advances in the study of the human genome in recent decades, pharmacogenetics is an expanding field of research. The option of using genetic information to predict response to medicines has led some to make the optimistic claim that the development of 'personalised' medicine, or 'the right medicine, for the right patient, at the right dose', is only a matter of time.
- 1.3 Such claims require careful assessment. Pharmacogenetics does have the potential to improve the quality of patient care significantly. Conversely, delaying its introduction could harm patients, whether through lack of training and education or for reasons of practical constraint. At the same time, just how quickly and effectively this technology can be deployed is unclear. There are few current applications of pharmacogenetic testing, and we do not know to what degree possible applications of pharmacogenetics can be realised given the constraints imposed by the complexity of our response to medicines and the current systems of healthcare delivery. Several different factors will influence the proportion of patients who will come to benefit from pharmacogenetics, including economic influences on the pharmaceutical industry, regulatory frameworks applied by relevant authorities, cost-benefit constraints of healthcare providers with limited budgets and the relationship between patients and physicians.
- 1.4 As with any new technology, the benefits of pharmacogenetics may be accompanied by unintended disadvantages. For example, the introduction of pharmacogenetics could lead to a further stratification of the market for medicines, discouraging pharmaceutical companies from developing medicines that would provide a significant benefit to only a small number of patients. The application of pharmacogenetics might impede healthcare delivery, by taking up a considerable amount of a clinician's time in conducting the test and explaining the results. It might exacerbate inequities in medical provision. The extensive acquisition of genetic information that a wide-ranging programme of pharmacogenetics would involve might also lead to violations of legitimate expectations of confidentiality and privacy, and unfair discrimination.
- 1.5 The aim of this Report is to give an account of the likely effect of pharmacogenetics on the design of medicines and on clinical practice and to highlight ethical, legal and regulatory issues that may be raised. Recommendations are made regarding decisions that will need to be taken if we are to derive the greatest benefit from the potential of these biomedical developments.

Box 1.1: Terminology

There is a lack of agreement about the precise terminology to describe how genetic information is related to individuals' responses to medicines. Various definitions of pharmacogenetics and pharmacogenomics have been put forward and the terms are sometimes used interchangeably. In this Report, we use the term 'pharmacogenetics' as follows:

Pharmacogenetics: the study of the effects of genetic differences between individuals in their response to medicines.

These differences may or may not be related to the disease being treated. Research in pharmacogenetics involves comparing genetic data from individuals who have different responses to a medicine.

The term 'pharmacogenomics' is not distinctly differentiated from pharmacogenetics, but implies the examination of whole genomes or substantial numbers of genes in order, for example, to identify putative targets for medicines or to identify large-scale differences in the patterns of gene expression in response to chemical compounds.

Pharmacogenetic test: a genetic test can be defined as a test to detect the presence or absence of, or change in, a particular gene or chromosome.* This can be done directly, by analysing the chromosomes or DNA of an individual, or indirectly, by examining the products of their DNA, such as RNA or proteins (Appendix 1 explains in more detail how genes work). In some cases, the presence or absence of particular genes can be determined by consideration of the family history of an individual, or simply by clinical observation. In the context of pharmacogenetics, the same types of direct or indirect tests for a gene sequence or gene product are applied to test for response to a medicine. We use the term pharmacogenetic test to refer to both types of test. A pharmacogenetic test might examine inherited DNA or somatic mutations in DNA (see paragraphs 2.6-2.10).

An important aim of pharmacogenetics is the improvement of the safety of medicines. There is a range of terminology to refer to the negative or unintended consequences of administering a medicine. In this Report, we use the term adverse reaction to refer to an untoward medical occurrence caused by and arising after the administration of a medicine under normal conditions of use.†

* Advisory Committee on Genetic Testing (1997) *Code of Practice and Guidance on Human Genetic Testing Services Supplied Direct to the Public* (London: Health Departments of the United Kingdom).

† A related term is 'adverse event', which describes any untoward medical occurrences arising after the administration of a medicine. Adverse events may be an adverse reaction to the medicine, but they may also be conditions arising independently of the medicine.

Ethical issues in genetics

1.6 There has already been considerable attention paid to the ethical implications of research in genetics and genetic testing.¹ Genetic testing is an established practice in some areas of medicine such as prenatal screening, and diagnostic and predictive testing for a range of diseases. Ethical debate has focused on the need to provide counselling for individuals who undergo testing and on the following questions: Under which conditions may samples for genetic analysis be collected? For how long and for which purposes should samples and information be stored? Who should have access to genetic information? Possibly in an attempt to distance present practice from past abuses of genetics, most ethical debate in Europe and the US has been focused on the implications of developments in genetics for individuals, rather than for populations or societies. This debate has led to the emergence of the following principles:

Consent: genetic information should only be obtained from persons when they have given genuine consent. Consent is genuine when the information has been communicated appropriately and agreement is given freely.

Privacy: every person is entitled to privacy. Privacy in the context of genetic testing can be understood as a person's right not to be obliged to disclose information about his or her genetic characteristics.

Confidentiality: where an individual has chosen freely to disclose private genetic information, the disclosure should be treated as confidential. This means that genetic information should not be communicated to others or used for new purposes without the consent of the person disclosing the information.

1.7 These are *prima facie* principles. They are valid in the absence of conflicting, equally strong principles. For example, the requirement of consent from an individual may in some cases be overridden where a person who is not able to give consent would benefit from the result of a genetic test. Privacy might be overridden in exceptional circumstances, for instance, when a genetic test would reveal a clear risk of a disease which might put other people at significant risk.² Similarly, in exceptional cases confidentiality may be overridden, for example when an individual cannot be persuaded to inform family members who have a legitimate right to know about a specific genetic condition that may affect their future.³ It is the subject of a continuing debate as to when there are grounds to justify breaching one or another of these principles. Views differ according to schools of thought and tradition. However, only very few ethical positions demand an absolute and non-negotiable status for such principles.

¹ See for example Nuffield Council on Bioethics (1993) *Genetic screening: ethical issues* (London: Nuffield Council on Bioethics); Nuffield Council on Bioethics (1998) *Mental disorders and genetics: the ethical context* (London: Nuffield Council on Bioethics); Nuffield Council on Bioethics (2002) *Genetics and human behaviour: the ethical context* (London: Nuffield Council on Bioethics), pp. 25-36; 119-30; Human Genetics Commission (2000) *Whose hands on your genes?* (London: Department of Health); Human Genetics Commission (2002) *Inside Information: Balancing interests in the use of personal genetic data* (London: Department of Health); Human Genetics Advisory Commission (1997) *The Implications of Genetic Testing for Insurance* (London: Department of Health); Human Genetics Advisory Commission (1999) *The Implications of Genetic Testing for Employment* (London: Department of Health).

² See also Article 8(2) of the European Convention on Human Rights which provides that the individual's right to personal privacy may be overridden, *inter alia*, by requirements prescribed by law, if it serves to protect health or morals or the rights and freedoms of others. Any such infringement of privacy must be both necessary and proportionate. See also General Medical Council (2000) *Confidentiality: Protecting and Providing Information* (London: GMC).

³ See also Nuffield Council on Bioethics (1993) *Genetic screening: ethical issues* (London: Nuffield Council on Bioethics).

Is genetic information qualitatively different from other medical information?

- 1.8 The continuing debate about the implications of genetic testing could suggest that it is categorically distinct from medical tests that do not concern DNA and therefore raises different ethical issues. Such a view has been called 'genetic exceptionalism'. The Human Genetics Commission (HGC) has identified seven factors which, although not unique to genetic information, could be used to argue that such information should be treated differently because of their cumulative effect. The HGC considers that genetic information:
- i. is uniquely identifying and provides information about family relationships;
 - ii. can be obtained from a small sample, possibly taken without consent;
 - iii. can be used to predict future events;
 - iv. may be used for purposes other than those for which it was collected;
 - v. is of interest to third parties such as employers and insurers, families, friends, potential spouses;
 - vi. may be important for determining susceptibility and effectiveness of treatment;
 - vii. can be recovered from stored specimens even after many years.⁴
- 1.9 However, against these arguments in favour of genetic exceptionalism, we observe that the majority of the seven features listed above have parallels in other areas of medical practice, for example testing for human immunodeficiency virus (HIV), and cholesterol testing. This is particularly the case when one enters the realm of complex disorders. The probabilistic information generated by genetic tests that indicate increased risk of or susceptibility to a disease can sometimes also be obtained by scrutiny of the family history of an individual. Equally, predictive environmental factors in an individual's life can often be identified. In the context of pharmacogenetics, the focus on genetics can be misleading, since information about response to medicines can also be obtained through blood tests and other non-genetic tests, without direct analysis of the DNA of the patient.
- 1.10 Given the similarities between genetic and other forms of personal information, it would be a mistake to assume that genetic information is qualitatively different in some way. In our view, the information provided by a medical test is the key to considering its implications, not whether the test involves genetic data. Non-genetic tests that obtain reliable and important information such as pregnancy tests and HIV tests may raise more ethical issues than genetic tests that have very weak predictive power. We accept that genetic tests can be rich in information and particularly significant for that reason. However, it is important to realise that the same may be true of non-genetic tests.
- 1.11 Importantly, in contrast to genetic tests for single-gene disorders, pharmacogenetic tests are likely to generate probabilistic information of varying degrees of clinical utility. For example, a pharmacogenetic test that aimed to determine whether an individual was at risk of suffering an adverse reaction might be able to predict that the individual would have a 95% chance of developing the adverse reaction. However, even with this high risk, five out of every 100 people with that genotype could take the medicine without suffering adverse consequences. In the context of predicting efficacy, it may be possible to say that an individual ought to take medicine A rather than medicine B because A is 70% likely to be effective, while for B the figure is only 50%. This may be useful information, but it is clear that not all of the people who take medicine A will find it effective and that quite a large proportion who take medicine B may benefit from it.

⁴ Human Genetics Commission (2002) *Inside Information: Balancing interests in the use of personal genetic data* (London: Department of Health), p. 30.

Public perceptions of pharmacogenetics

- 1.12 The view that genetic data are special is entirely understandable, even if in our view the important factor in considering the impact of any medical data is the information content, not whether that information was derived from DNA or another source. If there is a widespread belief that genetic data are special, then proper account must be taken of this fact. A belief does not need to be true to have real effects. Beliefs about genetic exceptionalism could be significant in the context of a policy that would substantially increase the volume of genetic testing as part of normal medical practice.⁵
- 1.13 There is currently very little information available regarding the attitude of patients towards pharmacogenetic testing, and research in this area would be welcome. However, there may be a general tendency towards genetic exceptionalism, both in the media, in the arena of policy-making and indeed in funding for research in bioethics. The sources of genetic exceptionalism are diverse, but they include the idea that genes are a direct and deterministic cause of traits and conditions. Genes may also be thought to constitute a person's identity and to be something that cannot be altered. Perhaps most importantly, genetic exceptionalism may arise because of the mistaken belief that all genetic tests convey highly predictive or diagnostic information about an individual and his or her relatives. This belief is entirely understandable, as most clinical applications of genetics to date have involved testing for disorders that are caused by mutations in single genes, such as Huntington's disease and muscular dystrophy. Other applications of genetic testing, such as paternity testing and the forensic use of DNA fingerprinting, also reveal a high level of important information about individuals.
- 1.14 The public perceptions of pharmacogenetics are important in part because resistance to pharmacogenetic testing could lead to patients not receiving the best care. Patients might not be given the most beneficial medicines if these may only be prescribed with a genetic test they refuse to take. Even more serious is the possibility that a medicine may be administered without an associated pharmacogenetic test, and result in a serious, predictable and avoidable adverse reaction. We think it likely that the acceptance of pharmacogenetics will depend not only on which tests are introduced and for which purposes they are used, but also on the way they are presented to the public at large and to individual patients. Whereas genetic tests which indicate susceptibility to a particular disease may engender feelings of powerlessness, pharmacogenetic tests may, on the one hand, enable the individual to know more about his or her condition, to feel more control over the treatment, and ultimately to receive a better level of care. On the other hand, if patients come to feel that pharmacogenetic testing is preventing them from having access to treatment they believe might be beneficial, they can be expected to be hostile.

The aims and structure of the Report

- 1.15 Pharmacogenetics does not make a special call on our attention because research and practice based on genetic information are categorically distinct from the rest of biomedicine. But it would also be fallacious to argue that our rejection of genetic exceptionalism means that the development of new genetic technologies such as pharmacogenetics does not raise ethical issues that need to be considered. On the contrary, such developments may highlight issues that ought to have been considered in the context of other similar but non-genetic technologies and bring these issues into sharper focus.

⁵ The impact of pharmacogenetics was recognised by the Government in its recent White Paper on Genetics (Department of Health (2003) *Genetics White Paper. Our inheritance, our future – realising the potential of genetics in the NHS* (Norwich: The Stationery Office, CM 5791), paras. 2.17–2.22).

Furthermore, the fact that the technologies may not be qualitatively different does not entail that there will be no substantial change in practice as a result. An email message is perhaps not qualitatively different from a hand-written letter; but it does not follow from this that the introduction of email technology cannot substantially change people's lives. Therefore, we take the view that it is both important and appropriate to make a particular study of the ethical implications of pharmacogenetics, in the awareness that these considerations may also apply more widely.

- 1.16 It is important to consider the topic of pharmacogenetics because of its potential to improve patient care substantially, by reducing the number of adverse reactions, improving efficacy of treatment and facilitating the development of new medicines. And it is timely to consider pharmacogenetics, because it is a technology that is just beginning to find significant clinical application and whose range may accelerate in a period of just a few years, possibly more rapidly than other clinical applications of genetics. One function of this Report is thus to provide an accessible description of what may be an important and beneficial change in medical research and treatment. But it is not enough to learn how this technology might be applied and what it might achieve: it is also necessary to begin to think systematically about how it would be best managed. Like any substantial and new technology, pharmacogenetics will have unintended consequences and will raise ethical issues. If we wish to realise the potential of pharmacogenetics, we need to consider what incentives should be put in place to maximise possible benefits and what constraints should be imposed to minimise any harms.
- 1.17 This Report aims to contribute to that process of anticipating the proper structures of incentive and constraint to guide the development and use of pharmacogenetics, from an ethical perspective. It is not to be expected that this endeavour will yield a comprehensive set of recommendations. There is too much uncertainty about just how the technology and the practice will develop. Moreover, in the case of a number of the central issues that concern us, there are opposing forces at play and we are not able to predict what the actual impact will be. For example, the use of pharmacogenetic tests in clinical practice will add costs because of the expense of the tests themselves, but it could also save money by reducing the amount of medicine prescribed to people who are unable to benefit from it and by avoiding the costs of treating adverse reactions. The net economic impact of pharmacogenetics cannot be determined at this stage.
- 1.18 This Report attempts to isolate and analyse some of those component forces and the ethical issues they raise. These issues are diverse, including questions about whether pharmacogenetics will make it more difficult to encourage the development of effective medicines for what might be smaller populations, the management of the ethically responsible acquisition and use of genetic information, and how much freedom patients should have to purchase their own pharmacogenetic tests or to receive a medicine while refusing to take the associated test. The primary aim of this Report is to help people with diverse backgrounds and interests to think productively about the difficult and important ethical questions raised by pharmacogenetics.
- 1.19 The structure of the Report is as follows. Chapter 2 sets out the scientific background to pharmacogenetics and illustrates its potential applications through various case studies. In Chapter 3, we consider ethical, legal and regulatory issues raised by pharmacogenetics in the research and development of new medicines. Chapter 4 focuses on the implications of pharmacogenetics for public policy. Finally, in Chapter 5 we examine the ethical and practical implications for patients, families, health professionals and providers of healthcare of the application of pharmacogenetics in clinical practice.