Pharmacogenetics

ethical issues

NUFFIELD COUNCIL ON BIOETHICS

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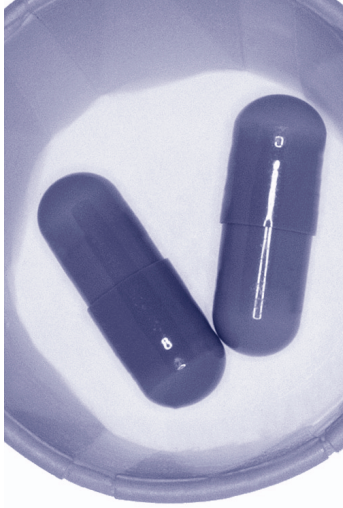

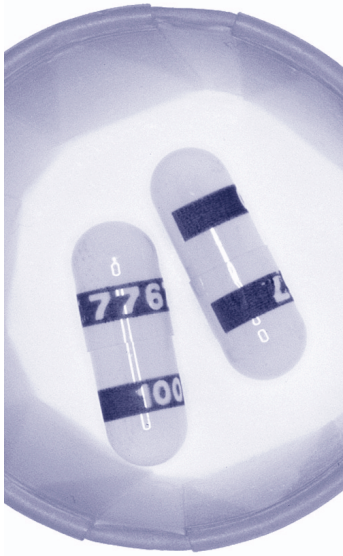

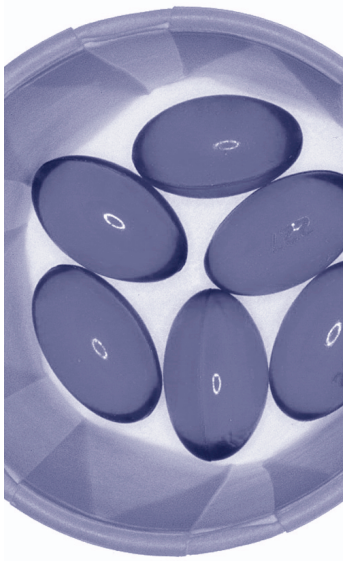

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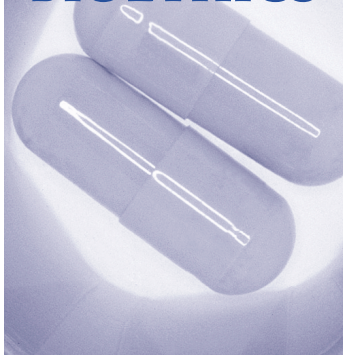

Nuffield Council on Bioethics

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The terms of reference are as follows:

1 to identify and define ethical questions raised by recent advances in biological and medical research in order to respond to, and to anticipate, public concern;

2 to make arrangements for examining and reporting on such questions with a view to promoting public understanding and discussion; this may lead, where needed, to the formulation of new guidelines by the appropriate regulatory or other body;

3 in the light of the outcome of its work, to publish reports; and to make representations, as the Council may judge appropriate.

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Preface

It is a familiar fact of medical life that a medicine effective for one patient may not work for another, even though both suffer the same condition. So when we are told that there is a pharmacogenetic technology around the corner that will provide simple genetic tests to determine in advance which drugs will work for a given individual and which will not, our first reaction may well be to wonder where the ethical issues lie, since we seem here to have a medical development whose impact can only be positive.

Pharmacogenetics may indeed yield a substantial medical benefit, but like any technology it will have diverse consequences that need to be taken into account if the benefits are to be maximised and the negative effects minimised. The course of development and application of pharmacogenetics will depend on scientific research, but it will also depend on decisions of policy and administration which need to provide a combination of incentives and constraints to give the most productive and just direction to pharmacogenetics.

The main purpose of this report is to encourage constructive thought and discussion about some of the ethical and policy issues that pharmacogenetics raises. Many of these fall into four broad categories. The first is information. Pharmacogenetic tests yield genetic *information* about individuals, and this raises complicated and delicate questions about consent and confidentiality. The second is *resource*. Certain aspects of the projected use of pharmacogenetics may lower the cost of developing and delivering medicines, but others may drive it up, and the net effect is difficult to calculate. The third is *equity*. Pharmacogenetics may significantly improve medical treatment for some people, but it may also result in more people falling into categories for which effective drugs are not developed, because of inadequate financial incentives to bring to market a drug that may be very effective but only for a small population or for a large but poor population. The fourth general category is *control*. Who should decide whether a patient takes a pharmacogenetic test? Should the tests be made available directly over the counter or the web? Should patients be entitled to a drug even if they do not wish to take an associated test?

These are some of the hard questions and problems that this report addresses. We make a number of recommendations; but what is at least as important is that this report encourage people from diverse backgrounds to think through the issues for themselves, from an informed position of what we know about this new technology and also of how much we do not know. It is early days for the application of pharmacogenetics, but certainly not too early to think about the issues of ethics and policy that pharmacogenetics raises.

This Report has been a group effort and there are many people to thank. It has been a privilege for me to work with such a high-powered interdisciplinary Working Party, with members so eager to make the issues clear and the arguments cogent. We received signal support from the members of the Council under the chairmanship of Professor Bob Hepple, from the specialists whose brains we picked during fact-finding meetings, and from the thoughtful, constructive and influential comments we received from respondents to our consultation document and from the referees of our draft Report. At the Council, we are particularly grateful to Dr Sandy Thomas for her oversight and support, and to Harald Schmidt, Natalie Bartle, Julia Fox and Nicola Perrin. And we wish to pay special tribute to Tor Lezemore, who has done an extraordinary job across the board, as researcher, writer, editor and conceptual analyst.

Peter Lipton

Acknowledgements

The Working Party wishes to thank the many organisations and individuals who have assisted its work, particularly those who attended fact-finding meetings or submitted responses to the public consultation. The Working Party is very grateful to Ruth Boardman, Professor Baruch Brody, Professor Normal Daniels, Professor Roger Higgs, Professor Alistair McGuire, Dr Duncan McHale and Professor Tony Monaco, who all reviewed an earlier draft of the Report. Their comments contained constructive criticisms and suggestions for further discussion, which were extremely helpful. The Working Party is also grateful to individuals who responded to requests for advice on specific parts of the Report, including Ian Dodds-Smith, Andrew Freeman, Dr Ian Hudson, Mike Stott, Professor Allen Roses and Dr Philip Wright. Finally, the Working Party is grateful to Jai Shah, who conducted background research for this paper during an internship at the Nuffield Council on Bioethics in 2002.

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Terms of reference

1 To explore what pharmacogenetics offers now and is likely to offer in the near future;

In particular to examine the effect of pharmacogenetics on:
a) the design of medicines, the promotion of efficacy and safety in the administration of medicines to individuals;
b) the conduct of trials in the context of pharmaceutical research & development;
c) clinical practice.

2 To consider ethical issues specifically raised by pharmacogenetics;

In particular to examine the areas of:
a) consent, privacy and confidentiality;
b) the management of information about response likelihood;
c) the implications of differentiating individuals into groups based on response likelihood.

3 To consider the implications for the provision of healthcare.

Summary and recommendations

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 safety and efficacy. Adverse reactions to medicines have significant costs, in both human and monetary terms. In addition, considerable resources are wasted on prescribing medicines that have little or no effect in particular patients.

2 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. Such claims require careful assessment. Pharmacogenetics does have the potential to improve the quality of patient care significantly. 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 in practice. Several different factors will influence the proportion of patients who will come to benefit from pharmacogenetics, not least the constraints imposed by the complexity of human responses to medicines.

3 As with any new technology, the benefits of pharmacogenetics may be accompanied by unintended negative consequences. 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 too much of clinicians' time. It might exacerbate existing 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 to unfair discrimination.

4 This Report considers ethical, legal and regulatory issues that may be raised by developments in pharmacogenetics, and makes a number of recommendations aimed at obtaining the greatest benefit from the potential of pharmacogenetics, while protecting the interests of patients and of society. The conclusions and recommendations made in the Report are summarised here.

The nature of pharmacogenetic information

5 There has been considerable debate about the implications of genetic testing. This might be taken to suggest that genetic tests are categorically distinct from medical tests that do not concern DNA, and that they therefore raise different ethical issues. Such a view has been called 'genetic exceptionalism'. In our view, there is no reason to assume that genetic information, including pharmacogenetic information, is qualitatively different from other medical information. The nature of the information provided by a medical test is the key to considering its implications, not whether the test involves genetic data (paragraphs 1.8-1.11). 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.

The development of new medicines

6 The application of pharmacogenetics to the development of new medicines has implications for the way in which basic research and clinical trials are designed and managed, and for the cost of undertaking clinical trials. The application of pharmacogenetic analysis could, in some cases, identify those individuals participating in research who are less likely to respond or who are at risk of adverse reactions, at later stages of clinical trials. These individuals could then be excluded from participating in the trials, which could lead to better protection of participants in research. The selection of smaller groups of genetically homogenous participants in clinical trials may be advantageous, leading to more robust and reliable scientific findings regarding the group of patients who might eventually be prescribed the medicine. There may be regulatory and legal pressures to incorporate pharmacogenetic analysis into clinical trials (paragraph 3.5) but such analysis will not always be feasible, nor will such an approach necessarily be appropriate, given available pharmacological evidence. **We recommend that the appropriate use of pharmacogenetic analysis in clinical trials should be promoted. Regulators should be encouraged to promote the collection and storage of samples in clinical trials such that they could be subjected to pharmacogenetic analysis either during the trial, or subsequently** (paragraph 3.12).

Using pharmacogenetics to improve existing medicines

7 Pharmacogenetics could be used to improve the prescribing of existing medicines, whether by reducing the incidence of adverse reactions, or by restricting prescription to those patients likely to benefit. Some potential examples include the medicine clozapine, used to treat schizophrenia, and the medicine warfarin, used to prevent the formation of blood clots (paragraphs 3.21-23). It is by no means certain that research would successfully identify genetic variants which could form the basis of a clinically useful test. Factors that will affect whether a test is likely to be of use in clinical practice include the scale of the negative effects experienced, the size of the patient population, the likely clinical value of the pharmacogenetic test, and the existence of other treatments. Nevertheless, in some cases, the development of a test could make a significant contribution to improving the prescription of existing medicines. It is not clear that the private sector will be motivated to pursue pharmacogenetic research in relation to medicines not covered by patent protection. **We therefore recommend that efforts should be made to encourage pharmacogenetic research on existing medicines, where there is reason to believe that such research could significantly improve efficacy or safety. Funding and support should be made available within the public sector and public–private partnerships encouraged.** We welcome the recent announcement by the Department of Health that £4 million will be directed towards research in pharmacogenetics over the next three years (paragraph 3.26).[1]

The use of pharmacogenetic information collected in research

8 There are numerous codes of practice and guidance regarding the conduct of clinical research. It is common practice to require consent for the collection and banking of tissue and DNA samples of participants in research, especially if it is intended to combine genetic information with other information from the patient's medical record. Most researchers obtain written consent from participants and are required to provide written information in advance of obtaining consent. In the context of pharmacogenetic research, as in other forms of research, the nature of the information likely to be revealed and its implications for the patient should

[1] 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).

be set out for prospective participants as part of the standard process of obtaining consent. Two important areas of concern are the voluntary nature of the consent and the privacy of the information which is obtained and stored.

Voluntary consent

9 There is a serious question regarding whether voluntary consent to pharmacogenetic testing can truly be obtained in the context of clinical trials or in clinical practice. If researchers require genotyping as a condition of enrolment in a study, patients might not feel able to refuse, especially if they think it is possible that they may get some personal benefit. Indeed, in some cases, taking part in a clinical trial may be the only way for a patient to have a chance of obtaining a particular medicine. While this perceived lack of choice on the part of patients may arise to a similar extent in any trial of a new medicine, it may be of particular concern when that research involves taking samples of DNA because of public perceptions and concerns (paragraph 3.30).

Privacy and confidentiality

10 The implications for patients of DNA samples being used in research will differ depending on how easily their samples can be traced back to them, and whether the research is likely to give rise to information that may be of personal clinical relevance. We take the view that, in the case of pharmacogenetic research, it is generally possible to obtain genetic and clinical information about a patient during a clinical trial and then to anonymise the samples so that the code linking the sample with the patient is destroyed. In most cases, new samples can be taken from patients suffering adverse reactions and from controls for the purposes of post-marketing surveillance without compromising the quality of the research. In some cases, for example trials that last for a very long period of time, anonymisation would not be able to take place without compromising the goals of the research. There may also be auditing requirements imposed by regulators which entail that samples cannot be anonymised, even for a number of years following the completion of a clinical trial. **We consider that to protect the privacy of participants in research, the greatest degree of anonymity should be imposed on samples, compatible with fulfilling the objectives of the research. Researchers should explain to prospective participants the implications of the manner in which samples will be stored for that participant** (paragraph 3.36).

11 It can also be argued that, whether samples are anonymised or not, there should be limits to the use to which they can be put, since there may be some types of research to which the participant does not wish to contribute. Thus, a distinction is often drawn between 'broad' and 'narrow' consent. The latter refers to instances where a sample is only to be used for a restricted range of purposes, perhaps only for a single research project, or research in relation to one particular medicine or condition. Broad consent entails that patients agree that their sample may be used for a variety of future studies which it may not be possible to specify in any detail at the time of consent. Usually, but not always, these future studies will be within the same broad areas of research as the initial project. For example, some researchers may wish to use samples taken for pharmacogenetic research in general studies examining the genetic basis of disease. In practice, there is no dividing line between broad and narrow consent. The breadth of the research proposed could range from any biomedical research to a particular study.

12 Allowing broad consent may be of significant benefit to researchers and to society's interest in the acquisition of knowledge about health and disease. **We consider that it is permissible to request broad consent to the use of samples which are anonymous or anonymised. Where samples collected for a particular study are coded or identified, broad consent to future research may also be permissible, but should be sought separately from consent to the initial study. This separate consent may be obtained when the samples are originally taken, or at a later date.** In general, the further removed the future research is from the original study, the more likely it is that separate broad consent should be obtained. An indication of the type or nature of the research likely to be carried out and its implications for the individual should be given where possible (paragraph 3.39).

13 A further question is whether data protection laws are compatible with the anonymisation of pharmacogenetic samples, in particular regarding obligations to disclose information to family members. In the case of pharmacogenetic information, the likelihood that test results would be of immediate relevance to a family member is low compared to other genetic tests such as those for monogenic disorders. **We received conflicting views as to whether the Data Protection Act (DPA) imposed an obligation on health professionals to disclose information to relatives. We recommend that even if secondary legislation is not required, clarification should be provided by the Information Commissioner to ensure that the DPA is not interpreted so as to require health information to be passed to relatives** (paragraph 3.43).

14 In some cases, researchers provide individual feedback to patients. In others, researchers elect to offer individual test results to patients who request the information. There is no clear guidance on this matter in the UK. We support the view of the Human Genetics Commission that the feedback of the overall results of research should be promoted (paragraph 3.44).[2] Regarding individual results, while we are sympathetic to the view that patients should have the opportunity to receive useful and validated information about their medical treatment, we consider that only on rare occasions will such information be obtained as part of research in pharmacogenetics. **In the atypical cases in which a clinical trial are likely to produce validated and clinically useful data regarding individual participants, we recommend that all participants should be offered the opportunity to receive individual feedback of such data as part of the process of obtaining consent. As far as possible, the nature and implications of the information to be obtained should be explained to participants.** We recognise that decisions about whether data that may be obtained in the course of research are likely to be clinically useful, and assessments of when findings can be said to be sufficiently well validated, will be complex. **We therefore recommend that researchers should explain their decisions regarding the provision of individual feedback to the relevant research ethics committee** (paragraph 3.49).

Regulation of pharmacogenetic tests

15 In the UK, the safety and efficacy of medicines is assessed by the Medicines and Healthcare Products Regulatory Agency (MHRA).[3] The MHRA licenses new medicines for use and oversees the provision of information and warnings about products. Regulation of the quality of genetic tests is also the responsibility of the MHRA. Depending on the evidence submitted to the MHRA by a pharmaceutical company that has developed a new medicine, the Agency may require the use of a pharmacogenetic test as part of the the conditions of issuing a licence for its use. Notification about the need to perform the test before prescribing the medicine would

2 Human Genetics Commission (2002) *Inside Information: Balancing interests in the use of personal genetic data* (London: Department of Health), para. 5.51.

3 The MHRA was formed in 2003 as a result of the merging of the Medicines Control Agency with the Medical Devices Agency.

then be included in the information about the medicine used by prescribers. This approach is analagous to that taken with medicines that require non-genetic tests to be carried out in order to assess the suitability of a patient for treatment or to monitor their response to the medicine. It is likely that pharmaceutical companies which have identified genetic variation that affects response to a new medicine will include this information in their application and will support its inclusion in the licence.

16 It is most important that pharmacogenetic tests are developed which are of high quality and able to identify the genetic variations in question. **We recommend that the European Medicines Evaluation Agency (EMEA) and the Food and Drug Administration (FDA) provide guidance for applicants as to the circumstances in which pharmacogenetic tests will be incorporated into the licence conditions of a medicine.** Relevant factors will include the reliability of the test, the level of information it provides, and the frequency and magnitude of the effect it predicts, whether an adverse reaction or a poor likelihood of response (paragraph 4.6).

Withdrawn medicines

17 The most common reason for medicines to be withdrawn from the market once they have been licensed is the subsequent occurrence in patients of serious adverse reactions, which were either unsuspected at the time of marketing authorisation or occur more frequently than was expected at the time of the grant of marketing authorisation.[4] If at least some adverse reactions can be explained by genetic variation, pharmacogenetic analysis might enable medicines that have previously been licensed but then withdrawn to be reinstated, by allowing the prior identification of individuals likely to suffer from adverse reactions. It may also be the case that compounds already rejected during the process of development could be reconsidered as potential treatments for genetically-defined groups of patients.

18 However, there are various reasons why the re-licensing of withdrawn medicines will be difficult (paragraph 4.9). We conclude that medicines that are found to cause adverse reactions are unlikely to be re-licensed, even if pharmacogenetic analysis is subsequently carried out which could lead to the development of a useful test. An exception might arise in cases where there is no alternative treatment available. The low likelihood of pharmacogenetic analysis leading to the re-licensing of medicines is unfortunate, because there would be obvious benefits in reintroducing a medicine that is effective in one group of patients while eliminating the threat it poses to another group (paragraph 4.10).

The allocation of resources

19 Both public and private providers of healthcare operate on limited budgets. In addition to the traditional requirements of quality, efficacy and safety for the regulatory approval of new medicines, public policy in many countries is developing the requirement to assess medicines for their cost-effectiveness. That is to say, the question is not simply whether the medicine has its intended effects and is safe when it is administered, but also whether the cost of the medicine represents good value for money, given the health benefits that it is expected to produce.

20 There are a number of approaches that could be taken by such bodies in determining whether to approve the use of a particular medicine. One approach would be to rely solely on the criterion of cost-effectiveness: to maximise the amount of benefit for the population as a

[4] It is comparatively rare for medicines to be withdrawn from the market once they have been licensed. Between 1998 and 2002, the MCA awarded over 200 new licences, of which 12 were subsequently withdrawn because of safety concerns (National Audit Office (2003) *Safety, quality, efficacy: regulating medicines in the UK* (Norwich: The Stationery Office, HC 505)).

whole, for any given level of expenditure. As has often been pointed out, however, such an approach risks ignoring considerations of justice or equity.[5] On this view, it is not the total increase in health which is important, but the fair distribution of that benefit among the members of a population. Unless such considerations are set alongside those of cost-effectiveness, those suffering from rare conditions may be overlooked in the allocation of resources because their numbers are not large enough to count against the more prevalent conditions. In liberal democratic societies there is a widespread sense of justice which includes the belief that everyone is owed a certain minimum entitlement, no matter how small the minority to which they might belong. These entitlements include access to health services relevant to the illnesses from which they are suffering. Hence, it may well be right to allocate resources to the treatment of those suffering from a rare condition, even if this means that these resources are less productive of overall benefit. **We endorse the approach taken by the National Institute of Clinical Excellence (NICE) of reviewing cases on an individual basis, not applying thresholds, and incorporating considerations of both equity and cost-effectiveness** (paragraph 4.21).

Stratification and the development of new medicines

21 Genetics may influence choice of medicine in several different ways. People are known to differ in the genetic variants they possess of a series of enzymes concerned with the absorption, metabolism and excretion of medicines (see Box 2.1). These are characteristics with which a person is born. They do not necessarily influence susceptibility to disease, but rather the way the individual body processes medicines to which it is exposed. They often affect classes of medicines rather than specific individual medicines (see Box 2.2, Case study 1). People with particular genotypes may find some medicines ineffective, or may need higher or lower doses in order to achieve a therapeutic effect because they break the substances down either more or less rapidly. There are a large but finite number of these systems for processing medicines, and as our understanding of them advances, predictive genetic testing may be used to determine which medicines to prescribe, and in what doses.

22 Some diseases, notably cancers, develop in cells which have an altered genetic constitution, so that the genetic make-up of the diseased tissue is no longer the same as that of the person in which it is present. Specific genes present in the diseased tissue may play a critical role in determining the optimum treatment. To establish this it will therefore be necessary to identify the genetic make-up of the cancer itself: testing the patient before a cancer has developed is of no use, because the genetic changes are only present in the cancer cells and not in the normal host tissues (see Box 2.3, Case study 2).

23 As more is learned about the vast subject of genetic variation which predisposes to disease, it is likely that newer, more precise classifications of common diseases will emerge (what has been called a molecular taxonomy of disease). Although this is still at a very early stage, it is likely that some conditions which are now considered to be single disorders, with a common set of symptoms, will be discovered to be more heterogeneous, with several different biochemical disorders leading to a common set of clinical features. In some of these cases, it may turn out that the nature and efficacy of treatment depends on which type of the disease is present. Such heterogeneity may be behind some of the well-known variation in efficacy of medicines given to people affected by what appears superficially to be the same disorder.

5 Campbell A (2003) Nice or nasty? Threats to justice from an emphasis upon effectiveness, in *International Perspectives in Equity and Health: As Seen from the UK*, A Oliver, Editor (London: Nuffield Trust), pp. 35-9; Daniels N (1985) *Just Health Care* (Cambridge: Cambridge University Press); Doyal L and Gough I (1991) *A Theory of Human Need* (Basingstoke: Macmillan).

24 This stratification of groups of patients on the basis of genetic information has implications both for patients and for those involved in developing new medicines. There may be both positive and negative effects. Some potentially valuable new medicines may not be developed if, as a result of genetic stratification, the number of patients who would benefit is too small to be profitable. However, stratification may also enable some medicines to be developed that would otherwise have failed because the subgroup in which the medicine is effective can now be distinguished. It is currently uncertain which of these trends is likely to prevail. **We therefore recommend that agencies responsible for the licensing of new medicines pay attention to the possible negative effects of stratification. If pharmacogenetic stratification does provide an economic disincentive for those developing new medicines, consideration should be given to preparing guidance notes that encourage applications to use existing orphan medicine legislation, or any other policy instrument with equivalent effect, to provide incentives for development. We further recommend that if orphan medicine legislation is to be applied, consideration is given by the International Conference on Harmonisation to a global approach to orphan medicine legislation. This should include reconsideration of the definition of an orphan medicine, with particular reference to the implications of genetic stratification of both patients and diseases** (paragraph 4.40).

Pharmacogenetics and racial groups

25 A particular case of the stratification of patient populations is stratification based on racial or ethnic groupings. Race and ethnicity cannot be given precise biological or genetic definitions. There is considerable genetic variation within racial and ethnic groups, whether defined by place of birth, self-identification or other criteria, as well as between them. Nonetheless, some genetic variants are more common in some racial or ethnic groups than in others. This has implications for the design of clinical trials and for the development of medicines and pharmacogenetic tests. Trials conducted in different countries, or statements about efficacy based on evidence in one particular population, may not be valid in other, genetically different populations, or may only be valid if a different prevalence in relevant genetic variants has been taken into account. **We recommend that bodies giving approval for the clinical use of pharmacogenetic tests require these to specify the population groups in which the tests have been validated, and to issue warnings where there is evidence that such tests may not be usefully predictive of response to medicines in other population groups** (paragraph 4.43).

26 Acknowledging that genetic variation between population groups should be taken into account in the design of medical research should not be taken to imply that there are sharp lines that can be drawn between groups on the basis of genetic information which coincide directly with racial categories. Particularly in countries where medicines are advertised directly to consumers, there is a risk that medicines could be marketed to particular racial groups in a misleading manner, giving the impression that all members of that group would be likely to benefit, or that the medicine was more effective than other, non-racially defined, medicines. More generally, such developments may reinforce tendencies to view race as a biologically-defined phenomenon. **We recommend that those involved in pharmacogenetic research and the development of new medicines should be sensitive to the potential for misunderstanding and prejudice arising from racial stereotyping. We recommend further that regulatory bodies exercise careful scrutiny over claims as to racial specificity in the marketing of pharmacogenetic tests and medicines** (paragraph 4.45).

27 Denying treatment to a particular racial group, using race as a proxy for a genetic profile, would be problematic, since not every member of the group could be expected to have the genetic variant in question. It is possible that health professionals would be tempted to use race as a proxy in determining treatment, if the pharmacogenetic test that would discriminate

more accurately was not readily available. **Since clear-cut divisions between racial or ethnic groups are highly unlikely, we take the view that membership of a particular racial group should not be used as a substitute for a pharmacogenetic test, even if it is the case that the genetic variant being tested for is known to be more or less prevalent in particular groups** (paragraph 4.46).

28 A further potential problem arises if stratification results in the members of some ethnic groups finding that they are denied access to medicines when others of different ethnic groups, but suffering the same condition, are allowed access. This would be a particular cause for concern if the group being denied treatment was already socially and medically disadvantaged. At the present stage of development, we cannot say how great a problem this is likely to be. However, it is something that should be monitored. **We recommend that those responsible for monitoring the relative access of different ethnic groups to treatment in the National Health Service (NHS) establish procedures for assessing whether problems emerge arising from the development and application of pharmacogenetics** (paragraph 4.47).

Clinical judgement and patient choice

Information, training and education

29 As pharmacogenetic tests and medicines become more widely used, there will be a need to educate health professionals including general practitioners (GPs) and pharmacists, as new findings emerge and new tests are developed. Reliable and easily accessible medical information is important for both health professionals and patients. While the internet has the positive effect of enabling patients to have access to more information, it also increases the risk of distribution of mis-information. The introduction of a new approach to medicine such as pharmacogenetics makes the requirement for reliable information particularly pressing. The recent White Paper on Genetics proposes various initiatives to 'support the integration of genetics knowledge and healthcare applications across the NHS', including an NHS Genetics Education and Development Centre to provide training for health professionals including GPs, the development of the National Electronic Library for Health to include current information about genetics to aid in clinical decision-making, and efforts to ensure that NHS Direct is kept abreast of developments in genetics to enable patients to access this information.[6] **We recommend that initiatives to provide independent and impartial information about pharmacogenetic tests and medicines to patients and health professionals, including GPs and pharmacists, should be encouraged** (paragraph 5.7).

30 It is not, however, sufficient to make accurate information readily available: the patient needs to be able to understand that information and its significance. The probabilistic nature of the information provided by pharmacogenetic tests raises issues regarding the ability of patients and physicians to engage in an informed discussion about treatment. Much research has been carried out into ways of communicating risk in the medical setting. **We recommend that research is conducted into methods of communicating information about pharmacogenetics to patients, and that health professionals are provided with appropriate training** (paragraph 5.8).

Consent in clinical practice

31 We have said that the important feature of a medical test is the content of the information it provides, not whether that information is genetic in nature (paragraphs 1.8 – 1.11). It is important not to fall into the trap of genetic exceptionalism and to demand higher standards

6 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), para. 4.35.

of consent for pharmacogenetic tests compared to non-genetic tests that might have similar risks associated with them, for example, tests for high blood pressure, which not only direct treatment, but also reveal information about the likelihood of future ill health. However, we recognise that one important feature of genetic data is that they may reveal information that is unrelated to the illness in question, or indeed to any disease, and that this additional information may not be known about at the time the genetic sample is taken. This makes obtaining informed consent to the test difficult. The ethically significant requirement of consent is not that it be complete, but that it be genuine, since achieving fully informed consent is not possible (paragraph 3.29). No consent form can inform a patient about eventualities that are not known about at the time. However, consent forms may be required in some cases. We give two examples: (i) if there is a significant chance that the sample or test results will be used for purposes that are substantially different from the original goal of aiding prescription, or will reveal information about the patient unrelated to the medicines in question; (ii) if the results of the test may have a particularly serious impact on the health or lifestyle of the patient. It should be noted that both examples could also arise when non-genetic tests are proposed (paragraph 5.16).

32 **We recommend that in assessing whether written consent forms are required for pharmacogenetic tests undertaken in clinical practice, each test should be judged according to the nature of the information it provides. If information about unrelated medicines or diseases is likely to be obtained, or if the results of the test will have a significant impact on the health or lifestyle of the patient, written consent may be appropriate. We take the view that, in most cases, written forms will not be required. However, written information for patients should be supplied, particularly if tests will reveal complex and probabilistic information.** In developing such information resources, relevant organisations should consider whether information about non-genetic tests which are similarly complex should also be developed (paragraph 5.17).

Responsibility for test and treatment

33 Some pharmacogenetic tests are likely to provide clear, readily interpretable information about medicines that can be purchased over the counter or obtained on prescription. If these tests are approved by the MHRA, we consider that there is no reason to prevent their provision directly to consumers. However, the majority of pharmacogenetic tests will be more complex, providing less certain predictions. In these cases, professional advice is likely to be needed both before and after taking the test, which means that the direct commercial provision of tests will be inappropriate (paragraph 5.22). The MHRA will be responsible for assessing the clinical validity and quality of tests (paragraph 4.3). **We recommend that the UK Genetic Testing Network should take responsibility for advising on the sale of pharmacogenetic tests directly to patients, and should take a case-by-case approach. We consider that pharmacogenetic tests which are not to be sold directly to patients should not be advertised to them** (paragraph 5.22).

34 A question arises regarding whether patients will have the option to receive treatment without taking an associated test. It cannot be assumed that patients will be keen to take a pharmacogenetic test, even if it will improve the likelihood of their receiving a safe and effective treatment. Such an aversion may be irrational, but may be based on a legitimate fear that information produced by the test could make it difficult to obtain insurance (paragraphs 5.36-5.41), or that it might indirectly reveal information about a medical condition which cannot be effectively treated.

35 The situation regarding patient choice is complicated. Health professionals are able to prescribe medicines to patients who do not have the characteristics for which the medicine was licensed, but they will be held accountable for problems that arise as a result. This is called 'off-label' prescribing. Where a pharmacogenetic test is part of the licence conditions of a medicine, it is unlikely that a health professional would wish to prescribe the medicine without the test, particularly if this would mean putting the patient at risk of an adverse reaction, or subjecting the patient to a medicine that might have very little beneficial effect. However, where tests are not part of the licence conditions, the information they provide may be just one factor among many in deciding whether to prescribe a medicine. If an individual has a low likelihood of response, but there are no alternative treatments and the adverse events associated with the medicine are not substantial, the medicine might be prescribed without making use of the test.

36 We note that advances in pharmacogenetics can be expected to lead to the licensing of medicines that would not have been licensed had there been no associated test, because of the serious danger those medicines pose to a subpopulation. To allow prescription without the test in such a case would be wrong. In other cases, pharmacogenetic tests may not be part of the licence conditions of a medicine. Health professionals will therefore be required to take decisions regarding the treatment of individual patients having regard to guidance from regulatory authorities or professional bodies. In practice, this may mean that patients are unlikely to be prescribed a particular medicine unless they take the associated pharmacogenetic test (paragraph 5.28).

Off-label use in developing countries

37 There may be countries in which medicines that were designed to be used based on pharmacogenetic information are purchased and prescribed without recourse to testing. The decision to allow the prescription of a medicine in a particular country is the responsibility of the regulatory authority for medicines in that country. Decisions will be made on a case-by-case basis, taking into account the seriousness of the condition, the availability of alternative treatments and the nature of the information provided by the pharmacogenetic test (paragraph 5.30).

Privacy and confidentiality of pharmacogenetic information

Implications for family members

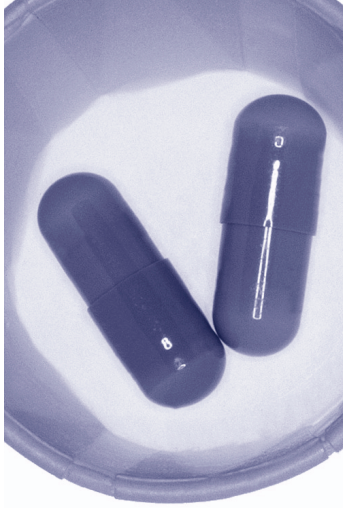
38 The likelihood that pharmacogenetic data will be of relevance to family members is low. In general it is likely that if a test is clinically indicated, it will be carried out on the individual in question, regardless of the results of tests taken by family members. There may be circumstances in which the obligation of health professionals to their individual patients comes into conflict with their obligations to others, and when they may therefore wish to encourage patients to share pharmacogenetic information with family members. We consider that this possibility can be dealt with by existing practice regarding the sharing of medical information (paragraph 5.35).

Use by insurers

39 Pharmacogenetic information could be of relevance to insurers providing various types of healthcare insurance including private medical insurance, critical illness cover, income protection insurance and long-term care insurance, as well as life insurers. Such information could be used at two different stages: in assessing premiums for people applying for policies, and in adjudicating claims in order to make decisions about payment to policy-holders. At the stage of assessing claims, pharmacogenetic information will be of value to insurers providing

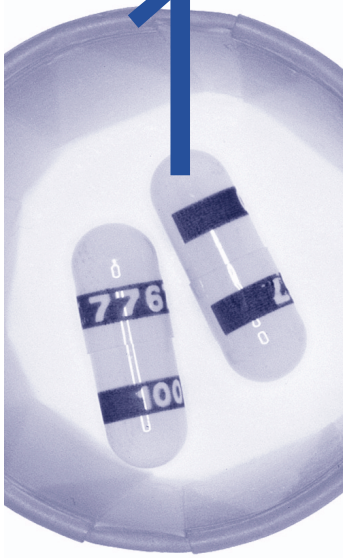
private medical insurance in the same way that it will be of value to the public healthcare system in deciding which treatments to fund.

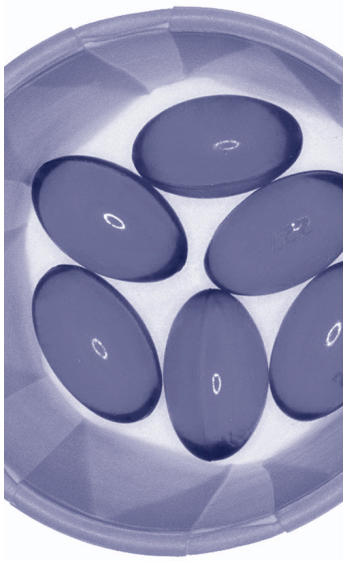
40 The UK has a moratorium on the use of results of genetic tests in setting insurance premiums until 2006 (excepting the results of tests for Huntington's disease in life insurance policies of over £500,000). If this situation were to change, there is a risk that patients would be discouraged from taking pharmacogenetic tests that could be of great value to them, for fear they would be unable to obtain insurance, whether this fear was real or perceived. **We note that pharmacogenetic information falls under the current moratorium in the UK and that insurance companies have expressed the view that the use of pharmacogenetic information in setting premiums would not be of value. In the light of these considerations, we recommend that the moratorium should continue** (paragraph 5.41).

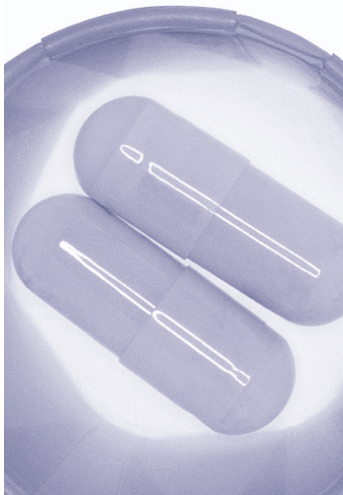


Chapter 1

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.

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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.

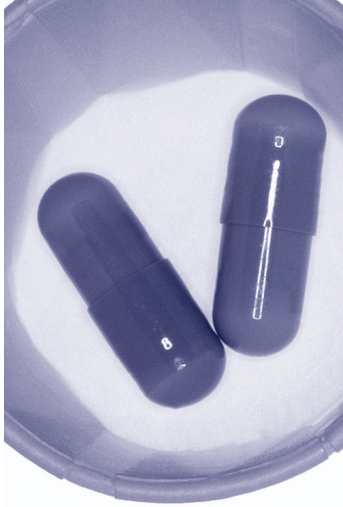
1.17 This Report aims to contribute to that process of anticipating the proper structures of incentive and constraint to guide the development and use of pharmacogenetics, from an ethical perspective. It is not to be expected that this endeavour will yield a comprehensive set of recommendations. There 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.

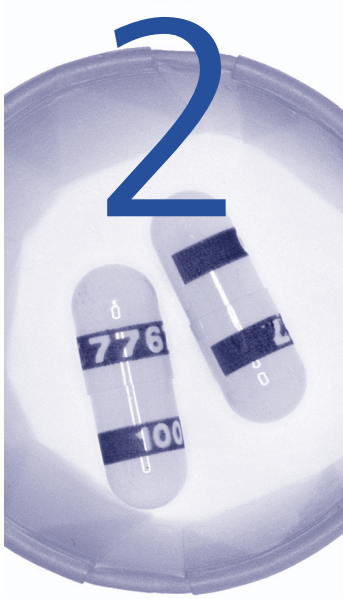
1.18 This Report attempts to isolate and analyse some of those component forces and the ethical issues they raise. These issues are diverse, including questions about whether pharmacogenetics will make it more difficult to encourage the development of effective medicines for what might be smaller populations, 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.

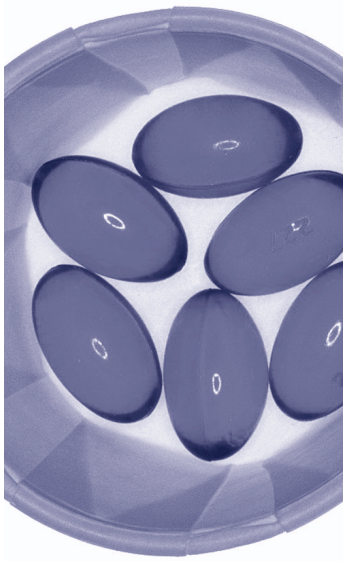
1.19 The structure of the Report is as follows. Chapter 2 sets out the scientific background to pharmacogenetics and illustrates its potential applications through various case studies. In Chapter 3, we consider ethical, legal and regulatory issues raised by pharmacogenetics in the research and development 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.

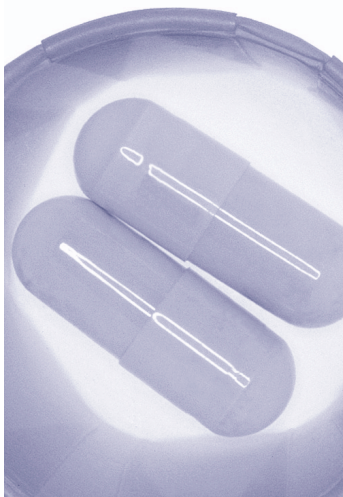
Chapter 2

Scientific background









Scientific background

Introduction

2.1 This chapter explains how genetic variation can affect response to medicines, and uses case studies to illustrate how information about such genetic variation can be applied to improving the safety and efficacy of medicines. We first describe the context for the modern development of pharmacogenetics.

2.2 Variation between individuals in their response to medicines has long been evident, and has posed significant challenges to scientific approaches in pharmacology. Sir William Osler observed in 1892 that 'if it were not for the great variability among individuals, medicine might as well be a science and not an art.'[1] In the 1950s, it was shown that some adverse reactions to certain medicines were caused by genetic variations that affected the metabolism of the medicine in the body.[2] In 1959, the term 'pharmacogenetics' was introduced to describe this phenomenon (see Boxes 1.1 and 2.1 for further definitions of the terms used in the Report).[3]

2.3 The Human Genome Project was established in 1990 to coordinate research that had been under way for some years to identify all the genes in human DNA. The map of the human genome, which identified the majority of the estimated 30,000-40,000 human genes, was completed in 2003. Scientists have made considerable advances in understanding how DNA functions, and how differences in DNA may lead to differences between people. These differences concern normal variation such as eye colour, or variation that causes diseases, such as cystic fibrosis or Huntington's disease. Researchers who have begun to examine the genome in more detail are now gaining a deeper understanding of how some variation between individuals in their responses to medicines can be explained in genetic terms.

2.4 This is a challenging enterprise, since the way in which medicines work in the body is complex (see Box 2.1). A number of different genes may be involved in the metabolism and processing of a particular medicine, and may affect different components of these processes. Environmental factors such as exposure to other medicines or chemicals can also influence the effectiveness of medicines, as can the health of the individual. For example, people with poor liver or kidney function are likely to differ from healthy people in how their body responds to a medicine. The compliance of patients with dosage schedules is also important; many failures or unexpected responses to medicines result from patients not taking the right amount of the medicine at the right time under the prescribed conditions. Medicines can even interact with common foods, for example, the consumption of grapefruit juice has been shown to influence the efficacy of some medicines.[4] All of these factors need to be taken into consideration if patients are to benefit fully from the medicines they are prescribed.

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1 Quoted in Roses AD (2000) Pharmacogenetics and the practice of medicine, *Nature* **405**: 857-65.

2 This phenomenon was described in Motulsky A (1957) Drug reactions, enzymes and biochemical genetics, *JAMA* **165**: 835-7.

3 Vogel F (1959) Moderne probleme der Humangenetik, *Ergeb Inn Med Kinderheilkd* **12**: 52-125.

4 Ameer B and Weintraub RA (1997) Drug interactions with grapefruit juice, *Clin Pharmacokinet* **33**: 103-21; Bailey DG *et al*. (1998) Grapefruit juice–drug interactions, *Br J Clin Pharmacol* **46**: 101-10. For a summary see UIC College-of-Pharmacy Drug Information Center Grapefruit Juice Interactions. Available: http://www.uic.edu/pharmacy/services/di/grapefru.htm. Accessed on: 14 Nov 2002.

Box 2.1: **How medicines work**

Pharmacology is the study of how a medicine acts in the body. It involves the consideration of both pharmacokinetics and pharmacodynamics.

Pharmacokinetics is the study of the processes and rate at which a medicine passes through the body:

- *Absorption* is the process by which a medicine enters the blood stream.
- *Distribution* refers to the transportation of a medicine to the site of action.
- *Metabolism* is the process whereby a medicine's structure and properties are altered, generally inactivating it and enabling it to be excreted by the body.
- *Excretion* is the removal of the medicine from the body through the kidneys and liver.

Genetic variation may influence all of these processes, since they involve numerous different molecules produced by genes, such as transport proteins and pumps, carriers and enzymes. Research in pharmacogenetics has traditionally focused on individual variation in the metabolism of medicines. The process of metabolism generally takes place in the liver where medicines are acted upon by enzymes. Variation in the rate of metabolism of a medicine by an enzyme can substantially alter how a person responds to that medicine. For example, rapid metabolism of a medicine can cause it to be ineffective, and slow or non-metabolism can lead to the accumulation of toxic amounts of the medicine in the body (See Box 2.2: Case study 1). Variation in proteins that metabolise medicines often affects response to more than one medicine.

Pharmacodynamics is the study of how a medicine works in the body. Most medicines work by interacting with the control systems of the body such as receptors, carrier molecules or enzymes. An individual's reaction to a particular medicine is therefore affected by genetic variation in these molecules. Historically, the development of medicines has proceeded on the presumption that these molecules are genetically homogeneous in the patient population. However, many studies in recent years have shown that this is not necessarily the case.

2.5 It is unrealistic to expect that by understanding the effects of genetic variation alone it will be possible to eliminate adverse reactions to medicines, or to ensure that we can all be treated more effectively. Research in pharmacogenetics is often welcomed as a step towards 'personalised' medicine. While this may be true in the sense that patients may be prescribed one medicine rather than another, or have the dosage of their medicine decided on the basis of information about their genetic make-up, it should not be taken to mean that individual patients will have medicines tailor-made for them. Moreover, one implication of developments in pharmacogenetics may be that some patients learn that it is very unlikely that the medicines available to treat their condition will be effective for them. In talking of personalised, targeted or tailor-made medicine, it is important not to mislead or to overestimate the possible benefits of pharmacogenetics.

The scientific basis of pharmacogenetics

2.6 Genetic factors may influence choice of medicine in several different ways. People are known to differ in the genetic variants they possess of a series of enzymes concerned with the absorption, metabolism and excretion of medicines (see Box 2.1). These are characteristics with which a person is born. They do not necessarily influence susceptibility to disease, but rather the way the individual body processes medicines to which it is exposed. They often affect classes of medicines rather than specific individual medicines (see Box 2.2: Case study 1).[5] People with particular genotypes may find some medicines ineffective, or may need higher or lower doses in order to achieve a therapeutic effect because they break the substances down either more or less rapidly. There are a large but finite number of these systems for processing medicines, and as our understanding of them advances, predictive genetic testing may be used to determine which medicines to prescribe, and in what doses.

2.7 Some diseases, notably cancers, develop in cells which have an altered genetic constitution, so that the genetic make-up of the diseased tissue is no longer the same as that of the person in which it is present. Specific genes present in the diseased tissue may play a critical role in determining the optimum treatment. To establish this, it will therefore be necessary to identify the genetic make-up of the cancer itself: testing the patient before a cancer has developed is of no use, because the genetic changes are only present in the cancer cells and not in the normal host tissues (see Box 2.3: Case study 2).

2.8 Genetic variation may also affect an individual's susceptibility to developing a particular disease. As more is learned about the vast subject of genetic variation which predisposes to disease, it is likely that newer, more precise classifications of common diseases will emerge (what has been called a molecular taxonomy of disease).[6] Although this is still at a very early stage, it is likely that some conditions which are now considered to be single disorders, with a common set of symptoms, will be discovered to be more heterogeneous, with several different biochemical disorders leading to a common set of clinical features. In some of these cases, it may turn out that the nature and efficacy of treatment depends on which type of the disease is present. Such heterogeneity may be behind some of the well-known variation in efficacy of medicines given to people who are affected by what appears superficially to be the same disorder.

2.9 This process of uncovering the genetic basis of predisposition to disease is also likely to lead to a better understanding of the biochemistry of disease processes, and of their corresponding healthy bodily functions. This knowledge of human biology in health and disease may help in designing and choosing which classes of chemical compounds are likely to be therapeutically useful and worth developing as medicines.

2.10 These different ways in which genetic variation can influence response to medicines are related and may often overlap. Nonetheless, they can raise different ethical issues, since the different kinds of information will be revealed by the various pharmacogenetic tests. In the following paragraphs (2.11 – 2.15) we explain each approach in more detail and provide examples. For simplicity, we divide the approaches outlined above into two broad

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5 For example, many substances, including medicines, are metabolised by a complex class of liver enzymes called cytochrome P450 (CYP). Genetic variation in some of these enzymes affects the rate of metabolism of many different medicines. Unlike this genetic variation in metabolising enzymes, genetic variation in receptors and other molecules more closely related to predisposition to individual diseases is more likely to affect a very small number of classes of medicine, perhaps just a single class.

6 For a summary of recent discoveries and future prospects in identifying subtypes of cancers on the basis of their genetic characteristics see Holmes B (2003) Stalking the enemy, *New Scientist* **179**: 52-5.

categories: those which examine differences in the DNA of individuals which are not related to the disease being treated, and those which examine differences in DNA which are related to the disease. We call the first approach 'differentiating people' and the second 'differentiating diseases'.

Differentiating people

2.11 Human beings share 99.9% of their DNA sequence with one another. It may seem quite extraordinary that such little variation can result in such great diversity. However, the 0.1% difference equates to 2–3 million individual differences in the DNA sequence of any two randomly selected people. On average, one in every 1,300 positions along the sequence will have different bases present in different people.[7] For example, some people might have an 'A' base whereas others have a 'G' base at a particular position. These two alternative possibilities are termed alleles. If the rarer of the two alleles is present in at least 1% of chromosomes in a population, it is termed a polymorphism. The simplest and most common type of variation, where a single base is substituted for another (as in the example above), is called a single nucleotide polymorphism (SNP). Some SNPs have a measurable effect on the individual; the majority have no effect. It is the former which are of primary interest in medicine, including in pharmacogenetics. These SNPs may be present in part of the gene that affects the production of a protein, or they may be in the regulatory region of the gene. Variation in the amount of product produced by a gene, rather than in the chemical nature of the product itself, can play an important role in determining how a patient responds to a medicine.[8]

2.12 There are numerous other forms of genetic variation that result in differences between people. Examples include:

- deletions: where a segment of DNA has been lost
- duplications: where an additional copy of a segment of DNA is present in the genome
- variable number of tandem repeats (VNTRs): a variable number of consecutively repeated sections of a short DNA sequence at a particular place in the genome

2.13 Genetic variation which does not influence the way a gene functions, or the proteins it produces, may still be relevant for research in pharmacogenetics. If a SNP or other polymorphism is closely associated with a genetic variant which affects response to a medicine, the two will be inherited together more frequently than would be expected by chance. The non-functional SNP can be used as a signpost, to help locate the important genetic variant. Groups of SNPs or genetic variants that are close together, so that they are often inherited together, are referred to as haplotypes.

2.14 Such genetic variation between people may affect how different individuals metabolise certain substances. A well-known example is the effect of variation in the aldehyde dehydrogenase (ALDH) gene on the response to alcohol. People with one variant of the gene are less efficient at breaking down alcohol once it enters the body. As a result, they suffer more severely from alcohol-induced nausea, facial flushing and headaches. Similarly, in the context of medical treatment, there are genetic variants which affect the metabolism

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[7] It is noteworthy that only a very small proportion of human DNA forms the genes. There is a considerable proportion of DNA whose function is at present not known; this kind of DNA is sometimes called 'junk DNA'. When comparing the genomes of different people, differences at the level of DNA are most commonly found in the areas that do not contain genes.

[8] See for example Drazen JM *et al*. (1999) Pharmacogenetic association between ALOX5 promoter genotype and the response to anti-asthma treatment, *Nat Genet* **22**: 168-70.

of certain classes of medicines (see Box 2.2: Case study 1). These variants may not have any noticeable effect on the individual until the particular medicine or substance is ingested, but they may make it possible to predict, to some extent, whether an individual will respond well to a medicine, whether it will have little effect on them, or whether it will cause an adverse reaction.

Box 2.2: **Case study 1 – CYP2D6**

CYP2D6 is an enzyme found in the human liver, which is involved in the metabolism of approximately 25% of all medicines that are currently prescribed, including some beta-blockers, used in the treatment of heart disease, and some of the tricyclic anti-depressant and anti-psychotic medicines. It is difficult to predict how a particular person will respond to a given dose of these medicines, in part due to the amount of variation in the CYP2D6 gene (over 70 alleles have been identified).

Approximately 7% of the Caucasian population has a genetic variant that results in reduced activity of the CYP2D6 enzyme: they are 'poor metabolisers'. A further 2%-30% have multiple copies of the CYP2D6 gene, arranged in tandem, so that these individuals metabolise the relevant medicines very quickly. In poor metabolisers, the medicine is not broken down quickly enough by the liver and accumulates in the body, which can have adverse consequences. A small number of medicines, such as codeine, only have an effect after they are processed by enzymes in the body. People who are deficient in the CYP2D6 enzyme may therefore derive no benefit from the normal dose of these medicines. Rapid metabolisers break down the medicine too quickly, and therefore require significantly increased concentrations of the medicine to achieve the desired pharmacological effect.

Although variation in the metabolism of a number of clinically important medicines is known to exist in populations due to differences in the CYP2D6 gene, pharmacogenetic testing for the relevant variants is not routinely performed in clinical practice (see paragraph 3.20). However, a P450 diagnostic chip that will test for a large number of 2D6 variants is to be introduced into the market in 2003.*

* Roche Diagnostics (2003) Roche Diagnostics launches the AmpliChip CYP450 in the US, the world's first pharmacogenetic microarray for clinical applications. Available: http://www.roche diagnostics.com/press_lounge/press_releases/division/2003_06_25.html. Accessed on: 25 June 2003.

Differentiating diseases

2.15 Genetic variation can affect an individual's susceptibility to a particular condition. It can also be an integral part of the process of disease, affecting only the diseased tissues, as in cancers. By understanding more about the genetic characteristics of a tumour, it may be possible to identify effective targets for medicines (see Box 2.3: Case study 2). In such cases, when viewed from the perspective of suitable therapy, a single disease such as breast cancer might be seen as a number of conditions which differ genetically. This genetic variation in the tumour may or may not turn out to be linked to genetic susceptibility to the disease.

Box 2.3: **Case study 2 – Herceptin**

Herceptin (trastuzumab) is used in the treatment of breast cancer and is an example of a medicine developed specifically to treat a subgroup of patients. In 1987, a connection was discovered between the expression of high amounts of a protein called HER2 and an aggressive form of breast cancer; 25 to 30% of patients with breast cancer express high amounts of HER2 due to a somatic mutation in the DNA of the cancerous cells, which contain many copies of the HER2 gene.* These women have a higher probability of metastasis, or spreading of the cancer; resistance to treatment with conventional chemotherapy; and a significantly shorter life expectancy. As a result of this discovery, the company Genentech developed the medicine Herceptin specifically to treat patients with this type of breast cancer by targeting over-expression of HER2. In determining whether a patient should receive Herceptin, the amount of HER2 in the tissue is measured (this does not involve examining the DNA directly). Patients with high levels of over-expression who receive Herceptin have an improved life expectancy compared to patients who receive standard chemotherapy.† Herceptin was licensed for use in the US in 1998 and in the UK in 2000, for patients with breast cancer who over-express HER2.

* Slamon DJ *et al.* (1989) Studies of the HER-2/neu proto-oncogene in human breast and ovarian cancer, *Science* **244**: 707-12.

† See prescription information about Herceptin: Genentech (2002) Herceptin full prescribing information. Available: http://www.gene.com/gene/products/information/oncology/herceptin/insert.jsp. Accessed on: 15 Nov 2002; National Institute for Clinical Excellence (2002) *Guidance on the use of trastuzumab for the treatment of advanced breast cancer,* Technology Appraisal Guidance - No.34 (London: National Institute for Clinical Excellence), pp. 3-5.

The application of pharmacogenetics

2.16 The application of pharmacogenetics has two main aspects: improvements in the safety and efficacy of medicines.

Improving safety

2.17 Pharmacogenetic tests that reveal genetic variations already known to be associated with adverse reactions could allow physicians to avoid exposing patients to medicines that would put them at risk. The majority of adverse reactions are caused because of an exaggerated effect of a medicine in the body.[9] Less often, an adverse reaction may be an idiosyncratic response to the medicine.

2.18 Adverse reactions to medicines have significant costs, in both human and monetary terms. However, it is difficult to ascertain the impact of genetic variation in response to medicines because data concerning adverse reactions often include problems caused by errors in prescription, and because information about other causes such as interaction between different medicines may be non-existent. According to one recent report, deaths in England and Wales from prescription errors and adverse reactions have increased by 500% over the past ten years: 1,100 people died for these reasons in 2002 at a cost to the NHS of more than £500 million.[10] In the US, approximately 400,000 adverse events associated with prescription or over-the-counter medicines were reported in 2001.[11] These events have been estimated

9 Phillips KA *et al*. (2001) Potential role of pharmacogenomics in reducing adverse drug reactions: a systematic review, *JAMA* **286**: 2270-9.

10 Audit Commission (2002) *A Spoonful of Sugar – Medicines Management in NHS Hospitals* (London: Audit Commission).

11 Quoted in O'Kane DJ, Weinshilboum RM and Moyer TP (2003) Pharmacogenomics and reducing the frequency of adverse drug events, *Pharmacogenomics* **4**: 1-4.

to be the fourth to sixth leading cause of death in the US.[12] It is difficult to estimate how many of these deaths, and what proportion of the financial costs could have been avoided through the use of pharmacogenetics. It is clear that pharmacogenetic testing has the potential to enable serious adverse reactions to medicines to be avoided in some cases (see for example Box 2.4: Case study 3), although it may be that programmes of education for physicians and patients would be more effective in reducing these problems.[13]

Box 2.4: Case study 3 – Abacavir

Abacavir is a medicine that is used widely in the treatment of HIV/AIDS. Clinical studies have shown that about 4% of patients experience a serious hypersensitivity reaction to the medicine, usually within the first six weeks of therapy. In rare cases, the adverse reaction is fatal.* In 2000, the company that makes abacavir, GlaxoSmithKline (GSK), announced the start of a research programme to identify genetic markers which would enable the prospective prediction of patients at an increased risk of a hypersensitivity reaction.

In 2002, two articles were published which linked a particular genetic variant called *HLA B5701* to the occurrence of hypersensitivity reactions.† The larger study, by the GSK group, found the *HLA B5701* SNP in 55% of Caucasian patients who had experienced a hypersensitivity reaction but only 1% of patients who were considered tolerant of abacavir.‡ While sample sizes for non-Caucasian patients were small, *HLA B5701* was not present in any of the nine black patients and in only one of the ten Hispanic patients who experienced the adverse reaction. Thus, many patients without the genetic variant experienced the hypersensitivity reaction.

The current position of GSK is that it would be premature to use *HLA B5701* testing to determine prospectively the risk of adverse response to abacavir. GSK also strongly recommends against testing once a patient has already experienced a hypersensitivity reaction. GSK aims to identify a set of genetic markers which might increase the predictive value of testing, with broad applicability across populations. Another group of researchers who have published similar results, however, have implemented genotyping of all patients in their hospital who have been prescribed abacavir on the basis of their research.§

* Hetherington S *et al*. (2001) Hypersensitivity reactions during therapy with the nucleoside reverse transcriptase inhibitor abacavir, *Clin Ther* **23**: 1603-14.

† Hetherington S *et al*. (2002) Genetic variations in HLA-B region and hypersensitivity reactions to abacavir, *Lancet* **359**: 1121-2; Mallal S *et al*. (2002) Association between presence of HLA-B*5701, HLA-DR7, and HLA-DQ3 and hypersensitivity to HIV-1 reverse-transcriptase inhibitor abacavir, *Lancet* **359**: 727-32.

‡ Hetherington S *et al*. (2002) Genetic variations in HLA-B region and hypersensitivity reactions to abacavir, *Lancet* **359**: 1121-2.

§ Mallal S *et al*. (2002) Association between presence of HLA-B*5701, HLA-DR7, and HLA-DQ3 and hypersensitivity to HIV-1 reverse-transcriptase inhibitor abacavir, *Lancet* **359**: 727-32.

12 Lazarou J, Pomeranz BH and Corey PN (1998) Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies, *JAMA* **279**: 1200-5.

13 We have already observed that many factors other than genetic variation affect the success or otherwise of medicines. In its response to our consultation paper, GeneWatch drew attention to a report by the Audit Commission which 'proposed a number of ways to improve medicines management, including increasing the role of pharmacists to ensure the optimal use of increasingly powerful medicines, encouraging patients to self-administer medicines whilst in hospital using individualized packs, and introducing better computer systems and monitoring.' Audit Commission (2002) *A Spoonful of Sugar – Medicines Management in NHS Hospitals* (London: Audit Commission).

Increasing efficacy

2.19 Results from pharmacogenetic tests may also inform physicians in selecting the medicine most likely to benefit a particular patient. Many medicines are effective in only a proportion of patients treated. Some common treatments for conditions including diabetes, depression and asthma are only effective in around 60% of patients, and for medicines used to treat cancer, this figure may be as low as 25%.[14] Sometimes, for a medicine to be effective, different doses are required for different patients. In the absence of a pharmacogenetic test for efficacy, the most appropriate medicine or dose is conventionally found by trial and error, although in some cases, tests of renal function may be used to predict the appropriate dose. It has been suggested that a 'trial and error' approach to prescription may reduce compliance for medicines that do work, since patients acquire a general aversion to taking medicines because of the unpleasant side-effects which they might experience.[15]

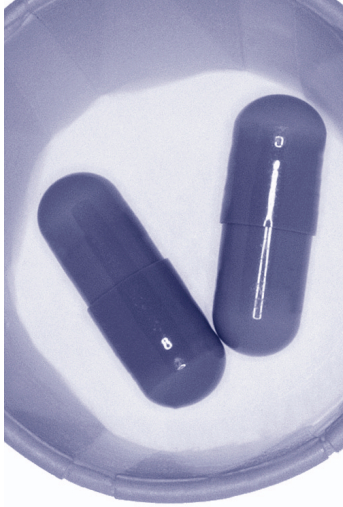
2.20 Bearing in mind the distinction made in paragraphs 2.6 – 2.10, there are two ways in which pharmacogenetics could improve this situation. First, it could enable medicines to be designed on the basis of information about the genetic characteristics of a disease (Box 2.3: Case study 2). Secondly, decisions about prescribing a medicine could be informed by knowledge of the genetic variation relevant to its metabolism in the body. In this latter case, the medicine itself may not have been developed with the genetic variation in mind, but its use could be restricted to those people whose genetic make-up identified them as being likely to respond well to the medicine, or the dosage adjusted to attain the maximum benefit (Box 2.2: Case study 1).

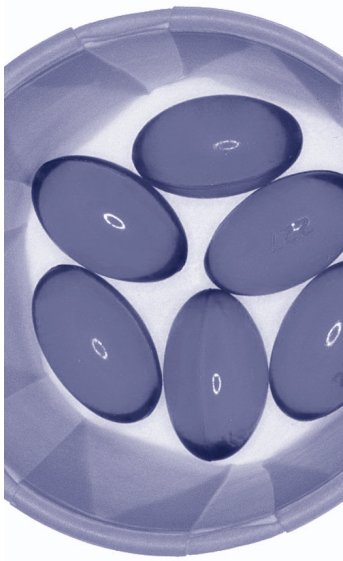
14 Spear BB, Heath-Chiozzi M and Huff J (2001) Clinical application of pharmacogenetics, *Trends Mol Med* **7**: 201-4.

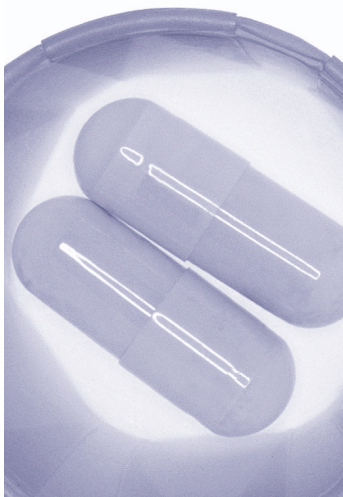
15 Professor Robert Kerwin, Professor of Clinical Neuropharmacology, Institute of Psychiatry, London, UK, speaking at the British Association Science and Public Affairs Forum, 6 Feb 2003.

Chapter 3

Research and development of new medicines







Research and development of new medicines

Introduction

3.1 In this chapter, we consider ethical, legal and regulatory issues raised by the application of pharmacogenetics in the research and development of new medicines. We examine the implications for the conduct and cost of clinical trials. Although there is not yet agreement on the extent to which pharmacogenetic testing will influence the development of new medicines, it is clear that some clinical trials already involve collecting genetic information for the purposes of identifying subgroups of patients who are more likely to suffer adverse reactions, or to respond well to particular treatments. We consider likely trends in the use of pharmacogenetics in clinical trials, and examine the implications for obtaining consent from research participants and the use and storage of DNA samples for pharmacogenetic research.

3.2 It should be borne in mind that the application of pharmacogenetics has the potential to bring substantial benefits to patients. Improving the safety and efficacy of medicines would be of great value, not only to individual patients, but also to society. The following discussions should be viewed in this context. It is important to articulate and to respond to legitimate concerns so that the benefits of pharmacogenetics may be realised and potential problems minimised.

The impact of pharmacogenetics

3.3 The application of pharmacogenetics to the development of new medicines and other products such as vaccines has implications for the way in which basic research and clinical trials are designed and managed, and for the cost of undertaking clinical trials.[1] Pharmacogenetics may be of relevance at various stages in the development of new medicines. The first stage, basic research, involves studying the biological mechanisms that contribute to the pathogenesis of a particular disease or whose modulation may alleviate its signs and symptoms. This may enable researchers to determine the main steps in the disease process and to identify likely targets for medicines. Pharmacogenetics could be of use in understanding features of diseases that may direct treatment, as in the case of Herceptin (Box 2.3: Case study 2). The next stage involves identifying compounds that may be suitable as medicines. Many compounds will be identified, and pharmacogenetics may sometimes be helpful in eliminating those that are unlikely to be effective in large groups of people.

3.4 Compounds that have been selected for further study are then tested in the laboratory and on animals. Those which seem promising may then be tested in human subjects to determine their safety and efficacy (see Box 3.1). If some individuals show little response to treatment, this does not prevent the development of the medicine, provided that there is a significant benefit in health to the group as a whole. In contrast, adverse reactions in a minority of participants in a clinical trial may sometimes mean that the medicine does not receive

[1] Although the focus of this Report is on the use of pharmacogenetics in connection with the treatment of disease, it should be noted that there is the potential to apply this technology to public vaccination programmes for the prevention of disease, where the vaccine in question is harmful for a small subpopulation that could be identified by genetic means. The ethical case for applying pharmacogenetics in such cases would be particularly strong, since those who are vaccinated are typically healthy children, and such vaccines are given not only for the benefit of the individual but for the general population. Under these circumstances there may be exceptional moral pressure to minimise the risk of harm to the individual being treated. However, given the very low probability of complications and the economic constraints on programmes of vaccination, such a screening test would need to be both extremely effective and inexpensive.

regulatory approval.[2] The application of pharmacogenetic analysis could, in some cases, identify those individuals participating in research who are less likely to respond or who are at risk of adverse reactions, especially in Phases II and III. These individuals could then be excluded from the trials. This could lead to better protection of participants.[3] Moreover, the medicines could then be considered for a specific, though possibly small, subgroup of the patients rather than the larger group for whom the medicine was originally intended. However, pharmacogenetic analysis may not be applicable to all clinical trials, and the benefits outlined above may be tempered by other effects of stratifying patients (see paragraphs 4.27 – 4.47).

Will pharmacogenetic testing in clinical trials become mandatory?

3.5 One recent survey suggested that most pharmaceutical companies believe that within five years, at least 50% of clinical trials will involve obtaining genetic data from participants.[3] Aside from economic considerations, there may be other pressures to incorporate pharmacogenetic testing into the process of developing new medicines. This could include testing samples taken from participants during the early stages of a clinical trial with a view to identifying pharmacogenetic effects on response to treatment, or testing patients during the phase of monitoring and surveillance if adverse reactions come to light. These pressures may come from regulators, concerned with ensuring the optimal conditions for the safe use of new medicines, or from the threat of legal challenges from patients affected by adverse reactions. We consider each of these in turn.

Regulatory requirements

3.6 There have recently been discussions by regulatory bodies including the Food and Drug Administration (FDA) and European Medicines Evaluation Agency (EMEA) regarding strategies for incorporating pharmacogenetic analysis into the process of licensing medicines. At a meeting in April 2003, the Science Advisory Committee of the FDA stated that it would not require pharmacogenetic testing in all clinical trials. However the draft proposal discussed at the meeting suggested that the FDA would require access to any data used in evaluating the safety or efficacy of medicines during development. This would include, for example, any data collected during the screening of patients before recruitment into a Phase I clinical trial and data used in determining dosage. In the case of pharmacogenetic data used solely for research purposes, the FDA plans to establish an Interdisciplinary Pharmacogenomics Review Group to consider data. However, these data would not be used in the process of approving or refusing a medicine. This 'safe harbour' would allow the FDA to become familiar with new technologies and products so that it would be equipped to evaluate similar information when products based on pharmacogenetic data begin to be produced.[4]

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2 Clinical trials require the approval of independent local or regional ethics review committees, which assess whether the trial will contribute to the improved treatment of the condition in question, and ensure that systems are in place for securing informed consent from participants, for monitoring their condition, and for enabling them to withdraw from the study if they wish. There is considerable guidance on the ethics of research on human subjects, including the following: World Medical Association (as amended 2000) *Declaration of Helsinki*; International Conference on Harmonisation (1997) *Note for Guidance on Good Clinical Practice*; MRC (1998) *Guidelines for Good Clinical Practice in Clinical Trials*; The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (1979) *The Belmont Report. Ethical Principles and Guidelines for the Protection of Human Subjects of Research*; National Bioethics Advisory Commission (2001) *Ethical and Policy Issues in Research Involving Human Participants.*

3 The SNP Consortium Ltd. Genotyping technology products user requirements survey. White Paper obtained through SNP Consortium (2000) Better Medicine through Genetics Hinges on Public Acceptance. Available: http://snp.cshl.org/news/medicine.shtml. Accessed on: 25 Feb 2002.

4 FDA Advisory Committee (2003) Pharmacogenomic Submissions Must Not Jeopardize Drug Development, Abbott's Spear Says. Available: http://www.fdaadvisorycommittee.com/FDC/AdvisoryCommittee/Stories/040903_SciBoardR.htm. Accessed on: 17 June 2003; Kling J (2003) US FDA contemplates collection of pharmacogenomic data, *Nat Biotechnol* **21**: 590.

Box 3.1: **The phases of clinical trials**

Phase I

These studies assess the pharmacodynamics and pharmacokinetics of a potential new medicine in a small number of healthy human volunteers (20–80). The aims are to identify the dosage range to be explored in the clinical trials involving patients and, sometimes, to confirm that the medicine produces, in humans, the effects anticipated in preclinical studies. Phase I studies usually take several months to complete.

Phase II

Approximately 70% of new medicines tested in Phase I pass to Phase II. Trials at this stage usually involve around 100–300 patients, and are designed to investigate whether the potential efficacy of the new medicine is actually realised. These trials will also provide preliminary data on the safety of the new medicine, and information about dosage. Phase II studies may take up to two years to complete. Only if Phase II testing is successful will the medicine progress to Phase III.

Phase III

At this stage, the medicine is investigated in a larger and more heterogeneous patient population. These studies will confirm or refute the safety and efficacy of the new medicine under conditions more closely resembling clinical practice. The trials are usually double blind and will normally be either placebo-controlled or include comparison with standard treatment, where this exists. Phase III studies may take several years to complete.

Phase IV (Post-marketing surveillance or Pharmacovigilance)

Following regulatory approval, sponsors (typically pharmaceutical companies) conduct further studies to evaluate the longer-term effects of the medicine. Such studies might include the analysis of the cost-effectiveness of the new medicine in comparison to traditional treatments, evaluations of the medicine in a particular population, or assessments of the outcomes for patients after many years of treatment. During this phase, research may also be undertaken to test whether the medicine can treat other conditions.

Programmes to develop new medicines can fail at any of these stages. In Phase I, obviously pharmacologically inactive or unsafe medicines are usually discarded. In Phase II, treatments which are not effective will be detected. In Phase III, both efficacy and safety are further characterised. Those medicines which are less effective than existing treatments or which display problems of safety may be discarded. It is more costly to abandon a new product at the later stages of a trial because the length of time required, the number of patients involved, and the amount of data generated all increase as the trial progresses. In Phase IV, after medicines have been licensed, rare adverse reactions may still be identified which, if serious, could lead to the withdrawal of the medicine.

Legal incentives

3.7 Legal obligations may be more stringent than the requirements set out by regulators. Successful litigation against companies who manufacture medicines would have an impact on the status of pharmacogenetic testing in clinical trials. Claims against the manufacturers of medicines by patients who have suffered adverse events can be advanced on two legal bases: fault liability (negligence) and strict liability. Claims in negligence relate to the obligation to take reasonable care and are often based on arguments that the manufacturer failed to carry out adequate research with regard to the medicine, and therefore failed to provide proper information about the risks associated with the product, and the balance between the risks and benefits, which could have been detected by such research. Thus, claims could arise from the occurrence of adverse effects, or from the failure of a manufacturer to provide information about patients for whom a medicine is likely to be of little or no benefit. Health professionals and health authorities can also be sued in negligence (see paragraphs 5.25 – 5.28).

3.8 Claims based on strict liability, which are normally limited to manufacturers of medicines, concern only the nature of the product: the reasonableness of the manufacturer's conduct is not the focus of the inquiry. However, if a medicine is not found to offer the safety that patients generally are entitled to expect, taking account of the warnings supplied in the product information and other relevant circumstances, the product is treated as 'defective' and manufacturers may be found liable for the adverse reactions caused. This may be because the research conducted during clinical trials was not sufficient to identify the adverse reaction, or because information about potential risks and benefits for particular groups of patients was not passed on. In the UK, manufacturers can mount the 'development risk defence' to argue that even though a medicine was defective, the problem could not have been identified at the time the medicine was supplied because the state of scientific and technical knowledge was not sufficiently advanced. In cases of negligence and of strict liability, having met the relevant regulatory requirements is not a sufficient defence. Courts may decide that additional research or activity was reasonable, or, for strict liability purposes, practical, in a particular case.

3.9 Regarding claims in negligence, claimants might argue that pharmacogenetic testing should be part of any 'reasonable' research into the development of a new medicine, since it has the potential to identify groups of patients who may be adversely affected or who will not benefit from the medicine. Likewise, in terms of strict liability, a failure to carry out such research when it is practicable to do so may render ineffective the 'development risk defence'. However, such an argument assumes that pharmacogenetics will be relevant for every new medicine that is developed. For medicines such as Herceptin, which are based on the genetic characteristics of a diseased tissue, pharmacogenetic testing is clearly an integral aspect of the process of development. In other cases, there might be no immediate reason to believe that genetic variation will play a sufficiently significant role in determining efficacy or safety to warrant pharmacogenetic analysis. In such cases, it could be that pharmaceutical companies collect genetic data in case problems arise in the future, but do not examine the data unless and until such problems become apparent.

3.10 The storage of blood and tissue samples from participants in clinical trials for extended periods of time is currently common practice. Such collection without testing could be problematic if a medicine is subsequently found to cause serious adverse reactions or to be ineffective in a number of patients and these characteristics could have been detected by pharmacogenetic testing. Having taken the samples, it could be argued by claimants that it was negligent not to conduct pharmacogenetic analysis in relation to such samples and to issue warnings that reflected the results of such research. In the context of strict liability, the

same proposition translates into the argument that, in the absence of such warnings, the product was defective and the defective nature of the product was discoverable through recognised research techniques. However, the developers of medicines will be likely to argue that, unless there is a compelling scientific reason to conduct pharmacogenetic analysis during a clinical trial, it would not be pragmatic to include this element in the research.

3.11 It has been suggested by one commentator that by 2014 'all new medicines [will be] required to use SNP analyses for clinical trials and surveillance'.[5] This projection is based on the presumed economic advantages to be gained by pharmacogenetic analysis in the development of new medicines. If, as this prediction suggests, panels of SNPs are developed and it becomes comparatively inexpensive to use such pharmacogenetic profiles in clinical trials, it is possible that there will be further regulatory and legal pressure on companies to pursue this approach. However, it is difficult to predict at this stage just how widespread the application of pharmacogenetics in research will become.

3.12 Pharmacogenetic analysis has the potential to improve our understanding of medicines and to produce safer and more effective medicines. **We recommend that the appropriate use of pharmacogenetic analysis in clinical trials should be promoted. Regulators should be encouraged to promote the collection and storage of samples in clinical trials such that they could be subjected to pharmacogenetic analysis either during the trial, or subsequently.** We consider questions of how best to obtain consent to the taking of such samples, and the manner in which data should be stored, in paragraphs 3.27 – 3.49.

The cost of clinical trials

3.13 The costs of developing a new medicine are substantial.[6] The development of a new medicine takes an average of 10–15 years (see Box 3.1). Currently, only around 2% of all programmes to develop new medicines result in clinical trials. Of the compounds that do reach the stage of Phase I testing, only 20% will eventually be approved for clinical use.[7] The effect of pharmacogenetics on the cost of clinical trials and therefore of new medicines is difficult to predict at this stage, though a number of speculative papers have been published on the topic.[8]

3.14 The selection of smaller groups of genetically homogeneous participants in clinical trials may be advantageous, leading to more robust and reliable scientific findings about the group of patients for whom the medicine might eventually be prescribed. However, there are various reasons to be cautious about claims that clinical trials will be reduced in size and therefore cost. First, larger numbers of patients may be needed in Phase II trials in order to identify relevant pharmacogenetic variants, since these variants may be relatively rare.

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5 Roses AD (2001) 2025: the practice of neurology: back from the future, *Arch Neurol* **58**: 1766-7.

6 The Tufts Center for the Study of Drug Development has estimated the cost of developing a new prescription medicine at $897 million (Kaitin K (2003) Post-approval R&D raises total drug development costs to $897 million, *Tufts Center for the Study of Drug Development Impact Report* **May/Jun; 5(3)**). However, the US national consumer group Public Citizen has suggested that the true costs are significantly lower (see Public Citizen (2001) New Study Expected to Significantly Overstate Drug Industry R&D Costs. Available: http://www.citizen.org/pressroom/release.cfm?ID=942. Accessed on: 31 Oct 2002.) See also Relman AS and Angell M (2002) America's other drug problem, in *The New Republic*, December 16, pp. 27-41.

7 Pharmaceutical Research and Manufacturers of America (2003) *Pharmaceutical Industry Profile 2003* (Washington, DC: PhRMA).

8 Tollman P *et al*. (2001) *A Revolution in R&D* (Boston: Boston Consulting Group). This paper suggests that pharmacogenetics will reduce the cost of developing new medicines. The savings would be achieved by refining trials, reducing the number of participants, and by bringing to market medicines that would otherwise have been lost because they are only effective in a subset of patients with a particular disease. See also Peakman T and Arlington S (2001) *Putting the Code to Work: The Promise of Pharmacogenetics and Pharmacogenomics* (PricewaterhouseCoopers).

Secondly, in order to identify adverse reactions, a large number of patients may still be required, since many reactions, including some of the most problematic, are relatively infrequent. This could mean that the numbers of participants in the later stages of clinical trials cannot easily be reduced, or that extended Phase IV monitoring is required. Thirdly, participants will still be required to take the medicine for similar periods of time as at present, in order to generate statistically significant information about its effects. Fourthly, costs may be increased because of expenditure on pharmacogenetic tests and analysis of the data they produce. Finally, it has been suggested that the cost of trials may increase because it would take longer to identify and recruit sufficient numbers of genetically similar participants. However, a counterbalance may be that the trials themselves, in which medicines targeted to the specific group of participants are tested, might produce results more quickly.

3.15 A number of respondents to the Working Party's consultation suggested that pharmacogenetics could be expected to increase the cost of clinical trials in the short term, but could contribute to a reduction in the long term:

> 'the economic impact of pharmacogenetics on the development of new medicines is difficult to gauge at present although in the short term costs may be higher. However many authors have cited the potential for pharmacogenetics to make clinical trials shorter and smaller thus reducing costs in development in the long term.'
> *(European Federation of Pharmaceutical Industries and Associations and Association of the British Pharmaceutical Industry)*

While the effect of pharmacogenetics may be to reduce some of the costs of developing new medicines, it would be imprudent to infer from this that the cost of purchasing medicines will necessarily fall. At this stage, it is not possible to predict the impact of pharmacogenetics on the cost of medicines.

The development of pharmacogenetic tests

3.16 A potential barrier to the development of pharmacogenetic tests concerns the application of intellectual property rights. Pharmacogenetic tests may be developed in a number of ways. The pharmaceutical company which is developing the medicine may also develop the pharmacogenetic test. Alternatively, a third party, such as another company or researchers from the public sector may develop the test independently. For example, in the case of Herceptin (Box 2.3: Case study 2), two independent companies produce the diagnostic tests which are used to assess the suitability of patients to receive the medicine.[9] It seems most likely that companies producing diagnostic tests will be involved in developing and marketing pharmacogenetic tests, since not all pharmaceutical companies will have the necessary skills, manufacturing capabilities and marketing force to successfully undertake production themselves.

3.17 What kind of patents might be used to protect pharmacogenetic tests? It is likely that the majority of pharmacogenetic tests will be based on the use of a small number of SNPs to identify the genetic variants which correlate with the response to treatment with one or more medicines. Individual SNPs are not patentable since they consist only of a single nucleotide base. Opinions differ as to whether a new variant of a known gene, in which

9 The two tests produced to determine whether a patient is suitable for treatment with Herceptin are the HercepTest, manufactured by Dako, and PathVysion, manufactured by Visis. The two tests determine whether the patient's tumour cells overexpress HER2. However they do so in different ways. HercepTest measures the protein in cancerous tissue while PathVysion measures the number of copies of the HER2 gene found in the tumour cells.

the novelty is the identification of a SNP, will meet the necessary legal criteria for patentability.[10] Variants in DNA sequence are more likely to be patentable when, for example, a particular SNP in coding DNA leads to an amino acid change which alters the response to a medicine, in other words, when a direct causal link has been demonstrated between the SNP and the phenotypic response. Patents which claim the substance(s) itself are called composition of matter or product patents and confer the most protection on biological molecules. It seems likely that patent protection will generally focus on claims which relate to the use of SNPs rather than the SNPs themselves.[11] It is currently unclear to what extent particular groups of SNPs associated with the pharmacogenetic response for different medicines will overlap. It may be that some groups will be specific to individual medicines while others may be generally applicable to a number of medicines in one class.

3.18 In broad terms, three types of patent claims can be expected: those relating to methods of testing, those relating to methods of treatment and those related to novel dosage forms of the medicine. These claims will be predicated on the identification of a novel association between genetic markers and a response to treatment with a specific medicine. Claims which relate to methods of testing will enable the identification of patients who are predicted to have a defined response to treatment through the testing for specific genetic variants, usually in the form of SNPs. Other novel features of the test will also be claimed. Claims which relate to methods of treatment, involving the administration of the medicine to patients of a defined response phenotype, are only strictly allowable in the US.[12] Claims which relate to the dosage of a medicine will specify the appropriate dosage for patients with particular genetic variants.

3.19 It may be necessary for companies or others developing pharmacogenetic tests to obtain a number of licences from other parties in order to develop their particular test. For example, there may be existing patents which assert property rights over DNA sequences within which the genetic variant of interest is found. It has even been suggested that the complexity of obtaining licences and the uncertainty of protection may adversely affect the development of the science.[13] It is too early to judge whether this will prove to be the case. However, we consider that it would be undesirable if the development of pharmacogenetic tests were to be inhibited by the need for complex cross-licensing arrangements. We recognise that the granting of protection of inventions through patents can be an important means of promoting development and innovation in healthcare, but it is important to ensure that they do not achieve the opposite effect.

Using pharmacogenetics to improve existing medicines

3.20 We have concluded that the application of pharmacogenetics to the development of new medicines offers potential benefits (paragraph 3.12). In the case of existing medicines, the application of pharmacogenetic analysis may be of value, but this will not necessarily be the case. We noted in Chapter 2 (Box 2.2: Case study 1) that genetic variations of CYP2D6 may result in differential metabolism of various medicines. This effect has been widely accepted for over 20 years, and it is known that 7% of Caucasians have genetic variations

10 Nuffield Council on Bioethics (2002) *The ethics of patenting DNA* (London: Nuffield Council on Bioethics).

11 Personal communications: Andrew Sheard, Patent Attorney, and Mike Stott, Corporate Intellectual Property, GSK, Brentford.

12 In Europe such claims have been limited to the so-called 'Swiss claims' which provide patent protection for the industrial aspects of preparing a compound for a particular use. Swiss claims are being superseded by 'compound for use' claims which will provide broadly the same degree of protection.

13 Personal communication (2003) Duncan McHale, Senior Scientist, Pfizer Ltd.

of CYP2D6 that cause poor metabolism of certain medicines and may therefore result in adverse reactions or reduced efficacy. But tests for these variants are not routinely carried out before prescribing the relevant medicines, which include common treatments for mental illness and heart disease. This is because the adverse reactions, while unpleasant, are rarely life-threatening and because alternative therapies exist. In addition, testing for the numerous variants has in the past been complicated and unreliable. This may change as knowledge develops and the technology of genetic testing improves. Nevertheless, it may be quicker and easier in many clinical settings simply to prescribe the medicines, observe any problems, and try a different medicine if necessary, rather than undertaking a pharmacogenetic test. It may be that for other existing medicines, pharmacogenetics could not generate predictive information of sufficient value to justify its use in clinical practice. The ability of a test to predict a particular outcome, may be proven. But such clinical validity does not necessarily correspond with clinical utility, that is, the ability of the use of the test to improve the treatment of patients.

3.21 In other cases, the application of pharmacogenetics to existing medicines could generate substantial benefits for patients. For example, clozapine is an antipsychotic medicine used in the treatment of schizophrenia which is effective in at least one third of patients who have failed to respond to other treatments.[14] However, it also causes a serious reduction in the white blood count of 1 in 200 patients. As a consequence, patients' blood counts have to be monitored, at monthly intervals, for long periods of time. If pharmacogenetic information could predict which patients are likely to respond well to clozapine, and which patients are likely to develop white blood cell problems, this would clearly be of value. Recently, research was published in which response to clozapine was successfully predicted in the majority of patients on the basis of six polymorphisms in genes related to neurotransmitter receptors. The researchers have suggested the first test to predict response to clozapine and other antipsychotic medicines could be available in 3–5 years.

3.22 A second example concerns warfarin, a medicine used to prevent the formation of blood clots, which is often prescribed for patients who have had a heart attack or surgery to replace heart valves. It has been estimated that over 500,000 people in the UK are receiving warfarin. However, its use can result in serious complications such as haemorrhage, which affects between eight and 26 patients of every 100 patients treated with warfarin for a year.[15] In order to minimise the risk of bleeding, it is important to obtain an accurate prediction of the dosage required. However, this is often difficult because there is wide variation between individuals in the dose necessary to maintain the appropriate degree of anticoagulation. Decisions about dosage are based on clinical judgement, and haemorrhages associated with warfarin remain a common problem. Warfarin is metabolised by the protein CYP2C9. Recent studies have shown that certain genetic variants of CYP2C9 result in a reduced ability to break down warfarin. Patients with these variants can only tolerate lower doses of the medicine.[16] Some researchers have suggested that the CYP2C9*2 and CYP2C9*3 variants are

14 Kane J *et al*. (1988) Clozapine for the treatment-resistant schizophrenic. A double-blind comparison with chlorpromazine, *Arch Gen Psychiatry* **45**: 789-96.

15 Petty GW *et al*. (1999) Frequency of major complications of aspirin, warfarin, and intravenous heparin for secondary stroke prevention. A population-based study, *Ann Intern Med* **130**: 14-22.

16 Taube J, Halsall D and Baglin T (2000) Influence of cytochrome P-450 CYP2C9 polymorphisms on warfarin sensitivity and risk of over-anticoagulation in patients on long-term treatment, *Blood* **96**: 1816-9; Higashi MK *et al*. (2002) Association between CYP2C9 genetic variants and anticoagulation-related outcomes during warfarin therapy, *JAMA* **287**: 1690-8.

associated with an increased risk of over-anticoagulation and bleeding, but there is a lack of consensus on the validity of these findings.[17]

3.23 Should all patients who are beginning treatment with warfarin receive a pharmacogenetic test? It is probably too early to make such a recommendation, as further research is required to validate these results. Moreover, the response to warfarin is not only determined by CYP2C9 but also by other metabolizing enzymes, and its interaction with other medicines. Research is required that takes account of all these factors before useful tests can be developed.[18] It should also be noted that new medicines have been developed that are as effective as warfarin, but which have fewer adverse reactions associated with them, reducing the incentive to develop pharmacogenetic tests.[19]

3.24 These two examples illustrate the potential benefits of pharmacogenetic analysis concerning existing medicines. It is not clear, however, who would conduct such research. For medicines still under patent, the opportunity of a patent extension might encourage pharmaceutical companies to do so. Once medicines are no longer protected by patents, however, the pharmaceutical companies who produce them have little financial incentive to invest in efforts to refine their use, especially if this refinement means that fewer patients are advised to take the medicine. In addition, manufacturers of generic medicines have limited funds for investing in research and development. However, if pharmacogenetic tests for existing medicines could be patented, this may provide a sufficient incentive for companies to develop them (paragraphs 3.16 – 3.19). Moreover, several companies market diagnostic products which, while not covered by patent protection, are nevertheless profitable. As diagnostic companies generally invest relatively little in research and development, research to identify genetic variants influencing response to medicines would need to be funded by and undertaken in the public sector. It is by no means certain that research would successfully identify genetic variants which could form the basis of a clinically useful test. However, if such variants were identified, the diagnostic industry could then provide the expertise to make a standardised test.

3.25 One method of encouraging the application of pharmacogenetics to existing medicines would be to promote research into pharmacogenetics within the public sector. In particular, collaborative research programmes could be encouraged, which merge the expertise of researchers in genetics with the expertise of clinicians who collect and evaluate data regarding response to medicines. Collaborations with industry could also be beneficial, if researchers were able to share clinical data. Another strategy would be to promote dialogue between healthcare providers and the pharmaceutical industry to identify fruitful areas of research. In the UK, a similar process took place concerning meningitis C. Until recently, no vaccine was available for this disease. The NHS consulted with industry and expressed interest in purchasing a vaccine for the disease, which resulted

17 Taube J, Halsall D and Baglin T (2000) Influence of cytochrome P-450 CYP2C9 polymorphisms on warfarin sensitivity and risk of over-anticoagulation in patients on long-term treatment, *Blood* **96**: 1816-9; Higashi MK *et al*. (2002) Association between CYP2C9 genetic variants and anticoagulation-related outcomes during warfarin therapy, *JAMA* **287**: 1690-8; Steward DJ *et al.* (1997) Genetic association between sensitivity to warfarin and expression of CYP2C9*3, *Pharmacogenetics* **7**: 361-7; Daly AK and King BP (2003) Pharmacogenetics of oral anticoagulants, *Pharmacogenetics* **13**: 247-52.

18 Pirmohamed M and Park BK (2001) Genetic susceptibility to adverse drug reactions, *Trends Pharmacol Sci* **22**: 298-305.

19 There is also some suggestion that pharmacogenetics could be useful in predicting which patients are likely to respond well to the use of statins for preventing cardiovascular disease. See Humma LM and Terra SG (2002) Pharmacogenetics and cardiovascular disease: impact on drug response and applications to disease management, *Am J Health Syst Pharm* **59**: 1241-52; Winkelmann B (2002) Lipid lowering responses modified by genetic variation, in *Pharmacogenomics: The Promise and Reality of Individualized Treatment*, 17-18 October, Paris.

in a vaccine being developed.[20] This strategy could be beneficial on both a national and an international level.[21]

3.26 In conclusion, the application of pharmacogenetics to existing medicines may have the potential, in some cases, to improve their safety and efficacy. The Government has proposed that pharmacogenetic research will be of particular value for medicines which are commonly used, for medicines which are used in otherwise healthy people, or for the examination of serious adverse reactions which occur in response to a number of different types of medicine.[22] We suggest that other relevant factors will include the scale of the negative effects experienced, the size of the patient population, the likely clinical value of the pharmacogenetic test and the existence of other treatments. It is not clear that the private sector will be motivated to pursue pharmacogenetic research in relation to medicines not covered by patent protection. **We therefore recommend that efforts should be made to encourage pharmacogenetic research on existing medicines, where there is reason to believe that such research could significantly improve efficacy or safety. Funding and support should be made available within the public sector and public–private partnerships encouraged.** We welcome the recent announcement by the Department of Health that £4 million will be directed towards research in pharmacogenetics over the next three years.[23]

The use of pharmacogenetic information collected in research

3.27 We now turn to consider ethical issues raised by the use of pharmacogenetic information in research. We focus, in particular, on the implications for consent, privacy and access to information by patients and other individuals such as health professionals. Debates about ethical issues arising from genetic testing have been taking place for some time. As a result, there is already considerable consensus, and many guidelines and recommendations for best practice (paragraphs 1.6 – 1.7). Nonetheless, it is useful to consider these issues in the context of pharmacogenetic testing and to assess whether additional guidance may be required, not least because the development of pharmacogenetics may lead to a substantial increase in the amount of genetic testing that takes place, and because what is considered a proper regime of testing will vary with the kinds of information the tests provide and the uses to which they are put.

Consent

3.28 The principle of consent in regard to participation in research was first established in the Nuremberg Code.[24] As the interests of researchers and interests of participants may conflict, the Code and other guidelines on the conduct of clinical research require that participants should be informed about the risks of the study, have the right to withdraw from studies at

20 For example, see Trotter CL, Ramsay ME and Kaczmarski EB (2002) Meningococcal serogroup C conjugate vaccination in England and Wales: coverage and initial impact of the campaign, *Commun Dis Public Health* 5: 220-5.

21 Public-private partnerships have been developed in recent years in relation to neglected diseases affecting developing countries, for example, the International AIDS Vaccine Initiative, the Global TB Alliance and the Malaria Vaccine Initiative.

22 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), para. 5.21.

23 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).

24 The Nuremberg Code (1947) arose from a trial at the end of the Second World War by the US Military Tribunal of 23 Germans accused of war crimes and crimes against humanity for their role in conducting unethical medical experiments on concentration camp inmates. The trial led to the production of a code which defined 'permissible medical experiments'.

any point, and must give their explicit consent to participation.[25] It is common practice to require consent for the collection and banking of tissue and DNA samples of participants in research, especially if it is intended to combine genetic information with other information from the patient's medical record. Most researchers obtain written consent from participants and are required to provide written information in advance of obtaining consent.

3.29 In the context of pharmacogenetic research, as in other forms of research, the nature of the information likely to be revealed and its implications for the patient should be set out for prospective participants as part of the standard process of obtaining consent. While the provision of information in obtaining consent is important, it should be noted that the ethically significant requirement of consent is not that it be complete, but rather that it be genuine. As we have discussed in a previous Report, since description can never be fully exhaustive, consent will always be to action that is incompletely described; moreover the descriptions offered are often incompletely understood.[26] This incompleteness cannot be remedied by devising more elaborate consent forms. Fully informed consent is therefore an unobtainable ideal. Obtaining genuine consent requires medical practitioners to do their best to communicate accurately as much as patients, volunteers or relatives can understand about procedures and risks, and to react to the limits of their understanding, and of their capacities to deal with difficult information. If all reasonable care is exercised, adequate and genuine consent may be established, although it will necessarily fall short of fully informed consent.

3.30 Two further important areas of concern are the voluntary nature of the consent and the privacy of the information which is obtained and stored. There is a serious question regarding whether voluntary consent to pharmacogenetic testing can truly be obtained in the context of clinical trials or in clinical practice. If researchers require a pharmacogenetic test as a condition of enrolment in a study (paragraph 3.5), patients might not feel able to refuse, especially if they think it is possible that some personal benefit may accrue. Indeed, in some cases, taking part in a clinical trial may be the only way for a patient to have a chance of obtaining a particular medicine. Testing may become an integral part of the methodology of clinical trials, so that taking part in a trial requires consent to pharmacogenetic testing. This may well be to the benefit of patients in general, but might cause concern to individuals if other issues about the storage of and access to data are not resolved. While this perceived lack of choice on the part of patients may arise to a similar extent in any trial of a new medicine, it may be of particular concern when that research involves taking samples of DNA because of public perception.

Privacy and confidentiality

3.31 The implications for patients of DNA samples being used in research will differ depending on how easily their samples can be traced back to them, and whether the research is likely to give rise to information that may be of personal clinical relevance. Two related questions arise: (i) what level of anonymisation of samples is appropriate, and (ii) should individual patients be given feedback regarding tests carried out on their samples?

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25 World Medical Association (2000) *Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects* (Adopted by the 52nd WMA General Assembly, Edinburgh, Scotland; Medical Research Council (1998) *Guidelines for Good Clinical Practice in Clinical Trials* (London: MRC); The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (1979) *The Belmont Report. Ethical Principles and Guidelines for the Protection of Human Subjects of Research*. For further information, see Eckstein S (editor) (2003) *Manual for Research Ethics Committees.* 6th edition. (London: Centre of Medical Law and Ethics, King's College).

26 Nuffield Council on Bioethics (1995) *Human tissue: ethical and legal issues* (London: Nuffield Council on Bioethics).

3.32 A recent Position Paper on Terminology in Pharmacogenetics by the EMEA/CPMP, published in December 2001, is a significant step toward the preparation of specific regulation on pharmacogenetics.[27] The paper emphasises the urgent need for harmonised terminology for protocols and guidelines including pharmacogenetic testing.[28] This is seen as a necessary requirement for the harmonisation of pharmacogenetic protocols in clinical trials. The paper sets out a classification scheme with respect to research samples used in clinical trials (see Box 3.2).

Box 3.2: **EMEA terminology in pharmacogenetics research**

Sample labelling code	Link between subject and data?	Records identifiable for clinical monitoring	Withdrawal of consent	Return of individual results?	Scope of subject's privacy protection
Identified	Yes, directly	Yes	Sample can be withdrawn with immediate effect for any prospective use	Possible	Similar to general healthcare confidentiality
Single-coded	Indirectly via a code key	Yes, via protocol specified procedures	Sample can be withdrawn with immediate effect for any prospective use	Possible	Standard for clinical research Conforms to principles of good clinical practice
Double-coded	Indirectly, via two code keys	Yes, via protocol specified procedures	Sample can be withdrawn with immediate effect for any prospective use	Possible	Standard for clinical research Conforms to principles of good clinical practice Offers added privacy protection over single code

continued >>

27 EMEA CPMP (2002) Terminology in Pharmacogenetics – Final Position Paper. Available: http://www.emea.eu.int/pdfs/human/press/pp/307001en.pdf. Accessed on: 5 Mar 2003.

28 The system set out by the EMEA is similar to that proposed by the Pharmacogenetics Working Group, which distinguished identified, coded, de-identified (double-coded), anonymised and anonymous categories. Spear BB *et al*. (2001) Terminology for sample collection in clinical genetic studies, *Pharmacogenomics J* **1**: 101-3. Different terms are used by the Medical Research Council in its publications. We use the EMEA terminology in this Report. The corresponding terms used by the MRC are as follows: linked (coded); linked anonymised (double-coded); unlinked anonymised (anonymised).

Sample labelling code	Link between subject and data?	Records identifiable for clinical monitoring	Withdrawal of consent	Return of individual results?	Scope of subject's privacy protection
Anonymised	No, key identifying the link between genetic data and the identity of the subject is deleted	No	Sample and data are not identifiable Sample cannot be withdrawn once key is deleted	Not possible	Data not linked to individuals
Anonymous	No	No	None	Not possible	Complete

3.33 Thus, *identified* samples are treated in the same way as samples acquired in other areas of medical practice. These samples are labelled with personal identifiers such as the donor's name or social security number. This allows for easy retrieval of the sample from a study, should the donor wish to withdraw, and it is similarly easy to provide feedback. In the case of *coded* samples, there are 'keys' connecting the sample to the participant. The clinical investigator holds the key which links the patient's name to the first code. In *single-coded* systems, the genetic researcher has access to this code. In *double-coded* systems, the genetic researcher only has access to a second code and the key linking the two codes together. *Anonymised* samples are like double-coded samples except that the identifying key is destroyed after the genetic and clinical information has been obtained. In the case of *anonymous* samples, no direct link between the sample and the donor exists from the time the sample is collected. Such a sample may be labelled with population information that indicates that the donor suffered from a particular disease, but it contains no individual identifying data. Of course, in principle, it would be possible to establish a link between an anonymous sample (or indeed, an anonymised sample) and the individual from whom it was obtained by matching the sample in question to another one from the same person. To do this, a second sample would have to be obtained, with the consent of the individual, and compared to all the samples in the database.

3.34 What are the relative merits of each approach? It is important to realise that pharmacogenetic analysis of samples could take place at various stages in a clinical trial. There might be basic laboratory research undertaken to examine how medicines interact with particular enzymes. Analysis could also be undertaken during a clinical trial to examine efficacy and safety in relation to genetic variation. Finally, once a medicine had been licensed, there might be additional research conducted if any problems were to arise in patients taking the medicine, although often at this stage new samples would be collected instead. There may be reasons to impose different degrees of anonymity in different types of research.

3.35 In general, anonymous samples are of little value in many types of pharmacogenetic research, since they do not allow the collection of data that links a particular patient's genotype to his or her response to the medicine being studied. Knowledge of a DNA sequence is of no worth without knowledge of what happened to that patient when he or she took the medicine being studied. Anonymised samples have the disadvantage that they preclude the follow-up or monitoring of an individual's condition in the longer term, once the key linking the sample to the patient has been destroyed. However, clinical information can be collected and linked to the sample prior to its anonymisation, which can provide sufficient information within the context of a clinical trial. Subsequent research in the post-marketing surveillance phase of a trial can be conducted on new samples in most cases. Single-coded or double-coded samples are more likely to be appropriate if researchers wish to trace participants once a clinical trial has ended and also when the trial is taking place, since clinical information may be collected at various stages. This approach has the potential but speculative benefit for participants that if the research subsequently reveals information of relevance to the participant's health or medication, the patient can be informed. However, if important information is discovered and the samples have been anonymised, participants may be re-tested as part of their ongoing clinical treatment (see paragraphs 3.44 – 3.49 for a discussion of providing individual feedback). Identified samples are rarely used. It should be noted that samples which are coded or identified could also later be anonymised and used in other research projects, depending on the nature of the consent obtained from participants.

3.36 In the specific case of pharmacogenetic research, we take the view that it is generally possible to obtain genetic and clinical information about a patient during a clinical trial and then to anonymise the samples. In most cases, new samples can be taken from patients suffering adverse reactions and from controls for the purposes of post-marketing surveillance without compromising the quality of the research. In some cases, for example, trials that last for a very long period of time, anonymisation would not be able to take place without compromising the goals of the research. There may also be auditing requirements imposed by regulators which entail that samples cannot be anonymised, even for a number of years following the completion of a clinical trial. **We consider that to protect the privacy of participants in research, the greatest degree of anonymity should be imposed on samples, compatible with fulfilling the objectives of the research. Researchers should explain to prospective participants the implications of the manner in which samples will be stored for that participant.**

3.37 It might be suggested that storing samples in a coded or identified form is acceptable only where the participant is aware of the precise nature of the research to be conducted. This could be argued on the grounds that future use of the sample could reveal information about the participant which he or she would not have wished to know. It can also be argued that, whether samples are anonymised or not, there should be limits to the use to which they can be put, since there may be some types of research to which the participant does not wish to contribute. Thus, a distinction is often drawn between 'broad' and 'narrow' consent. The latter refers to instances where a sample is only to be used for a restricted range of purposes, perhaps only for a single research project, or research in relation to one particular medicine or condition. Broad consent entails that patients agree that their sample may be used for a variety of future studies which it may not be possible to specify in any detail at the time of consent. Usually, but not always, these future studies will be within the same broad areas of research as the initial project. For example, some researchers may wish to use samples taken for pharmacogenetic research in general studies examining the genetic basis of disease. In practice, there is no dividing line between broad

and narrow consent. The breadth of the research proposed could range from any biomedical research to a particular study.

3.38 Allowing broad consent may be of significant benefit to researchers and to society's interest in the acquisition of knowledge about health and disease. Researchers may not be able to predict at the start of a study whether the information gathered may subsequently be useful in additional research. If this proves to be the case, the practical difficulties of contacting participants and obtaining new consent for the use of their data in a different project perhaps a number of years later, may be prohibitive.

3.39 Current guidance regarding obtaining broad consent in research has been provided by the Medical Research Council (MRC). The MRC proposes that where broad consent is desired, a two-phase process is used which enables participants to agree to a specific research project but to opt out of allowing their sample to be used for other purposes. The guidance states that:

> 'unless the sample is to be anonymised and unlinked prior to storage… it is not acceptable to seek unconditional blanket consent, for example using terms such as 'all biological or medical research'. If samples may be stored or used in a form that allows them to be linked to individuals, possible future research should be explained in terms of the types of studies that may be done, the types of diseases that could be investigated, and the possible impact of the research on them personally. The benefits of enabling more efficient use of valuable samples should be explained to donors.'[29]

Having obtained broad consent, all future projects must be approved by a competent Local Research Ethics Committee. **We consider that it is permissible to request broad consent to the use of samples which are anonymous or anonymised. Where samples collected for a particular study are coded or identified, broad consent to future research may also be permissible, but should be sought separately from consent to the initial study. This separate consent may be obtained when the samples are originally taken, or at a later date.** In general, the further removed the future research is from the original study, the more likely it is that separate broad consent should be obtained. An indication of the type or nature of the research likely to be carried out and its implications for the individual should be given where possible.

3.40 A further question is whether data protection laws are compatible with the anonymisation of pharmacogenetic samples. Countries vary in their regulations regarding data protection. In the UK, the Data Protection Act 1998 (DPA) is the primary means by which the storage and processing of personal data is regulated. The DPA defines a special class of 'sensitive personal data' which includes health data and information about racial origin but does not specifically mention genetic information. Research using anonymous or anonymised samples is not subject to the Data Protection Act. Under the DPA, those who collect personal data are responsible for ensuring that the patient has explicitly consented to the processing of the data. However, there is a specific provision that permits the processing of sensitive data by health professionals, or others subject to an equivalent duty of confidentiality, without consent.[30] Nonetheless, organisations storing DNA samples are likely to be obliged to obtain explicit consent to comply with other laws, such as the common law of confidence. A patient has the right to request access to his or her personal

29 Medical Research Council (2001) *Human Tissue and Biological Samples for Use in Research – Operational and Ethical Guidelines* (London: MRC).

30 Data Protection Act 1998, schedule 3, para. 8.

data at any time, unless this is judged likely to cause serious harm to the physical or mental health of the patient or any other person.[31]

3.41 In 2002, the Information Commissioner published guidance to clarify the application of the DPA in the case of health records.[32] In the context of clinical trials, this states that:

- Uses and disclosures of the information should be explained, including that this use of personal data is optional.
- Consent to processing is required to meet common law obligations, and should be 'explicit' to conform to the requirements of the DPA. (This will generally mean written consent must be obtained.)
- Privacy-enhancing technologies should be used to protect the identity of patients.
- Patients must be told about secondary use of the data that is anticipated when the data are first collected. The exemption provided for in section 33 of the DPA, which allows research to be carried out without notice being given to the individual, is unlikely to apply. It applies only where, *inter alia*, the data are only processed for research and are not processed to support decisions about the individual, such as their treatment.

3.42 In addition to the rights of patients to have access to their data, the DPA also provides that holders of data have a positive obligation to inform individuals if they hold information about them. In the context of genetic information, this has given rise to concern about the possibility that health professionals might be obliged to inform relatives about genetic test results, if those results may also apply to other family members. The Human Genetics Commission has said that:

> 'It is not clear how the DPA deals with information relating to a subject which also contains information about a relative. It could be that relatives could prevent such information being processed, or that the DPA might require data controllers to pass on such information to the relatives.'[33]
>
> 'We believe that there may be a need for secondary legislation to ensure that the holders of information about genetic relatives in a clinical context are specifically exempted from their normal obligations of notification and provision of information to such relatives under the DPA.'[34]

However, it has also been argued that unless the holders of personal data also have, or are likely to obtain, additional information that identifies the relative in question, the DPA does not require the data to be disclosed.

3.43 There is a considerable literature on the obligation to disclose information to relatives, both in genetics and in the case of infectious disease. In difficult cases raised by genetic testing, decisions should be driven by clinical judgement and by awareness of the particular features of the case, not by legislation. In the case of pharmacogenetic information, the likelihood

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[31] The right of access is subject to a number of other exceptions. For example, it is also sometimes possible to refuse to release information in response to repeat requests.

[32] Information Commissioner (2002) Use and Disclosure of Health Data: Guidance on the Application of the Data Protection Act 1998. Available: http://www.dataprotection.gov.uk/dpr/dpdoc.nsf/ed1e7ff5aa6def30802566360045bf4d/7b7d02d29c28e76d80256bb5005d7bb3/$FILE/HealthGU.doc. Accessed on: 5 Mar 2003..

[33] Human Genetics Commission (2002) *Inside Information: Balancing interests in the use of personal genetic data* (London: Department of Health), para. 3.37.

[34] Human Genetics Commission (2002) *Inside Information: Balancing interests in the use of personal genetic data* (London: Department of Health), para. 4.7.

that test results would be of immediate relevance to a family member is low compared to other genetic tests such as those for monogenic disorders (see paragraphs 5.34 – 5.35). **We received conflicting views as to whether the Data Protection Act (DPA) imposed an obligation on health professionals to disclose information to relatives. We recommend that even if secondary legislation is not required, clarification should be provided by the Information Commissioner to ensure that the DPA is not interpreted so as to require health information to be passed to relatives.**

Individual feedback

3.44 In some cases, researchers provide individual feedback to patients. In others, researchers elect to offer individual test results to patients who request the information. (If data have been anonymised, individual feedback is of course not possible without additional samples being obtained.) There is no clear guidance on this matter in the UK. The MRC observed in 2001 that there is no consensus on the question of individual feedback and requires only that researchers should decide what level of feedback they will provide and inform patients as part of the process of obtaining consent.[35] In other countries, there is a similar degree of flexibility. For example, in France, the overall results of a research project must be communicated to participants. Depending on the type of research conducted and on the results obtained, ethical review committees may also approve the feedback of individual results.[36] We support the view of the Human Genetics Commission that the feedback of the overall results of research should be promoted.[37]

3.45 As already noted, in the UK, research participants are able to request access to information about themselves under the DPA, provided their data have not been anonymised. However, there is some uncertainty about how far this right of access extends. If the information requires specialist knowledge and processes to be conveyed to the individual in a meaningful form, it may be argued that the holder of the information does not have to make it available. Section 8(2) of the DPA states that where the data provided are 'expressed in terms which are not intelligible without explanation, the copy must be accompanied by an explanation of these terms', but there is uncertainty as to how far this obligation extends.

3.46 Information of immediate clinical relevance to a research participant would be passed automatically to the individual, usually through his or her physician.[38] But the definition of immediate clinical relevance is not straightforward. A simple rule would be to convey information about test results outside the normal range, but in pharmacogenetic studies, this is not likely to apply. A more useful definition might be information which would reasonably be thought to indicate the presence of or significantly increased susceptibility to

35 Medical Research Council (2001) *Human Tissue and Biological Samples for Use in Research – Operational and Ethical Guidelines* (London: MRC).

36 Article L.1122-1 of the Code of Public Health, as modified by the law of March 4, 2002.

37 Human Genetics Commission (2002) *Inside Information: Balancing interests in the use of personal genetic data* (London: Department of Health), para. 5.51.

38 The storage of genetic information obtained in the course of research in medical records might be thought problematic if third parties such as insurers were able to obtain access to it. However, the Association of British Insurers has issued the following statement on this matter: 'Insurers are only interested in the results of genetic tests where the results have been communicated to patients as part of a clinical diagnostic process and then, only if the test has been approved by the Genetics and Insurance Committee (GAIC) (or is one of the tests submitted to GAIC by December 2000). Research projects rarely, if ever, produce tests that meet these criteria, and in these circumstances, insurers would not be interested in any test results that the projects did produce. In addition, whatever the circumstances, insurers do not take account of genetic test results that are made available to policyholders after their policy has been taken out.' Joint statement on genetic research and insurance produced by the UK Forum on Genetics and Insurance, 24 April 2001.

a disease, or which might affect the current treatment of the participant. The feedback of information that is not of immediate clinical relevance but which still has implications, or may do in the future, for the health or treatment of the participant, raises difficult issues.

3.47 Arguments against providing individual feedback in such circumstances tend to focus on the uncertain nature of research results. An important point is that tests carried out in a research setting are not as reliable or as stringent as those conducted in clinical practice. Tests would need to be repeated in a clinical setting to provide results that could form the basis for treatment. In addition, the information generated may be difficult to interpret and the relevance to the patient hard to estimate, especially if research is exploratory or at an early stage. Explaining the relevance of the data might require specialist expertise that would be difficult and costly to provide to the thousands of participants in a clinical trial. It could be argued that passing on individual results of research whose findings have not been replicated is irresponsible, since participants are unlikely to be informed subsequently if later research comes to a different conclusion. It is also unclear whether participants in clinical trials involving pharmacogenetics will necessarily have an interest in receiving individual feedback.[39]

3.48 However, proponents of individual feedback argue that while information may be uncertain and complex, and while not all participants may be interested in receiving feedback, a decision about whether or not the information is given should be in the hands of the individual, not the researchers. From this perspective, allowing researchers to determine whether individual feedback is provided, is unjustified paternalism which assumes that participants are not capable of understanding or dealing with information about themselves. While not recommending the unrestricted provision of individual feedback, the MRC has said that 'participants have a right to know individual research results that affect their interests, but should be able to choose whether to exercise that right.'[40]

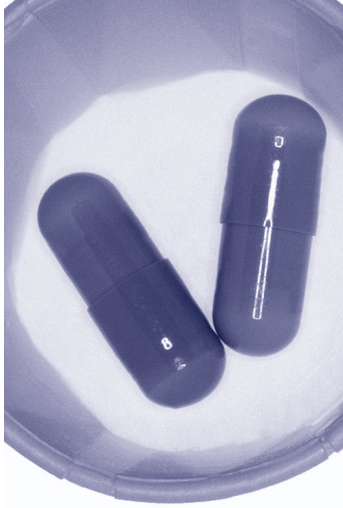
3.49 While we are sympathetic to the view that patients should have the opportunity to receive useful and validated information about their medical treatment, we consider that only on rare occasions will such information be obtained as part of research in pharmacogenetics. **In the atypical cases in which a clinical trial is likely to produce validated and clinically useful data regarding individual participants, we recommend that all participants should be offered the opportunity to receive individual feedback of such data as part of the process of obtaining consent. As far as possible, the nature and implications of the information to be obtained should be explained to participants.** We recognise that decisions about whether data that may be obtained in the course of research are likely to be clinically useful, and assessments of when findings can be said to be sufficiently well validated, will be complex. **We therefore recommend that researchers should explain their decisions regarding the provision of individual feedback to the relevant research ethics committee.**

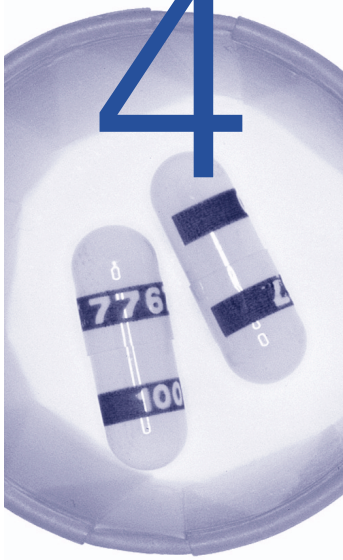
39 Corrigan O (2003) Response to Nuffield Council on Bioethics Consultation, Cambridge. In a recent phase I clinical trial conducted with pharmacogenetic testing, none of the 23 volunteer subjects were interested in knowing their CYP2D6 status.

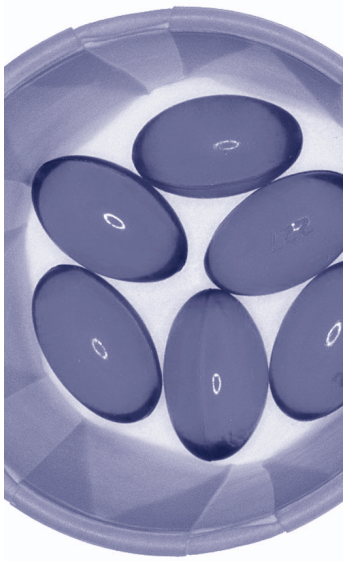
40 Medical Research Council (2001) *Human Tissue and Biological Samples for Use in Research – Operational and Ethical Guidelines* (London: MRC).

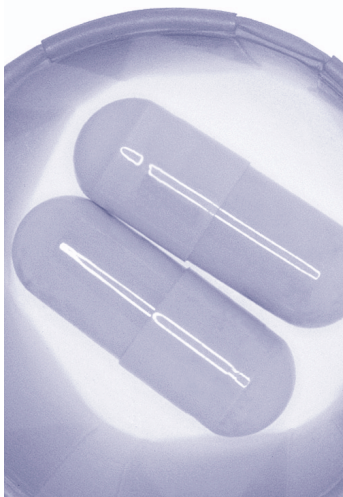
Chapter 4

Regulation and public policy









Regulation and public policy

Introduction

4.1 All medicines are required to meet standards of safety and efficacy. In addition, in the UK and a number of other jurisdictions, requirements of cost-effectiveness are also applied, so that medicines offer reasonable value for money. We have already seen that the application of pharmacogenetics will have implications for the number and variety of patients who may benefit from a particular medicine. These implications raise important issues of public policy concerning equity and fairness, which we seek to address in this chapter.

4.2 We begin by considering the implications for regulators regarding the licensing of pharmacogenetic tests and medicines, both for new tests and medicines and for those medicines which have previously been withdrawn from the market. In particular, we consider the contribution that pharmacogenetics could make to improving cost-effectiveness through the reduction of wasteful prescribing, and questions of the just allocation of resources that arise as a result of the stratification of patient groups through pharmacogenetic testing.

Regulation

4.3 In the UK, the safety and efficacy of medicines is assessed by the Medicines and Healthcare Products Regulatory Agency (MHRA).[1] The MHRA licenses new medicines for use and oversees the provision of information and warnings about products. Regulation of the quality of genetic tests is also the responsibility of the MHRA. A European directive on *in vitro* diagnostic medical devices (98/79/EC) was agreed in 1998 which sets out the requirements for licensing diagnostic tests.[2] The MHRA is responsible for the implementation of this directive in the UK.

Pharmacogenetic tests

4.4 Depending on the evidence submitted to the MHRA by a pharmaceutical company that has developed a new medicine, the Agency may require the use of a pharmacogenetic test as part of the conditions of issuing a licence for its use. Notification about the need to perform the test before prescribing the medicine would then be included in the information about the medicine used by prescribers. This approach is analagous to that taken with medicines that require non-genetic tests to be carried out in order to assess the suitability of a patient for treatment or to monitor their response to the medicine. Such tests are currently used for various medicines and include tests of liver or kidney function. It is likely that pharmaceutical companies which have identified genetic variation that affects response to a new medicine will include this information in their application and will support its inclusion in the licence. There will be legal incentives for this approach, as including the information in the product licence will discharge a company's legal obligation to make prescribers and patients aware of relevant information about safety and efficacy. Furthermore, regulators may require the disclosure of such information. Companies could advise prior testing for all potential patients for whom the medicine is intended, or for specific groups considered to be at risk

1 The MHRA was formed in 2003 as a result of the merging of the Medicines Control Agency with the Medical Devices Agency.

2 Directive 98/79/EC of the European Parliament and of the Council of 27 October 1998 on *in vitro* diagnostic medical devices. Available: http://europa.eu.int/smartapi/cgi/sga_doc?smartapi!celexapi!prod!CELEXnumdoc&lg=EN&numdoc=31998L0079&model=guichett. Accessed on: 20 Jun 2003. For further discussion of the regulation of tests, see Melzer D *et al*. (2003) *My Very Own Drug: What Must I Know?* (Cambridge: Department of Public Health and Primary Care, University of Cambridge).

due to factors such as sex, age or ethnicity. If it would be unsafe to prescribe a medicine in the absence of a test, or if the test provides very strong predictions of efficacy, it will be in the manufacturer's interest to ensure that the test is available, either from the manufacturer or from a diagnostic company.

4.5 In the case of medicines that have already been licensed, pharmacogenetic tests that are subsequently developed will not be part of the licence conditions. However, the MHRA reviews the conditions of licences once every five years, and could decide to include a pharmacogenetic test as part of a review, or at another time. This possibility is illustrated by the example of a pharmacogenetic test that predicts response to the medicine 6-mercaptopurine for children with acute lymphoblastic leukaemia (ALL). This rare childhood cancer is commonly treated with 6-mercaptopurine, which is metabolised by the enzyme thiopurine methyltransferase (TPMT). Around 10% of Caucasians have genetic variants that lead to reduced levels of the enzyme.[3] In these patients, 6-mercaptopurine can build up in the blood stream and lead to serious toxicity. Patients deficient in TPMT can be identified through the use of a pharmacogenetic test and their dosage of the medicine reduced accordingly.[4] This pharmacogenetic test is marketed and used, although it took about 20 years for the discovery of this phenomenon to be incorporated into clinical practice, and in the UK, most physicians only use the test once a patient has shown signs of an adverse reaction.[5] In the US, the FDA has recently announced that it is considering recommending the use of the pharmacogenetic test to guide dosing.[6]

4.6 It is most important that pharmacogenetic tests are developed which are of high quality and able to identify the genetic variations in question accurately. The MHRA is responsible for ensuring that only pharmacogenetic tests of high quality are approved for use. **We recommend that the European Medicines Evaluation Agency (EMEA) and the Food and Drug Administration (FDA) provide guidance for applicants as to the circumstances in which pharmacogenetic tests will be incorporated into the licence conditions of a medicine.** Relevant factors will include the reliability of the test, the level of information it provides, and the frequency and magnitude of the effect it predicts, whether an adverse reaction or a poor likelihood of response.

Withdrawn medicines

4.7 The most common reason for medicines to be withdrawn from the market once they have been licensed is the subsequent occurrence in patients of serious adverse reactions, which were either unsuspected at the time of marketing authorisation or occur more frequently than was expected at the time of the grant of marketing authorisation.[7] If at least some

3 McLeod HL and Siva C (2002) The thiopurine S-methyltransferase gene locus – implications for clinical pharmacogenomics, *Pharmacogenomics* **3**: 89-98; Collie-Duguid ES *et al*. (1999) The frequency and distribution of thiopurine methyltransferase alleles in Caucasian and Asian populations, *Pharmacogenetics* **9**: 37-42.

4 It should be noted, however, that the TPMT test, while providing high specificity (i.e. a patient who tests positive is definitely at high risk) has quite limited sensitivity (i.e. a significant number of patients who test negative will still have the adverse reaction). Thus, the pharmacogenetic test does not remove the need to monitor patients closely when they receive the medicine.

5 Weinshilboum R (2001) Thiopurine pharmacogenetics: clinical and molecular studies of thiopurine methyltransferase, *Drug Metab Dispos* **29**: 601-5.

6 FDA Advisory Committee (2003) Pharmacogenetics To Be Discussed By Clinical Pharmacology Subcommittee. April 23. Available: http://fdaadvisorycommittee.com/FDC/AdvisoryCommittee/Stories/042303_pharmacogeneticsA.htm. Accessed on: 2 Apr 2003.

7 It is comparatively rare for medicines to be withdrawn from the market once they have been licensed. Between 1998 and 2002, the Medicines Control Agency awarded over 200 new licences, of which 12 were subsequently withdrawn because of safety concerns (National Audit Office (2003) *Safety, quality, efficacy: regulating medicines in the UK* (Norwich: The Stationery Office, HC 505)).

adverse reactions can be explained by genetic variation, pharmacogenetic analysis might enable medicines that have previously been licensed but then withdrawn to be reinstated, by allowing the prior identification of individuals likely to suffer from adverse reactions. It may also be the case that compounds already rejected during the process of development could be reconsidered as potential treatments for genetically-defined groups of patients.

4.8 It has been suggested that pharmacogenetics will be of value in retrieving withdrawn medicines.[8] An example that has been cited is the medicine Lotronex, used for the treatment of irritable bowel syndrome. This medicine was approved in 2000 in the US, but was subsequently withdrawn by the manufacturer, GlaxoSmithKline (GSK) when it became apparent that some patients experienced adverse reactions. The FDA and GSK are now working to re-examine the medicine, and one element of this process includes the pharmacogenetic analysis of samples from the patients who have been prescribed the medicine.[9] However, it is not clear at this stage whether this will enable the prediction of patients who are likely to be adversely affected. It is worth noting in this context that regulatory bodies such as the FDA have been exploring methods of enhancing post-market surveillance by pharmaceutical companies.

4.9 There are various reasons why re-licensing a medicine that has previously been withdrawn may not be possible. First, although regulatory requirements for re-licensing a medicine are not formally set at a higher level than those for the original licence, a convincing case for re-licensing must be made. Secondly, pharmaceutical companies may not have stored genetic information from patients either during clinical trials or subsequently, in which case it would be very difficult to identify relevant pharmacogenetic variants, as new samples could not be collected once the medicine has been withdrawn. Even if some data are stored, they may not be sufficient to obtain a statistically significant result. Thirdly, if alternative treatments are available which do not require pharmacogenetic tests, there will be less reason to invest in producing a medicine which also requires a test, since this is unlikely to be competitive. Fourthly, unless medicines are protected by patents, there will be little incentive to invest in further research. Finally, negative attitudes towards the medicine may have become established, which could be difficult to surmount.

4.10 We conclude that medicines that are found to cause adverse reactions are unlikely to be re-licensed, even if pharmacogenetic analysis is subsequently carried out which could lead to the development of a useful test. An exception might arise in cases where there is no alternative treatment available. The low likelihood of pharmacogenetic analysis leading to the re-licensing of medicines is unfortunate, because there would be obvious benefits in reintroducing a medicine that is effective in one group of patients while eliminating the threat it poses to another group.

The allocation of resources

4.11 Both public and private providers of healthcare operate on limited budgets. In addition to the traditional requirements of quality, efficacy and safety for the regulatory approval of new medicines, public policy in many countries is developing the requirement to assess medicines for their cost-effectiveness. That is to say, the question is not simply whether the medicine has its intended effects and is safe when it is administered, but also whether the

8 Melzer D *et al*. (2003) *My Very Own Drug: What Must I Know?* (Cambridge: Department of Public Health and Primary Care, University of Cambridge); Buchanan A *et al*. (2002) *Pharmacogenetics: Ethical and Regulatory Issues in Research and Clinical Practice.* Report of the Consortium on Pharmacogenetics, Findings and Recommendations.

9 The full agreement can be viewed on the FDA website. Center for Drug Evaluation and Research (2002) Lotronex Information. Available: http://www.fda.gov/cder/drug/infopage/lotronex/lotronex.htm. Accessed on: 25 Feb 2003.

cost of the medicine represents good value for money, given the health benefits that it is expected to produce. In this section, we consider the implications of pharmacogenetics for providers of healthcare. We focus primarily on public provision, since in the UK, most medicines are provided by the National Health Service (NHS).

4.12 Cost-effectiveness is a measure of the ratio between what a medicine costs to deliver and what benefits it is intended to produce. In principle, it can be assessed in a number of ways. In the simplest imaginable case, the assessment rests upon the comparison of two medicines with equal effectiveness but which cost different amounts, as is alleged to be the case between some branded medicines and their generic equivalents. Clearly, in this sort of case, the more cost-effective medicine would be the cheaper of the two. However, comparisons are rarely so simple, and the difference in the cost of two medicines is likely to be matched by differences in efficacy of treatment and the probability of adverse reactions. Given these differences, an approach is needed which sets the cost of the medicine against some measure of their benefits in order to assess which is the more cost-effective of the two.

4.13 Health economists have developed a number of ways of assessing cost-effectiveness in these sorts of cases, all of which depend upon being able to place a numerical value upon the benefits that a medicine produces. One approach compares the costs and benefits of a healthcare intervention, representing the benefits in non-monetary terms such as life years gained, or number of days free of pain. This approach can be extended to a cost-utility analysis, which seeks to place a value on the benefits that recipients of a medicine derive based upon the patients' own evaluation of alternative outcomes. One particularly influential variant of this approach uses the notion of 'quality adjusted life years', or QALYs.

4.14 A QALY assessment can take many forms. However, it can be illustrated as follows. Respondents to a survey may be asked their relative evaluations of health outcomes associated with different levels of distress or disability. A fully healthy individual will be one having a year of life with no distress or disability. Varying combinations of distress or disability will reduce the value of that life year, and the task of researchers is to scale those combinations relative to the alternative of full health. For example, a state in which someone's choice of work is severely limited will be matched against a state in which there is only slight impairment of work ability but there is associated pain. The scales derived from these comparisons are then used to adjust the value of the estimate of life years gained. A QALY is the arithmetic product of the number of life years gained by an intervention and the quality of life during these years. In effect, the value of an added year is adjusted to take into account deterioration in the quality of life.

4.15 The use of QALYs has been criticised on a number of grounds. They are difficult to calculate in a way that carries inter-subjective conviction. The amount of research into measuring QALYs in relation to particular conditions varies: in the case of subgroups of diseases that are identified as a result of pharmacogenetics this could be especially problematic. The difficulties of producing a single QALY estimate for a disease suffered by a number of people are considerable. Despite these problems, QALY estimates do address the important issue of estimating not simply length of extended life but also the quality of life that is experienced, and it is for this reason that they have been taken up by policy-makers. Provided that they are used as an aid to judgement rather than a substitute for judgement, they can play a constructive role in decision-making.

4.16 Various countries have developed systems for assessing whether medicines should be provided as part of a public healthcare system. In Australia, the Pharmaceutical Benefits Advisory Committee is an independent statutory body that advises the Ministry of Health

and Aged Care and the Pharmaceutical Benefits Pricing Authority about which medicines should be made available through the public healthcare system. No new medicine may be made available unless the Committee has so recommended. The Committee is required to consider the effectiveness and cost of a medicine compared to alternative therapies. In Canada, the Canadian Coordinating Office for Health Technology Assessment is a national, non-profit organisation that reviews research on medical technologies such as devices and medicines, focusing on evaluations of clinical effectiveness and cost-effectiveness, to aid decision-making by the ministries of health, Health Canada, hospitals and health practitioners. In New Zealand, PHARMAC (Pharmaceutical Management Agency), a government body, is responsible for national pharmaceutical policy. Decisions on the subsidisation of medicines are made by PHARMAC with input from independent medical experts on the Pharmacology and Therapeutics Advisory Committee and its specialist sub-committees, and the staff of PHARMAC.

4.17 In England and Wales the responsibility for assessing cost-effectiveness falls to the National Institute for Clinical Excellence (NICE). In Scotland, NHS Quality Improvement Scotland has invariably accepted guidance from NICE. There is currently no analogous body in Northern Ireland, although guidance produced by NICE may be adopted. For the purposes of this section, we will focus on NICE, as the organisation covering the largest proportion of the population of the UK. The remit of NICE includes the appraisal of technologies and the production of clinical guidelines. In terms of technology appraisal, NICE assesses the evidence base for clinical and cost-effectiveness of new and existing health technologies such as medicines, diagnostic tests, clinical devices and procedures. The Institute receives requests for examination of particular health technologies from the Department of Health (DoH) and the Welsh Assembly Government and undertakes a detailed process of appraisal over a period of approximately 12 months. As part of the appraisal process NICE invites contributions from relevant stakeholders and considers, in particular, five areas:

- Disease background: epidemiology, aetiology, pathology and prognosis.
- Description of the technology: mode of action, indication, projected cost of treating the targeted disease.
- Clinical effectiveness: evidence of the quality of the technology, benefits and disadvantages over competing products, including adverse effects.
- Cost-effectiveness: the balance between benefits and cost, usually expressed as cost per QALY or cost per life year gained.
- Wider implications for the NHS: health gains expected from the intervention, likely budgetary impact, required changes in work pattern or reconfiguration of services, education and training issues.

After further consultation, the outcome of the appraisal system falls in three broad categories:

- The technology is recommended for routine use in the NHS, for all licensed indications, for specific indications, or for specific subgroups only.
- The technology is recommended only for use in appropriate clinical trials.
- The technology is not recommended for use in the NHS for any group of patients for specified reasons relating to lack of clinical or cost-effectiveness.

NICE does not operate a 'threshold' cost per QALY or life year gained. Instead, the probability that a technology will be recommended for routine or selective use in the NHS

decreases as cost-effectiveness decreases. While NICE has been more reluctant to recommend treatments with a cost per QALY of over £30,000, it has endorsed one treatment at £49,000 per QALY.[10]

4.18 It is important to underline the fact that NICE does not operate by imposing thresholds. A simple application of a threshold would be tantamount to saying that cost-effectiveness was the only principle of allocation that is relevant to the allocation of resources and that the sole aim of public policy should be to maximise the amount of benefit, measured in terms of QALYs, for the population as a whole, for any given level of expenditure. As has been pointed out, however, such an approach risks ignoring considerations of justice or equity.[11] On this view, it is not the total increase in QALYs which is important, but the fair distribution of that benefit among the members of a population. Such considerations need to be set alongside those of cost-effectiveness.

4.19 The difficulty of relying solely on the principle of cost-effectiveness is that it may lead to those suffering from rare conditions being overlooked in the allocation of resources because their numbers are not large enough to count against the more prevalent conditions. Yet, in liberal democratic societies, a widespread sense of justice includes the belief that everyone is owed a certain minimum entitlement, no matter how small the minority to which they might belong. These entitlements include access to health services relevant to the illnesses from which they are suffering. Hence, it may well be right to allocate resources to the treatment of those suffering from a rare condition, even if this means that these resources are less productive of overall benefit.

4.20 In recognising the case for such entitlements, we should not dispense with information about the relative cost-effectiveness of different medicines. However, the recognition of arguments about equity does affect our interpretation of such data. In particular, we should not assume that estimates of cost-effectiveness carry the implication that the goal of public policy should be to maximise the gain in health of the population. Instead, we should take estimates of cost-effectiveness as information to aid in a process of decision-making which comprises substantive considerations of justice and overall social well-being.

4.21 The issue is important because by and large the decisions of bodies such as NICE have considerable influence. In the UK, despite there being controversy over a few appraisals of medicines, of which the case of beta interferon was the most significant, the recommendations of NICE have not only imposed a fair and rational framework on decision making, but have generally received wide acceptance.[12] If the advent of pharmacogenetics looks as though it will disrupt this legitimacy, then care needs to be taken as to how principles of allocation can be developed. **We endorse the approach taken by the National Institute of Clinical Excellence (NICE) of reviewing cases on an individual basis, not applying thresholds, and incorporating considerations of both equity and cost-effectiveness.**

4.22 How will pharmacogenetics affect decisions on the allocation of resources, and what are the relevant principles to be borne in mind? We noted in paragraph 3.15 that the aggregate effect of the development of pharmacogenetics in terms of the total cost of medicines for

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10 For the use of Glivec (iminitab) for chronic myeloid leukaemia in blast-crisis phase (National Institute for Clinical Excellence (2002) *Guidance on the use of iminitab for chronic myeloid leukaemia*, Technology Appraisal – No.50 (London: National Institute for Clinical Excellence)).

11 Campbell A (2003) Nice or nasty? Threats to justice from an emphasis upon effectiveness, in *International Perspectives in Equity and Health: As Seen from the UK*, A Oliver, Editor (London: Nuffield Trust), pp. 35-9; Daniels N (1985) *Just Health Care* (Cambridge: Cambridge University Press); Doyal L and Gough I (1991) *A Theory of Human Need* (Basingstoke: Macmillan).

12 Ellis SJ (2002) Bad decision NICE, *Lancet* **359**: 447; Burke K (2002) No cash to implement NICE, health authorities tell MPs, *BMJ* **324**: 258.

a healthcare system is difficult to assess. There are competing forces at work in this area. On the one hand, pharmacogenetics provides the ability to target the development of medicines more precisely, possibly leading to lower development costs. Moreover, the ability to identify those patients most likely to benefit from a particular pharmaceutical product means that those investing in medicines research should have greater certainty of return. On the other hand, pharmacogenetics threatens to fragment the market, reducing the economies of scale that have been associated with the profitable 'blockbuster' products of the past. How these competing forces will balance out is impossible to say at the present time. The implication is that it is not clear whether the search for cost-effective medicines will be made easier through an overall lowering of the costs of development or harder through an overall increase in the cost of supplying medicines. However, whichever of these outcomes prevails, the search for cost-effective allocation will take place within an overall constraint on costs.

4.23 In this context, there are likely to be at least three ways in which the application of pharmacogenetics will affect the search for a fair and reasonable way of obtaining value for money in the use of pharmaceuticals: from the greater ability to avoid adverse reactions; from the greater ability to identify potential response rates by different classes of patients to any medicine; and from the possibility of identifying additional groups of patients who can be thought of as having an 'orphan' condition. We consider the question of adverse reactions first, before turning to the issues raised by the stratification of patient populations.

The prediction of adverse reactions

4.24 If we consider the application of pharmacogenetics in the identification of adverse reactions, then the effects on cost-effectiveness should in general be wholly positive. By definition, a group of patients suffering an adverse reaction is experiencing a loss of benefit. If it is possible in advance to identify the patients for whom the medicine should not be prescribed, then not only are the patients protected, but the cost of prescription is avoided for a group for whom the medicine would not be of benefit in any case.

4.25 Pharmacogenetics promises a situation in which there is less trial-and-error prescribing. For example, we heard evidence from the charity Rethink about the difficulties that patients suffering from schizophrenia experience, before the right treatment regime is found for their condition. If the difficulties arising from this trial-and-error prescribing could be avoided, then there would be an improvement in the quality of treatment. Such an improvement in quality is an enhancement of benefit for which in economic terms there ought to be a greater willingness to pay, and this ought to be reflected in economic and ethical assessments.

4.26 A special case would arise if a pharmacogenetic test reveals that a group of patients are likely to suffer an adverse reaction, but it is still to the overall benefit of those patients to continue taking the medicine because the benefits outweigh the disadvantages. In this situation all the pharmacogenetic test has done is to identify which type of patients will be adversely affected without there being any corresponding improvement in cost-effectiveness. However, this is no different from the situation that would have existed without the pharmacogenetic test. The best that one can hope for in this context is that the information revealed in the pharmacogenetic research proves useful for developing better medicines for the adversely affected subgroup.

Stratification and the allocation of resources

4.27 We observed in paragraphs 2.6 – 2.10 that the application of pharmacogenetics could lead to the stratification of patients into different groups according to their response to medicines, or according to the features of their disease. The first approach is, in many cases, already current practice, although not based on genetic data: it would mean that a doctor would choose between a variety of medications, or, less commonly, between a variety of dosages. The second might entail that a variety of specialised medicines will be recognised as effective treatment of similar symptoms or conditions in different groups of patients, according to their genotypes. However, as we observed in paragraph 2.5, it is impractical to suggest that truly personalised medicines will be developed for each individual patient.

4.28 Whatever the likely consequences in terms of the match between the individual patients and medicine might be, it is clear that distinguishing patients into subgroups raises serious ethical problems. In order to appreciate these problems, consider a highly simplified example. Suppose that there is a condition that has been treated by a particular medicine. Genetic tests now show that potential patients can be divided into two groups of equal size: Group A, who have an 80% chance of responding positively to the medicine and Group B, who have a 15% chance of responding positively. If £10,000 per patient is spent on each group, then in Group A the overall cost per QALY might be £12,500 and in Group B over £66,000 per QALY. We noted earlier that the probability of a body such as NICE recommending a technology decreases as cost-effectiveness decreases. In this situation, therefore, it is likely that such an authority might reject the medicine for patients falling into Group B whilst recommending use in those who fell into Group A. Is this fair?

4.29 One reason why one might think that it is fair to advise in such a way is that the situation is no different, from an ethical point of view, to one in which there were two groups of patients with disease conditions which could be treated by different medicines, but where one medicine was much more expensive than the other. This reflects the fact that low cost-effectiveness can arise in two ways. Health gain may be low in a group of patients or overall costs may be high. Either way, it might be argued, in so far as considerations of cost-effectiveness have any independent weight, we may find ourselves in a situation in which the medicine is recommended for one group but not the other. All that we have done with pharmacogenetic information is to acquire the ability to predict in advance which groups of patients are likely to be high or low responders. Prior to the advent of any pharmacogenetic test it would still have been possible to assess effectiveness biochemically or pharmacologically and cease treatment for those not responding. In other words, the pharmacogenetic technology does not change the situation in respect of its underlying ethical dimensions. If it was ethical to apply the arguments about cost-effectiveness before the pharmacogenetic intervention, it should be so afterwards.

4.30 Of course, considerations of cost-effectiveness are not the only considerations that have weight. As we have already noted (paragraph 4.19) concerns of justice and equity will mean that sometimes it will be right to allocate resources to conditions that in other circumstances might be considered to be cost ineffective. However, at some point, considerations of cost-effectiveness will imply that resources will not be allocated to patients who are expensive to treat where the estimate of the cost of treatment will be dependent on a pharmacogenetic test. In practice, decisions regarding cost-effectiveness are likely to be more complex than the simplified example in paragraph 4.28 suggests.

4.31 It might seem that it is artificial to be drawing distinctions between groups of patients. However, although drawing the line is in some ways artificial, this does not mean that it is unfair. Where there is a valuable social purpose to be served and some form of restriction

needs to be put in place, then given the nature of human attributes this will almost certainly mean drawing clear lines, or setting thresholds, in continuous distributions. So long as the distinction is not made so as to produce some form of favouritism, then one can justify the allocation.

4.32 We conclude therefore that although the partitioning of patients into genetically distinct subgroups is going to make decisions on the evaluation of medicines more difficult, with finer lines to be drawn, we do not think that there are new ethical issues that arise from this fact alone. However, it is important that such evaluation is undertaken in a context in which a range of relevant considerations is allowed to influence the decision, and this point reinforces our earlier endorsement of the rejection by NICE of a simple threshold test (paragraph 4.21).

Stratification and the development of new medicines

4.33 Stratification is relevant to the development of medicines targeted at genetic features of diseases, such as subgroups of cancers. But it may also arise in the development of other medicines, especially if relatively cheap and reliable pharmacogenetic tests can be developed which are good predictors of safety or efficacy. What might be the implications of such stratification for patients and for pharmaceutical companies? From an economic perspective, it could be argued that the identification of smaller, more narrowly defined groups of patients for whom a medicine is appropriate will have a negative effect on profitability. So-called 'blockbuster' medicines generate substantial revenue because they are sold to a very large patient population identified as having the symptoms or condition in question.[13] If such a population is stratified, a company wishing to reach the same total patient group that had previously been prescribed a single medicine would have to meet the additional expense of developing a number of medicines. However, reductions in the size of markets as a result of stratification may be offset by the ability of companies to develop targeted medicines that may otherwise have been rejected during development. This could occur by producing pharmacogenetic tests to identify and exclude those at risk of adverse reactions, or by defining a specific group of patients in whom the medicine will be particularly effective.

4.34 It has been suggested that if stratification means that medicines are considerably more effective in defined patient groups, they may command a premium price, making their development profitable despite the smaller market.[14] This however presumes that providers of healthcare, whether public or private, are able or willing to meet such higher costs. It is also possible that the application of pharmacogenetics could have the opposite effect. Rather than distinguishing small subgroups of patients, the developers of new medicines might seek instead to maximise the number of patients who would benefit from a medicine by using pharmacogenetic information to identify medicines most suited to large groups of patients.

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13 In recent years, most pharmaceutical companies have focused on the commercialisation of a relatively small number of medicines, each of which has an exceptionally promising market potential. In practice, a minority of the products of a company generate most of its revenue. In 1999, 18 pharmaceutical companies produced at least one medicine which had global sales of at least US$750 million annually, and six had three or more such products (Mercer Management Consulting (2001) *Where are the next profit zones in pharmaceuticals?* (Boston: Mercer Management Consulting)).

14 See for example Peakman T and Arlington S (2001) *Putting the Code to Work: The Promise of Pharmacogenetics and Pharmacogenomics*. (Price Waterhouse Coopers). Eisenberg suggests that 'patients should be willing to pay more for drugs that have been preselected to work well for them than they now pay for drugs that might have no benefits or toxic side effects'. Eisenberg RS (2002) Will pharmacogenomics alter the role of patents in drug development? *Pharmacogenomics* **3**: 571-4.

4.35 It is not clear whether research in pharmacogenetics will produce data that are sufficiently predictive to be used in clinical practice, and therefore lead to increased stratification of patients and of diseases. There are recent examples where new medicines have been developed and licensed despite, or perhaps as a result of stratification, such as Herceptin (Box 2.3: Case study 2). It remains a possibility, however, that if a market segments into a number of parts, each may be too small to provide an incentive for research and development. Estimates about the degree to which it may be in the interest of pharmaceutical companies to develop medicines for smaller groups of patients are currently highly speculative, but the possibility of unprofitable markets emerging as a result of pharmacogenetics cannot be ruled out. If this possibility were realised, it could be argued that incentives should be put in place to promote the development of medicines for patients who might otherwise be neglected in virtue of the rarity of their condition, or their unresponsiveness to existing medicines. In such cases, what kinds of incentive might be needed to encourage the development of new medicines?

4.36 Formal regulatory incentives to develop medicines currently exist in the case of rare diseases. These diseases are called 'orphan diseases' and the medicines that treat them are called 'orphan medicines', because they are unlikely to generate sufficient economic revenue to the pharmaceutical industry to be developed without subsidy or some other public policy measure. The basic principle behind this willingness to provide special incentives for the development of orphan medicines can be simply stated. The legal and economic conditions under which medicines are developed, and in particular the terms under which patents are awarded, will determine the rate of return for an investment in the development of a medicine. However, the operation of those terms can lead to a situation in which there is no economic incentive to develop the medicine, even though the benefits of the development, in terms of the number of patients treated, would, in the long run, outweigh the costs. Hence, the question is whether the benefits could be achieved by enabling companies to realise the potential returns by altering the terms under which they can bring a product to market.[15]

4.37 In such cases, what kinds of incentive might be needed to encourage the development of new medicines? In a number of countries, specific legislation has been enacted to provide incentives to industry to undertake research and development for orphan diseases (see Box 4.1). Definitions of orphan medicines specify the level of incidence of a disease below which treatments will be eligible for orphan medicine status (see Box 4.2). In the US, the status of orphan medicine can also be granted when there is a reasonable expectation that the cost of developing the medicine will not otherwise be recouped.[16] It should be noted that the criteria in Box 4.2 depend on the incidence of the disease on a national level. Companies who develop medicines, however, operate on a global level. If numbers of patients for a prospective orphan medicine are aggregated across countries, the number of potential recipients clearly increases, notwithstanding the additional costs of different regulatory and marketing requirements in each country. It could therefore be argued that incentives for pharmaceutical companies might not be required if a global perspective is taken. Additionally, if a medicine is effective in prolonging the lives of patients who would otherwise have died, the patient population will increase over time. (This possibility is accounted for in the European system, which allows for the status of orphan medicine to be reassessed and withdrawn if the criteria are no longer met.)

15 Rai AK (2002) Pharmacogenetic Interventions, Orphan Drugs, and Distributive Justice: The Role of Cost–Benefit Analysis, *Social Philosophy and Policy* **19**: 246-70.

16 Orphan Drug Act 1994, 21 USC §360ee(b)(2).

Box 4.1: **Orphan medicine regulation in Europe and the US**

General features of regulation relating to orphan medicines are that governments offer patent protection beyond the normal periods, as well as tax credits and incentives for research. The relevant regulation in the European Union is the *European Regulation on Orphan Medicinal Products* (2000). In the US, incentives for the development of orphan medicines are provided for by the Orphan Drug Act (1983) (ODA). The features of both sets of regulation are set out below.

	Europe	***US***
Tax incentives	Developed by individual member states	Up to 50% of clinical trial costs may be credited against tax
Designation criteria	Based on prevalence or on the likelihood of profitability Requires that 'no other method' exist (unless there is a significant additional benefit to patients)	Based on prevalence or on the likelihood of profitability
Market exclusivity	Given for 10 years but reassessed after 6 years and withdrawn if criteria are no longer met, for example, if the prevalence of the disease has increased, or if another product has been developed which is safer and more effective	Given for 7 years (no reassessment).
Organisations involved	European Commission, European Medicines Evaluation Agency (EMEA), member states of the European Union	Food and Drug Administration (Office of Orphan Products Development)
Other incentives	Assistance with developing research protocols Grants to encourage research into rare diseases Fee exemptions Centralised regulatory procedures	Assistance with developing research protocols Grants to encourage research into rare diseases Waiver of certain application fees

Box 4.2: **Criteria for granting the status of orphan medicine**

Europe	US	Japan	Australia
5 in 10,000 (approx. 190,000 patients)	7.5 in 10,000 (approx. 200,000 patients)	7 in 10,000 (approx. 100,000 patients)	1 in 10,000 (approx. 2,000 patients)

4.38 It is not clear how orphan medicine legislation will be applied to pharmacogenetic medicines. The medicine Herceptin (see Box 2.3: Case study 2) was not granted the status of orphan medicine in the US. It is estimated that of the more than 1.5 million women in the US who have been diagnosed with breast cancer, approximately 165,000 have metastatic breast cancer. Up to 30% of these 165,000 women could benefit from Herceptin.[17] Since the criterion for orphan disease status in the US is that 200,000 or fewer patients are affected, both metastatic breast cancer and the subset of metastatic breast cancers that would respond to Herceptin might seem eligible. However, the FDA took the view that the patient population for Herceptin comprises people with breast cancer, who number considerably more than 200,000. The FDA was apparently not inclined to define a subset of patients as having a distinct condition based on the genetic characteristics of their tumours.[18] (Interestingly, Herceptin was granted the status of orphan medicine for the subset of pancreatic cancers that over-express HER2.) Medicines are most commonly denied orphan medicine status because of disagreements over how target populations are defined. Although rejections might, in many cases, be justified, to prevent pharmaceutical companies from dividing markets in a creative way, these cases nevertheless suggest that the seemingly academic issue of reclassification of disease through pharmacogenetic analysis might have significant implications for regulatory frameworks. The potential need for regulatory agencies to reconsider definitions of orphan medicine in the light of advances in pharmacogenetics was highlighted by numerous respondents to our consultation, including the Association of British Pharmaceutical Industries, Pfizer, Indiana University Center for Bioethics, and the Pharmacogenetics Evaluation Policy Project.[19]

4.39 Although it might seem plausible to argue that incentives and forms of subsidy should be expanded as much as possible to encourage the development of appropriate medicines for groups of patients no matter how rare the incidence of their condition might be, such arguments need to be more nuanced. For example, subsidies allocated under such regulations may have an impact on the pharmaceutical market, as the reduction of risk for pharmaceutical companies indirectly increases the rate of return. Further, it is likely that the provision of public subsidies for medicines to treat particular rare conditions will be influenced by the respective lobbying power of particular patient groups. One respondent to our public consultation observed that orphan medicine legislation involves 'subsidy, directly or indirectly, of the pharmaceutical industry by the public purse, except where the

17 Figures from Genentech press release. Genentech (2001) FDA Advisory Committee Unanimously Recommends Approval of Breast Cancer Test to Select Candidates for Herceptin Therapy. Available: http://www.gene.com/gene/news/press-releases/detail.jsp?detail=4690&pNo=5. Accessed on: 25 Feb 2003.

18 Fogarty M (1998) Up for adoption: pharmacogenetics and the Orphan Drug law. Welltopia.com. Available: http://www.welltopia.com/OrphanDrugs.html. Accessed on: 7 July 2003.

19 See also Melzer D *et al*. (2003) *My Very Own Medicine: What Must I Know?* (Cambridge: Department of Public Health and Primary Care, University of Cambridge).

cost of medicines is borne entirely by individual patients'.[20] Hence policies to provide further incentives through public subsidy require careful examination.

4.40 In conclusion, pharmacogenetics is likely to influence the development of new medicines by affecting the conduct of clinical trials and perhaps by redefining groups of patients. Some potentially valuable new medicines may not be developed if, as a result of genetic stratification, the number of patients who would benefit is too small to be profitable. However, stratification may also enable some medicines to be developed that would otherwise have failed because the subgroup in which the medicine is effective can now be distinguished. It is currently uncertain which of these trends is likely to prevail. **We therefore recommend that agencies responsible for the licensing of new medicines pay attention to the possible negative effects of stratification. If pharmacogenetic stratification does provide an economic disincentive for those developing new medicines, consideration should be given to preparing guidance notes that encourage applications to use existing orphan medicine legislation, or any other policy instrument with equivalent effect, to provide incentives for development. We further recommend that if orphan medicine legislation is to be applied, consideration is given by the International Conference on Harmonisation to a global approach to orphan medicine legislation. This should include reconsideration of the definition of an orphan medicine, with particular reference to the implications of genetic stratification of both patients and diseases.**

Pharmacogenetics and racial groups

4.41 A particular case of the stratification of patient populations is stratification based on racial or ethnic groupings. Race and ethnicity cannot be given precise biological or genetic definitions. There is considerable genetic variation within racial and ethnic groups, whether defined by place of birth, self-identification or other criteria, as well as between them. Nonetheless, some genetic variants are more common in some racial or ethnic groups than in others. Some early research in pharmacogenetics, before genetic markers were available, hinged on the interpretation of differences that were observed between various racial or ethnic groups. An example of a variant that has different frequencies in different population groups is the CYP2D6 genetic variant discussed in Box 2.2: Case study 1. This variant is present in approximately 7% of Caucasians, but only 1% of Chinese people. Similarly, one variant of the TPMT gene, TPMT*3A, which affects response to a medicine used in the treatment of childhood leukaemia (paragraph 4.5), is present in 4% of Caucasians but is not found in Chinese or Japanese populations.[21]

4.42 The fact that some genetic variants are more or less likely to be found within particular groups has implications for the design of clinical trials and for the development of medicines. In the case of research and development, it means that comparisons of trials conducted in different countries, or statements about efficacy based on evidence in one particular population, may not be valid in other, genetically different populations, or may only be valid if a different prevalence in relevant genetic variants has been taken into account. This problem of comparability between different groups has always been present and has been addressed by various bodies.[22] Pharmacogenetic testing may simply make it

20 Royal Pharmaceutical Society of Great Britain (2003) Response to the Nuffield Council on Bioethics Consultation.

21 McLeod HL and Siva C (2002) The thiopurine S-methyltransferase gene locus – implications for clinical pharmacogenomics, *Pharmacogenomics* 3: 89-98.

22 ICH Topic E5 – Note for Guidance on Ethnic Factors in the Acceptability of Foreign Clinical Data (CPMP/ICH/289/95)

more explicit. Some pharmacogenetic research examines genetic variants which are not themselves causally related to the effect being studied, but which are associated with the genetic variation that is responsible for the effect. In such cases, the problem of translating research results across populations becomes more acute. It is possible that the non-functional genetic variation which is tested for may not co-occur with the functional genetic variation in other groups.

4.43 It is important that applications seeking approval for a medicine or a pharmacogenetic test are supported by data collected in the relevant population. This will be particularly important if pharmacogenetic research is conducted in groups of patients that are genetically relatively homogeneous. In the US, the FDA requires that analyses of data regarding effectiveness and safety for important demographic subgroups, including race, be included in applications for the approval of new medicines.[23] This information must be included on product labels.[24] A similar requirement exists in the UK. However, there is no parallel requirement for genetic tests. **We recommend that bodies giving approval for the clinical use of pharmacogenetic tests require these to specify the population groups in which the tests have been validated, and to issue warnings where there is evidence that such tests may not be usefully predictive of response to medicines in other population groups.**

4.44 Acknowledging that genetic variation between population groups should be taken into account in the design of medical research should not be taken to imply that there are sharp lines that can be drawn between groups on the basis of genetic information which coincide directly with racial categories. Given the variation within racial groups, and the myriad ways in which these are defined, there has been considerable debate about whether racial categorisations are meaningful in the field of genetics.[25] Outside genetics, such categories are being used in the development and marketing of medicines. In 2001, research was published which showed that a treatment for heart failure called enalapril was less effective in black patients than in white patients.[26] In 2002, the FDA approved a clinical trial of a new medicine for heart disease that would only recruit black participants.[27] This trend is likely to be magnified by the increased application of pharmacogenetics.

4.45 In those countries where medicines are advertised directly to consumers, there is a serious risk that medicines could be marketed to particular racial groups in a misleading manner, giving the impression that all members of that group would be likely to benefit, or that the

23 FDA (1998) Investigational New Drug Applications and New Drug Applications (demographic rule), 63 FR 6854. In January 2003, the FDA issued Draft Guidance for Industry on the Collection of Race and Ethnicity Data in Clinical Trials, which sets out the categories of race and ethnicity that should be used. FDA (2003) FDA issues guidance for collection of race and ethnicity data in clinical trials for FDA regulated products. Available: http://www.fda.gov/bbs/topics/ANSWERS/2003/ANS01193.html. Accessed on: 3 Apr 2003.

24 Center for Drug Evaluation and Research (2000) Content and Format of the Adverse Reactions Section of Labeling for Human Prescription Drugs and Biologics. Available: http://www.fda.gov/cder/guidance/1888dft.htm. Accessed on: 3 Apr 2003; Center for Drug Evaluation and Research (2001) Guidance for Industry Clinical Studies Section of Labeling for Prescription Drugs and Biologics – Content and Format. Available: http://www.fda.gov/cder/guidance/1890dft.htm. Accessed on: 3 Apr 2003.

25 Risch N *et al*. (2002) Categorization of humans in biomedical research: genes, race and disease, *Genome Biol* **3**: comment2007; Rosenberg NA *et al*. (2002) Genetic structure of human populations, *Science* **298**: 2381-5; Wilson JF *et al*. (2001) Population genetic structure of variable drug response, *Nat Genet* **29**: 265-9. The FDA draft guidance on the collection of race and ethnicity data in clinical trials, has been criticised on the grounds that 'race and ethnicity data alone are insufficient to predict variable drug response' and arguing that such guidance reifies race by perpetuating its use as a variable in scientific research. Haga SB and Venter CJ (2003) FDA races in wrong direction, *Science* **301**: 449.

26 Exner D V *et al*. (2001) Lesser response to angiotensin-converting-enzyme inhibitor therapy in black as compared with white patients with left ventricular dysfunction, *N Engl J Med* **344**: 1351-7.

27 Taylor AL *et al*. (2002) The African-American Heart Failure Trial: background, rationale and significance, *J Natl Med Assoc* **94**: 762-9.

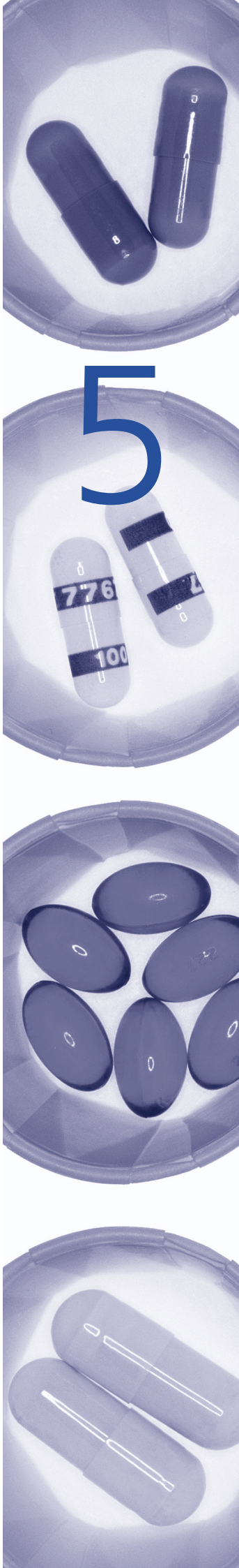
medicine was more effective than other, non-racially defined medicines. More generally, such developments may reinforce tendencies to view race as a biologically-defined phenomenon. **We recommend that those involved in pharmacogenetic research and the development of new medicines should be sensitive to the potential for misunderstanding and prejudice arising from racial stereotyping. We recommend further that regulatory bodies exercise careful scrutiny over claims as to racial specificity in the marketing of pharmacogenetic tests and medicines.**

4.46 Denying treatment to a particular racial group, using race as a proxy for a genetic profile, would be problematic, since not every member of the group could be expected to have the genetic variant in question. It is possible that health professionals would be tempted to use race as a proxy in determining treatment, if the pharmacogenetic test that would discriminate more accurately was not readily available. **Since clear-cut divisions between racial or ethnic groups are highly unlikely, we take the view that membership of a particular racial group cannot be used as a substitute for a pharmacogenetic test, even if it is the case that the genetic variant being tested for is known to be more or less prevalent in particular groups.**

4.47 A further potential problem arises if stratification results in the members of some ethnic groups finding that they are denied access to medicines when others of different ethnic groups, but suffering the same condition, are allowed access. This would be a particular cause for concern if the group being denied treatment was already socially and medically disadvantaged. At the present stage of development, we cannot say how great a problem this is likely to be. However, it is something that should be monitored. **We recommend that those responsible for monitoring the relative access of different ethnic groups to treatment in the National Health Service establish procedures for assessing whether problems emerge arising from the development and application of pharmacogenetics.**

Chapter 5

Ethical issues in treatment and clinical practice



Ethical issues in treatment and clinical practice

Introduction

5.1 In this chapter, we consider ethical issues raised by the use of pharmacogenetic tests and medicines in clinical practice and examine the implications of pharmacogenetics for the individual patients and their physicians. There are currently relatively few clinical applications of pharmacogenetics. Moreover, it is important to realise that the discovery of genetic factors that influence response to medicines may not equate with direct or immediate changes in clinical practice, since the factors influencing the efficacy and safety of medicines are varied and complex, and since the use of pharmacogenetic tests may not necessarily be cost-effective or clinically useful.

5.2 Notwithstanding these caveats, there will be situations in which pharmacogenetic tests provide information of considerable clinical value. The medicine Herceptin (Box 2.3: Case study 2) and the test used in patients with acute lymphoblastic leukaemia who are to be treated with 6-mercaptopurine (paragraph 4.5) are two good examples. Herceptin has been licensed in the UK for use only in patients with the relevant type of tumour, which means that tests must be undertaken to determine the genetic characteristics of the disease before the medicine can be prescribed.[1] There are various other medicines which are metabolised by cytochrome P450 enzymes which contain warnings regarding potential adverse reactions in patients with particular variants of these enzymes (such as variants in CYP2D6 - see Box 2.2: Case study 1). However, there is no requirement in the licence conditions of these medicines for patients to undertake a pharmacogenetic test before prescription. Preliminary findings, such as the research into adverse reactions in response to abacavir (Box 2.4: Case study 3), have not been transferred to clinical practice in most countries, as further research is still taking place.

Delivering pharmacogenetics

5.3 Whatever its financial implications and however issues of resource allocation are settled, if pharmacogenetics becomes widely applicable, it will pose considerable challenges to the NHS for the arrangement of effective delivery. If pharmacogenetic testing becomes widespread, capacity in testing facilities will be required and systems will have to be put in place to enable pharmacogenetic tests to be conducted quickly and efficiently, in order not to delay the process of prescribing medicines. Given that the duration of consultations with general practitioners (GPs) is already under pressure, attention will need to be given to the question of how sufficient time can be found to make use of pharmacogenetic tests and to engage patients in decisions about their use. It is currently unclear what proportion of pharmacogenetic tests would require specialised or centralised testing. An assessment of the current and newly emerging diagnostic technologies will be needed to allow strategic decisions to be made regarding the need for investment in appropriate testing facilities. Some tests may be carried out at the point of care, for example in a pharmacy or GP's surgery, while others may be conducted at specialised testing facilities.

5.4 The effective delivery of pharmacogenetics will require the cooperation of patients, doctors, pharmacists and other healthcare professionals. Questions about who should have control

[1] British National Formulary (2002) *BNF*, 44 ed (London: British Medical Association and the Royal Pharmaceutical Society of Great Britain).

over various aspects of the process will need to be addressed. In the case of conventional medicines, a decision has to be taken at the national level regarding whether and in what way the supply of a medicine is to be under the control of the patient, the pharmacist or the doctor. The distribution of control varies by medicine, in the decision as to whether it requires prescription, has to be approved by a pharmacist, or is available freely over the counter. This is already a complicated arrangement. Depending on the extent to which pharmacogenetics is incorporated into routine practice, it may impose further requirements such as additional levels of decision-making over the administration of the test, and over whether the availability of the medicine is dependent on taking the associated test.

5.5 Pharmacogenetic tests based on genetic variation between individuals are unlikely, in general, to allocate patients to exclusive categories of those who do respond to a medicine and those who do not. Rather, they will present a probabilistic outcome regarding safety or efficacy. This may complicate decisions about treatment. For example, a doctor might advise against a specific treatment if a test revealed that a patient only had a small likelihood of response, or a high risk of adverse reaction. Nonetheless, the patient may want to receive the treatment, especially if there is no effective alternative. Are health professionals and patients in a position to assess the value of pharmacogenetic information? Where should responsibility for the decision about the treatment lie? We need to consider the provision of pharmacogenetic information, the psychological effects on patients of test results, the question of who decides whether a test is taken and whether a medicine can be prescribed without an associated test, and some of the legal implications.

Clinical judgement and patient choice

Information, training and education

5.6 As pharmacogenetic tests and medicines become more widely used, there will be a need to educate health professionals, including GPs and pharmacists, as new findings emerge and new tests are developed. Patients should also have easy access to reliable information about tests and treatments. It has recently been reported that GPs obtain most of their information about medicines from pharmaceutical companies.[2] GPs have an essential role to play in providing their patients with relevant medical information, but there must also be other sources. Reliable and easily accessible medical information is important for both health professionals and patients. While the internet has the positive effect of enabling patients to have access to more information, it also increases the risk of the distribution of mis-information. The introduction of a new approach to medicine such as pharmacogenetics makes the requirement for reliable information particularly pressing. Some have suggested the establishment of a single, independent body to provide information to patients.[3]

5.7 The recent White Paper on Genetics proposes various initiatives to 'support the integration of genetics knowledge and health care applications across the NHS', including an NHS Genetics Education and Development Centre to provide training for health professionals including GPs, the development of the National Electronic Library for Health to include current information about genetics to aid in clinical decision-making, and efforts to ensure that NHS Direct is kept abreast of developments in genetics to enable patients to access this information.[4] **We recommend that initiatives to provide independent and impartial**

2 Dobson R (2003) Pharmaceutical industry is main influence in GP prescribing, *BMJ* **326**: 301.

3 See Consumers' Association (2003) *Patient Information: What's the Prognosis?* (London: Consumers' Association).

4 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), para. 4.35.

information about pharmacogenetic tests and medicines to patients and health professionals, including GPs and pharmacists, should be encouraged.

5.8 It is not, however, sufficient to make accurate information readily available: the patient needs to be able to understand that information and its significance. The probabilistic nature of the information provided by pharmacogenetic tests raises issues regarding the ability of patients and physicians to engage in an informed discussion about treatment. And the use of pharmacogenetic information is complicated by its dual nature, as it includes both information about the test and information about the treatment. This is information of different sorts. Information about the test requires understanding of what these tests will and will not disclose. Information about treatment is primarily information about physical effects and requires education about how to think about risks and benefits. Much research has been carried out into ways of communicating risk in the medical setting. **We recommend that research is conducted into methods of communicating information about pharmacogenetics to patients, and that health professionals are provided with appropriate training.**

Consent

5.9 In clinical practice, consent is obtained from patients not only as a means of respecting their autonomy but also to act as a legal mechanism to protect health professionals from charges of assault. Written consent forms are used primarily for procedures requiring sedation or anaesthesia. They are rarely required in relation to the prescription of medicines, with some exceptions: medicines known to harm fetuses, or those with serious risks of adverse reactions. More stringent requirements for obtaining consent are in place for some diagnostic tests for genetic diseases, such as Huntington's disease or the inherited forms of breast cancer. This is because of the significance of the implications of a positive result for patients and family members.

5.10 Currently in the UK, written consent forms are not used when patients have samples taken to test for over-expression of HER2, to determine whether the medicine Herceptin should be prescribed. It seems likely that the reasons for this are that the test is only used to determine treatment for the condition, and because the genetic information concerns somatic mutations in the diseased tissue, not the individual's inherited DNA. These factors make it unlikely that the test result will be of relevance to the patient other than in aiding prescription of the correct medicine, and are therefore not seen as requiring special consent. However, it has been suggested that written consent forms and genetic counselling be provided for patients undergoing pharmacogenetic tests in clinical practice.[5]

5.11 Before coming to a decision on this question, it is important to consider the information a pharmacogenetic test might generate. As we observed in paragraphs 1.8 – 1.11, the primary issue is the nature of the information that is obtained and its implications for the patient and others, rather than whether that information can be described as genetic. A pharmacogenetic test could be undertaken with regard to a specific medicine which a physician hopes to prescribe. Such a test could be of relevance to more than one medicine. Alternatively, a test could be undertaken as part of a screening programme to obtain information that may subsequently be of use. Differences in the aim of the test may therefore correspond to differences in the scope of the genetic information that is obtained.

[5] Human Genetics Alert (2002) Evidence gathered as part of the Human Genetics Commission's consultation for Genes Direct. Available: http://www.hgc.gov.uk/genesdirect/evidence_hga.htm. Accessed on: 11 June 2003.

5.12 Is pharmacogenetic information different in its implications from information about genetic susceptibility to disease? The former is often claimed to be less ethically problematic, because it only reveals information about what kind of medicines to use, rather than more sensitive information about the risks of developing a disease. However, there are reasons to think that such a distinction, though of some significance, is neither sharp nor straightforward. First, pharmacogenetic information may also be an indication of a patient's prognosis, either because it reveals that there is no effective treatment, or that the patient has a particular subtype of a disease, with a distinct prognosis. Secondly, pharmacogenetic information about response to a medicine may also indicate susceptibility to disease, since genetic variants can influence a number of traits which may be otherwise unrelated. For example, a genetic variant in the *ApoE* gene has implications for the likelihood of developing Alzheimer's disease as well as cardiac problems. A patient who is informed today that a genetic variant means they should take a different medicine may learn subsequently that this also means he or she is at increased risk of a serious illness. Another possibility is that susceptibility to other traits, such as addiction, may be identified.[6] It is difficult to predict how large the overlap is between genetic variants that affect response to medicines and those that affect susceptibility to disease or other traits, but such cases may occur.[7] Where this information is known in advance, it can be included in the information given to patients, or, the undesired information could be excluded from the result of the pharmacogenetic test. However, where knowledge about susceptibility to disease is subsequently discovered, it may turn out that predictive information has been inadvertently acquired.

5.13 The nature of the information obtained from a pharmacogenetic test may differ depending on whether the test concerns the genetic characteristics of diseased tissue, or genetic variation in inherited DNA. We noted in paragraph 5.10 that one test of the first kind, linked to the use of Herceptin in treating breast cancer, has not been viewed as raising ethical concerns. In this case, the test obtains information about the mutated DNA in a diseased tissue, a cancerous tumour, which is not of relevance outside the context of the specific treatment and illness in question. In cases of the second kind, the genetic information will often be unrelated to the causation of the disease, although it could have relevance for such things as likely response to other medicines or susceptibility to other conditions. Again, in current practice, written consent and counselling for these pharmacogenetic tests would not be required, unless the medicine also happens to involve particularly serious adverse reactions.

5.14 The psychological effects of a pharmacogenetic test also need to be taken into account. A test may reveal that a patient is effectively untreatable, because all the medicines for that person's condition would be likely to be ineffective or to have unacceptable side-effects. Such information could be as distressing as the information that one was likely to contract a disease. Other issues may arise if patients have the impression of reduced choice when they find themselves confronted with diagnostic information that may limit their available options for treatment. The use of pharmacogenetics may be viewed as an approach that does not take into consideration the whole person but only their genome. However, non-

6 See for example Tyndal R (2001) Pharmacogenetics – Research Annual Report 2001. Centre for Addiction and Mental Health. Available: http://www.camh.net/research/research_ar2001/pharmacogenetics.html. Accessed on: 20 May 2003.

7 Genetic variants that influence the metabolism of medicines will also affect the body's handling of toxic substances in the environment. Consequently, these genetic variants have the potential to affect susceptibility to diseases such as cancer. One example that has been reported is a small increased risk of bladder cancer in individuals with a variant in the enzyme N-acetyltransferase 2 which leads to poor metabolism of carcinogens. This enzyme is also relevant in the metabolism of a number of medicines. Green J *et al*. (2000) N-acetyltransferase 2 and bladder cancer: an overview and consideration of the evidence for gene-environment interaction, *Br J Cancer* **83**: 412-17.

genetic tests that have very similar consequences regarding the limitation of choice have been used in clinical practice for many years, for example testing for oestrogen-receptor status in breast cancer.

5.15 What should these considerations lead us to think about the need for written consent and genetic counselling in the case of pharmacogenetic tests? It can be argued that patients receive information of a similar nature to that generated by pharmacogenetic tests already, without special precautions being taken. Patients may be informed without the aid of a pharmacogenetic test that there is no effective treatment for their condition, for example in the case of some forms of malignant brain tumour. Similarly, they may be told that there is a treatment but that it is not available through the NHS. With regard to the interpretation of information, this is a problem that affects many aspects of therapy. It is not clear that pharmacogenetic information is different from that which routinely has to be communicated to patients by their physicians following non-genetic tests.

5.16 We have said that the important feature of a medical test is the content of the information it provides, not whether that information is genetic in nature. It is important not to fall into the trap of genetic exceptionalism and to demand higher standards of consent for pharmacogenetic tests compared to non-genetic tests that might have similar risks associated with them, for example tests for high blood pressure which not only direct treatment, but also reveal information about the likelihood of future ill health. However, we recognise that one important feature of genetic data is that information may be revealed that is unrelated to the illness in question, or indeed to any disease, and that this additional information may not be known about at the time the genetic sample is taken. This makes obtaining informed consent to the test difficult. In paragraph 3.29 we noted that the ethically significant requirement of consent is not that it be complete, but that it be genuine, and that achieving fully informed consent is not possible. It is worth reiterating this point. No consent form can inform a patient about eventualities that are not known about at the time. However, consent forms may be required in some cases. We give two examples: (i) if there is a significant chance that the sample or test results will be used for purposes that are substantially different from the original goal of aiding prescription, or will reveal information about the patient unrelated to the medicines in question; (ii) if the results of the test may have a particularly serious impact on the health or lifestyle of the patient. It should be noted that both examples could also arise when non-genetic tests are proposed.

5.17 **We recommend that in assessing whether written consent forms are required for pharmacogenetic tests undertaken in clinical practice, each test should be judged according to the nature of the information it provides. If information about unrelated medicines or diseases is likely to be obtained, or if the results of the test will have a significant impact on the health or lifestyle of the patient, written consent may be appropriate. We take the view that, in most cases, written forms will not be required. However, written information for patients should be supplied, particularly if tests will reveal complex and probabilistic information.** In developing such information resources, relevant organisations should consider whether information about non-genetic tests which are similarly complex should also be developed.

Responsibility for test and treatment

5.18 Who should be responsible for decisions about a patient's treatment with pharmacogenetics-based medicines? At least three different sorts of decision need to be distinguished: the decision whether to take a test, the decision to make a medicine available after the test, and the decision whether to make a medicine available if the patient is unwilling to take the associated test.

5.19 Most people accept that not all medicines should be freely available over the counter or on the internet. But what about pharmacogenetic tests? Here there is a *prima facie* case for more extensive patient control, on the grounds that tests do not pose the same direct physical risks as medicines. But the situation is complicated. Within a public health system, risk to health is not the only reason for keeping professional control over treatment, and in so far as patients expect the state to pay for pharmacogenetic tests, they will have to submit to some kind of restrictions on their use. Moreover, as we have noted, the results of pharmacogenetic tests could have negative psychological effects, which might provide a justification for a system that would control the use of tests. The argument would be strongest in the context of a system where not only were tests freely available but where many of those tests were unreliable or difficult to interpret. However, there are strong arguments for giving patients considerable control over the acquisition of information about themselves. Thus, we allow the purchase of pregnancy tests over the counter, knowing full well how psychologically potent the results of these tests may be, and knowing that the tests are not 100% reliable. But these tests are useful and easy to interpret, and in so far as a pharmacogenetic test has a similar status, the case for patient choice may be strong.

5.20 There has recently been debate regarding the provision of genetic tests directly to consumers.[8] The Human Genetics Commission (HGC) has recommended that stricter controls should be put in place on direct genetic testing, and that predictive tests that rely on home sampling or testing should be discouraged.[9] The HGC focused primarily on tests to predict or diagnose an illness, but noted that the development of pharmacogenetics was a relevant issue. The framework of controls proposed by the HGC places responsibility for the regulation of the safety of direct genetic tests on the Medicines and Healthcare products Regulatory Agency (MHRA), and responsibility for reviewing the effectiveness of tests on the UK Genetic Testing Network. The HGC concluded that the presumption should be that genetic tests are offered and interpreted by health professionals, in view of the complexity and sensitivity of the information they may provide. However, direct genetic tests could be approved if a company was able to put forward a convincing case that:

> 'the test is sufficiently well validated and that anyone involved in providing the test has the right training and expertise to give good quality advice to the consumer. For example, we recognise that certain genetic tests to guide the prescribing of medicines might properly be provided via certain pharmacists.'[10]

5.21 Many of the respondents to our public consultation broadly supported the presumption in favour of the involvement of health professionals because of the complex nature of the information pharmacogenetic tests would generate, and because such information would be only one part of a decision about which medicine to prescribe. The availability of tests over the counter could lead to pressure on physicians to prescribe more expensive medicines even when the additional benefit is small, putting a strain on the NHS budget. Moreover, physicians may wish to repeat tests that have been conducted by private companies to confirm the results. It is even possible to imagine that tests would be made quite freely available as part of a campaign aimed at marketing a particular medicine, unless controls to avoid this were in place. Patients with conditions that are relatively difficult to treat would

8 Human Genetics Commission (2002) *The supply of genetic tests direct to the public: a consultation document* (London: Department of Health).

9 Human Genetics Commission (2003) *Genes Direct: Ensuring the effective oversight of genetic tests supplied directly to the public* (London: Department of Health).

10 Human Genetics Commission (2003) *Genes Direct: Ensuring the effective oversight of genetic tests supplied directly to the public* (London: Department of Health), para. 3.33.

be particularly vulnerable to such an approach, which may suggest that an expensive medicine is more likely to benefit them than a much cheaper substitute, even though the differences are relatively small and neither medicine is likely to be of great benefit.

5.22 We conclude that some pharmacogenetic tests are likely to provide clear, readily interpretable information about medicines that can be purchased over the counter or obtained on prescription. If such tests are approved by the MHRA, we consider that there is no reason to prevent their provision directly to consumers. However, the majority of pharmacogenetic tests will be more complex, providing less certain predictions. In these cases, professional advice is likely to be needed both before and after taking the test, which means that the direct commercial provision of tests will be inappropriate. The MHRA will be responsible for assessing the clinical validity and quality of tests (paragraph 4.3). **We recommend that the UK Genetic Testing Network should take responsibility for advising on the sale of pharmacogenetic tests directly to patients, and should take a case-by-case approach. We consider that pharmacogenetic tests which are not to be sold directly to patients should not be advertised to them.**

5.23 What about the option to receive treatment without taking an associated test? If patients know that their only chance of being prescribed a potentially life-saving medicine is if they agree to be tested, in what sense can their consent to the test be considered voluntary? Consider, however, the analogy with the decision whether to take a potentially life-saving medicine itself, in a situation where there is no pharmacogenetic test. Here too there is a serious question as to whether the decision can be considered truly voluntary; but it is equally clear that it may be morally permissible, indeed even morally obligatory, to offer the medicine. In our view the same would apply to offering a pharmacogenetic test as a condition of treatment, so long as there is a clear, substantial and avoidable risk if the medicine is taken without the test.

5.24 It cannot be assumed that patients will be keen to take a pharmacogenetic test, even if it will improve the likelihood of their receiving a safe and effective treatment. Such an aversion may be irrational, but may be based on a legitimate fear that information produced by the test could make it difficult to obtain insurance, or that it might indirectly reveal information about a medical condition which cannot be effectively treated. Many respondents to our consultation took the view that the ultimate responsibility for decisions about treatment lies with the person writing the prescription. Nonetheless, a number of respondents felt that patients should be able to refuse a pharmacogenetic test, even if they were advised to take it, and still receive the medicine in question. The responses highlighted the responsibility of patients in making decisions about their treatment and of health professionals in ensuring patients were adequately informed:

> '[Patients should be able to refuse a pharmacogenetic test and still receive the medicine] as long as they have informed choice.' *(Association of Genetic Nurses and Counsellors)*

> 'The Society would support a position that patients should be able to refuse a genetic test to determine response to medicines and still expect to receive a prescription. Patients should be given full information as to the adverse side effects and make a decision on that basis'. *(Alzheimer's Society)*

These comments raise the question of whether genetic information should be treated differently to other medical information. Would the view that patients could refuse to allow their physician to find out non-genetic information relevant to deciding whether a medicine would be of benefit, but still expect to receive the medicine also be supported?

5.25 The situation is complicated. Health professionals are able to prescribe medicines to patients who do not have the characteristics for which the medicine was licensed, but they will be held accountable for problems that arise as a result. This is called 'off-label' prescribing. Where a pharmacogenetic test is part of the licence conditions of a medicine, it is unlikely that a health professional would wish to prescribe the medicine without the test, particularly if this would mean putting the patient at risk of an adverse reaction, or subjecting the patient to a medicine that might have very little beneficial effect. However, where tests are not part of the licence conditions, the information they provide may be just one factor among many in deciding whether to prescribe a medicine. If an individual has a low likelihood of response, but there are no alternative treatments and the adverse events associated with the medicine are not substantial, the medicine might be prescribed without making use of the test.

5.26 With regard to legal liability, the physician's responsibility is to ensure that, on balance, the effect of prescribing the medicine to the patient is likely to be beneficial. Physicians would be required to inform the patient that a pharmacogenetic test was available, even if the patient chooses not to make use of it. It might be argued in some cases that this could extend to informing the patient of the test's existence even if it were not available through the NHS. The physician would also be required to inform the patient of the implications of refusing the test. If the patient, having considered the relevant information, refused to take the test, the physician may decide not to prescribe the medicine. The law is not inclined to require physicians to act against their clinical judgement, but when finely-balanced decisions are involved and competing views exist, the views of patients should be taken seriously.

5.27 We noted in paragraphs 4.16 – 4.17 that bodies such as NICE may provide guidance about the circumstances in which medicines may be provided, and this may include reference to the results of a pharmacogenetic test, as in the case of Herceptin. Although not formally binding on health professionals, such guidance would be referred to in any legal dispute between a patient and a physician. Thus, physicians may feel obliged to restrict prescription to those individuals who have taken the relevant pharmacogenetic test and who meet the necessary criteria set out in such guidance, and indeed, health providers may impose such requirements. In these circumstances, patients who felt that they were unjustly being withheld treatment that could benefit them may be able to challenge the decision by judicial review.

5.28 We note that advances in pharmacogenetics can be expected to lead to the licensing of medicines that would not have been licensed had there been no associated test, because of the serious danger those medicines pose to a subpopulation. To allow prescription without the test in such a case would be wrong. In other cases, pharmacogenetic tests may not be part of the licence conditions of a medicine. Health professionals will therefore be required to take decisions regarding the treatment of individual patients having regard to guidance from regulatory authorities or professional bodies. In practice, this may mean that patients are unlikely to be prescribed a particular medicine unless they take the associated pharmacogenetic test.

5.29 In the case of those individuals with mental illness who have been judged unable to make decisions about their treatment, or are detained under the Mental Health Act and are receiving medicines without their consent, pharmacogenetic tests may be required by physicians on the grounds that such tests would be in the patients' best interests. The compulsory treatment of those with mental illnesses is a sensitive issue, and the application of pharmacogenetics in this area may raise particular concerns. Pharmacogenetic tests might be used to insist on pharmacological treatment for mental illness or for behavioural

problems, or for the treatment of those convicted of offences, adding to an existing trend towards medicalisation in the field of mental health.

Off-label use in developing countries

5.30 The potential for off-label prescribing also exists in countries in which pharmacogenetic testing facilities are simply not available. There may be countries in which medicines that were designed to be used in conjunction with pharmacogenetic tests are purchased and prescribed without recourse to testing. The lack of such facilities may be of particular concern if the pharmacogenetic test can reliably predict those individuals that will suffer a serious adverse reaction to a medicine. This dilemma is not new: there are a number of medical treatments which cannot safely be administered in poorer countries because of the expensive technology required to monitor and treat potential adverse reactions. However, pharmacogenetics, among other developments in medical science, may lead to an increase in such situations. We note that the decision to allow the prescription of a medicine in a particular country is the responsibility of the regulatory authority for medicines in that country. Decisions will be made on a case-by-case basis, taking into account the seriousness of the condition, the availability of alternative treatments and the nature of the information provided by the pharmacogenetic test.

Privacy and confidentiality of pharmacogenetic information

5.31 It is unlikely that pharmacogenetic testing will become a major part of routine clinical practice for some years. It is therefore difficult to predict how pharmacogenetic data may be obtained and stored in this context. Approaches could range from the establishment of an organisational structure that allows genetic tests to be carried out in tandem with prescriptions, to the provision of a large population database that contained data about genetic variation of each individual, and which could be accessed as and when required. These two approaches raise quite different logistical and ethical questions. At least in the short term, it seems unlikely that using large databases would be desirable or practical, since the majority of people may never have a pharmacogenetic test. If it turned out that there were a relatively limited number of genes that determined clinically important reactions to a number of classes of medicine, it could be argued that routine testing in advance for information about that particular range of predictors might be valuable. However, it might be just as cost-effective to carry out the test as and when it was needed.

5.32 Storage of genetic information by general practitioners or pharmacists raises questions about the privacy of such information, as it does in relation to the storage of any medical data. One way of reducing the potential for abuse or misuse of the information would be to restrict pharmacogenetic tests to the precise genetic variant in question, and to ensure that additional data about an individual's genotype were not obtained. The result of the test could also be stored in a patient's medical records without the specific genetic variant being described. However, the application of pharmacogenetics entails that genetic information will not only be present in the form of clinical information. If a patient receives a specific medicine that takes into account his or her genetic variation, then the medicine might indirectly reveal his or her genotype. This may be relevant where the medicine is prescribed to patients in whom abnormally functioning enzymes are involved in the metabolism of many medicines. Provision with the respective medicine might indicate indirectly that the affected patient is also likely to have a particular response to some other medicines.

5.33 Researchers at the University of Sheffield on behalf of the Department of Health recently conducted a survey of public attitudes to the storage and use of health data. This found that most individuals were content for their information to be shared among the medical team

directly responsible for their care, but that they were apprehensive about access by other groups such as social workers and physiotherapists. Individuals did not seem concerned about electronic storage compared to paper records. However, they were anxious about anonymisation of information, as there was a common feeling that this procedure could not be trusted.[11] We note that the question of the storage of genetic information within the NHS has been considered by the HGC, and agree with its conclusion:

> 'We do not believe that it is feasible for separate arrangements to be made for the storage of genetic information within the health service, but nonetheless we point out that the potentially sensitive nature of this information underlines the importance of protecting the confidentiality of patient medical information in general.'[12]

Use by third parties

Family members

5.34 Genetic tests for serious diseases may have implications for family members as well as for the individual who is tested, as they may reveal information about whether other family members are likely to be affected by the disease in question. However, it cannot be assumed that individuals will be willing to share the results of tests with their families. Might similar tensions arise in relation to pharmacogenetic testing? If pharmacogenetic tests were developed that provided information about adverse reactions to medicines that might be used in emergency situations, it could be in the interests of family members to be aware of the possibility that they may be at risk and to have a precautionary test. If a pharmacogenetic test also indicated susceptibility to another disease, family members might also wish to be informed. (The implications of the Data Protection Act for revealing information to family members are discussed in paragraphs 3.40 – 3.43.)

5.35 However, as we noted, the likelihood that pharmacogenetic data will be of relevance to family members is low. There are some cases, for example regarding allergic reactions to penicillin, in which it is of value for family members to be aware of a familial problem, and this information is routinely shared between family members and with health professionals. Similarly, there may be cases in which the results of pharmacogenetic tests taken by members of a patient's family could suggest to a health professional that a test should be conducted on that patient. However, in general it is likely that if a test is clinically indicated, it will be carried out on the individual in question, regardless of the results of tests taken by family members. For example, two sisters with breast cancer would both be tested for HER2 expression, since the results in one sister could not be assumed to apply to the second. There may be circumstances in which the obligation of health professionals to their individual patients comes into conflict with their obligations to others, and when they may therefore wish to encourage patients to share pharmacogenetic information with family members. We consider that this possibility can be dealt with by existing practice regarding the sharing of medical information.

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11 The lead researcher was Dr Darren Shickle, University of Sheffield. Further information about the survey is available at www.shef.ac.uk. A similar study that obtained somewhat different results was conducted by interviewing a much smaller group of 39 patients in a rural area of the UK. In this study, some patients expressed concern about doctors not directly responsible for their care, and nurses, having access to their records. The patients interviewed in this study all expressed concern about the use of electronic medical records as opposed to paper records. (Carman D and Britten N (1995) Confidentiality of medical records: the patient's perspective, *Br J Gen Pract* **45**: 485-8.)

12 Human Genetics Commission (2002) *Inside Information: Balancing interests in the use of personal genetic data* (London: Department of Health), para. 3.36.

Insurers

5.36 There has been considerable debate about the use of genetic information by insurers.[13] In the context of pharmacogenetics, a particular anxiety is that individuals may be categorised as 'difficult to treat' and thereby be denied insurance, on the grounds that they will be especially expensive to care for, since existing medicines will not be effective. In a system of public healthcare such as that in the UK, this may be less likely than in systems of private healthcare. The Consortium on Pharmacogenetics has hypothesised that:

> 'if an individual has a genotype which indicates that the only effective drug (or group of drugs) for his serious condition will not be efficacious for him, or cannot safely be taken by him, he might be classified by insurers or employers as having an untreatable serious illness. This risk would only arise in cases in which (a) there is no alternative effective treatment for the condition in question, or the alternative treatment is much more expensive, or (b) the condition is serious enough to be of concern to insurers or employers, and insurers and/or employers are able to take this sort of information into account in making decisions.'[14]

5.37 Pharmacogenetic information could be of relevance to insurers providing various types of healthcare insurance including private medical insurance, critical illness cover, income protection insurance and long term care insurance, as well as life insurers. Such information could be used at two different stages: in assessing premiums for people applying for policies, and in adjudicating claims in order to make decisions about payment to policy-holders.

5.38 At the stage of assessing claims, pharmacogenetic information will be of value to insurers providing private medical insurance in the same way that it will be of value to the public healthcare system in deciding which treatments to fund. Such information is already used in the case of medicines such as Herceptin, where decisions to prescribe the medicine are dependent on its predicted efficacy, which is measured using a pharmacogenetic test. New tests that examine the genetic characteristics of the individual rather than the disease could be similarly useful. However, this is not to say that patients will receive treatment for which they may not subsequently be refunded by a private health insurer, as medicines which are not predicted to be effective will be most unlikely to be prescribed in the first instance.

5.39 With regard to setting premiums, it seems unlikely that pharmacogenetic information will be widely used by insurers, since the tests will be of comparatively low predictive value, much lower than genetic tests for single-gene disorders or non-genetic information such as whether or not an individual smokes. The administrative cost of obtaining and processing the information may well outweigh its value in assessing risk. In its response to our consultation, the Association of British Insurers made the following statement:

> 'The only area where pharmacogenetic information might be of some relevance for [critical illness cover, long term care cover and income protection] would be where a claim was made for an illness which has been caused by the claimant's response to a medicine. If the illness had been caused because the claimant had refused to follow

13 Nuffield Council on Bioethics (1993) *Genetic screening: ethical issues* (London: Nuffield Council on Bioethics); Human Genetics Advisory Commission (1997) T*he Implications of Genetic Testing for Insurance* (London: Department of Health); House of Commons Select Committee on Science and Technology (2001) *Genetics and Insurance, Fifth Report* (Norwich: The Stationery Office); Human Genetics Commission (2001) *The use of genetic information in insurance: Interim recommendations of the Human Genetics Commission.* The HGC convened various meetings to discuss insurance and genetics and the relevant minutes are collected at http://www.hgc.gov.uk/topics.htm#ins. Accessed on: 19 July 2002.

14 Buchanan A *et al.* (2002) *Pharmacogenetics: Ethical and Regulatory Issues in Research and Clinical Practice.* Report of the Consortium on Pharmacogenetics, Findings and Recommendations.

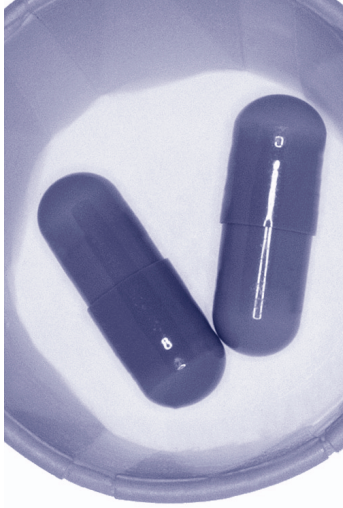
> medical advice, for example following a pharmacogenetic test which indicated that that individual was highly likely to have an adverse reaction to a particular medicine, this could be relevant to the insurer's consideration on whether to pay the claim or not. However, the pharmacogenetic information would, in such a case, only act as confirmatory evidence in the event of a dispute. The actual reason why the claim might be turned down – 'failure to follow medical advice' – is a standard exclusion in many health insurance policies.'

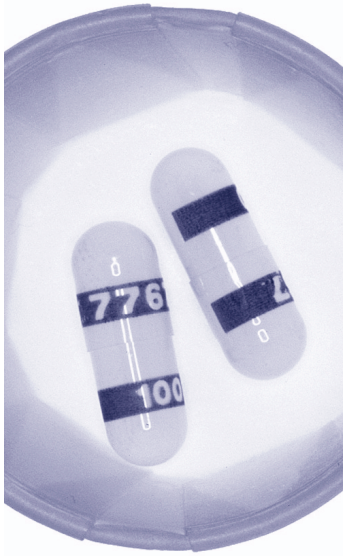
This indicates that insurers will be less interested in the content of a pharmacogenetic test, than in the indirect implications of that information for the health of the patient.

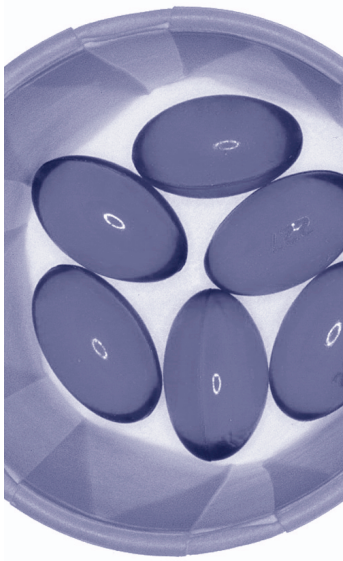
5.40 We note that even if the results of genetic tests were not provided to insurers, relevant pharmacogenetic information would be divulged indirectly, since the fact that a patient was receiving a particular medicine, or no medicine, could indicate that other, more commonly used medicines, were not appropriate. Applicants for private insurance consent to information being provided on their medical history by their GP. This information will include current prescriptions. Such information may be as of much value to insurers as knowledge of the particular DNA sequence of an applicant. The fact that an individual's medical history may indirectly provide pharmacogenetic information to insurers is important. In the existing debate about genetics and insurance, questions have been asked about the potential inconsistency in not allowing insurers to have access to genetic information, but allowing them access to family histories. Given the case against allowing access to genetic information, one option that has been put forward is therefore to restrict access to family histories. In the case of pharmacogenetics, the same argument would mean that insurers should not have access to information about the particular patient who has applied to them. But such a prohibition would be in conflict with the basic premises of systems of private insurance. Thus, the case of pharmacogenetic information may be thought to give weight to arguments in favour of systems of insurance that rely on solidarity, rather than the pooling of risks.

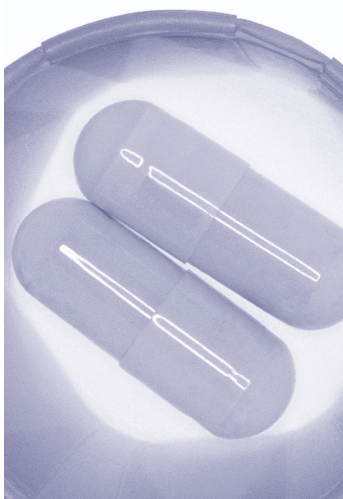
5.41 The UK has a moratorium until 2006 on the use of genetic information by life insurers in setting premiums (excepting the results of tests for Huntington's disease in life insurance policies of over £500,000). If this situation were to change, there is a risk that patients would be discouraged from taking pharmacogenetic tests that could be of great value to them, for fear they would be unable to obtain insurance, whether this fear was real or perceived. **We note that pharmacogenetic information falls under the current moratorium in the UK and that insurance companies have expressed the view that the use of pharmacogenetic information in setting premiums would not be of value. In the light of these considerations, we recommend that the moratorium should continue.**

Appendices









Appendix 1: How genes work

Genes are made of the chemical substance DNA (deoxyribonucleic acid). This substance encodes genetic information. DNA can be found in most cells in a human body, where it is assembled into units called chromosomes. On every chromosome there are between 200 and several thousand genes. Humans have 23 pairs of chromosomes on which 30,000 - 40,000 genes are located. The total complement of this genetic information is called the genome of an individual.

A DNA molecule consists of two strands that wrap around each other to resemble a twisted ladder – the famous double helix. Each strand of DNA is made up of a string of smaller units called nucleotides, or bases. There are four different bases: adenine (A), thymine (T), guanine (G) and cytosine (C). These bases pair together: A with T, and C with G. Each base pair forms a rung of the ladder. The way these pair together causes the strands to coil up into the spiral twisted ladder. It also allows the DNA to replicate or copy itself.

Every gene contains the instructions for making a specific protein or ribonucleic acid (RNA). Each set of three base letters, for example ACG, is part of a code providing the instructions to assemble a protein. Proteins carry out the work of a cell. Each three-letter code is specific to one of the 22 amino acids, the chemical building blocks of proteins. The sequence of the gene determines the order that these blocks assemble together, and hence which protein is made. Different proteins have different specialised functions, such as making muscle, binding oxygen from the air, transmitting nerve impulses, and breaking down food or other substances. Many proteins are enzymes, with the specialised function of synthesising, breaking down or altering other chemical molecules. The chemical molecules that are processed by enzymes may be produced by other cells of the body. They can also be introduced externally, for example, when a patient takes a medicine. The activity of the enzymes will then influence the concentration of the medicine in the blood and other important locations in the body over time. Thus, as specific genes determine which form of proteins or enzymes are produced in a cell, genetic analysis may reveal how a patient is likely to respond to a medicine.

Appendix 2: List of regulatory authorities

UK

Medicines and Healthcare products Regulatory Agency (MHRA)

- Previously two separate bodies: the Medicines Control Agency (MCA) and Medical Devices Agency (MDA)
- Executive agency of the Department of Health
- Assesses the quality, safety and efficacy of medicines, issues licences and monitors medicines and medical devices, including genetic tests

Committee on the Safety of Medicines (CSM)

- Independent
- Advises MCA and assists in monitoring licensed medicines

Human Genetics Commission

- Superseded the Advisory Committee on Genetic Testing which had produced a voluntary code of practice on genetic testing services supplied directly to the public.
- Published Genes Direct, a report on the provision of genetic tests directly to the public in 2003.

Europe

European Medicines Evaluation Agency (EMEA)

- Responsible for licensing and monitoring medicines in the European Union

Committee for Proprietary Medicinal Products (CPMP)

- Subcommittee of the EMEA

US

US Food and Drug Administration (FDA)

- Assesses efficacy and safety of medicines and devices

International

International Conference on Harmonisation

- A joint initiative involving the regulatory authorities of Europe, Japan and the US and experts from the pharmaceutical industry, which aims to achieve greater harmonisation in the interpretation and application of technical guidelines and regulation regarding medicines.

Appendix 3: Methods of working

In December 2001, the Council held a Workshop that addressed issues arising from developments in pharmacogenetics. Subsequently, in September 2002, the Working Party on Pharmacogenetics was established. The Working Party met six times between September 2002 and June 2003. As part of its work, the Working Party held five fact-finding sessions with experts in a number of fields. The Working Party also held a consultation with the public, the responses to which are summarised in Appendix 4.

Mr Jai Shah prepared background research for the Working Party while working as an intern at the Nuffield Council on Bioethics between 8 July 2002 and 12 September 2002. This research formed part of his MSc in International Health Policy at the London School of Economics.

Fact-finding meetings

The Working Party is very grateful to the following individuals for taking the time to meet with members of the Working Party and for providing insights into issues relating to pharmacogenetics.[1]

25 November 2002, London

Professor David Goldstein
Wolfson Professor of Genetics, University College London

Dr Rashmi Shah
Senior Clinical Assessor, Medicines Control Agency

Mr Adrian Towse
Director, Office of Health Economics

25 February 2003, London

Professor Alastair Bellingham CBE
Chief Executive, NHS Information Authority

Mr Cliff Prior
Chief Executive, Rethink (formerly the National Schizophrenia Fellowship)

Dr Virginia Warren
Assistant Medical Director, BUPA

25 February 2003, London

Dr Kevin Cheeseman
Director of Development Pharmacogenetics, AstraZeneca

Mr Andrew Freeman
RADEX Operations and Policy, GlaxoSmithKline

Dr Duncan McHale
Clinical Pharmacogenetics, Pfizer

Dr Philip Wright
Director, Association of the British Pharmaceutical Industry

1 Institutional affiliations at the time of the meeting are listed.

13 March 2003, London

Professor Jonathan Montgomery
Professor of Health Care Law, University of Southampton

Mr John Wilkinson
Partner and Joint Head of the Life Sciences Group, Bird and Bird

20 March 2003, London

Mr Ian Dodds-Smith
Partner, Co-Head of Food, Drug and Medical Devices Practice Group and Head of European Product Liability Practice Group, Arnold and Porter

Dr Kathleen Fadden
Senior Associate, Arnold and Porter

Appendix 4: Consultation with the public

A consultation with the public was held between November 2002 and February 2003. Approximately 420 consultation documents were disseminated and a further 2,500 were downloaded from the website of the Nuffield Council. Eighty-four responses were received from individuals and organizations from a variety of backgrounds (see Figure 1). The responses came not only from the UK, but also from 15 other countries (see Table 1). Those who responded are listed at the end of this Appendix and the Working Party is grateful to them all.

Figure 1: **Area of expertise of respondents**

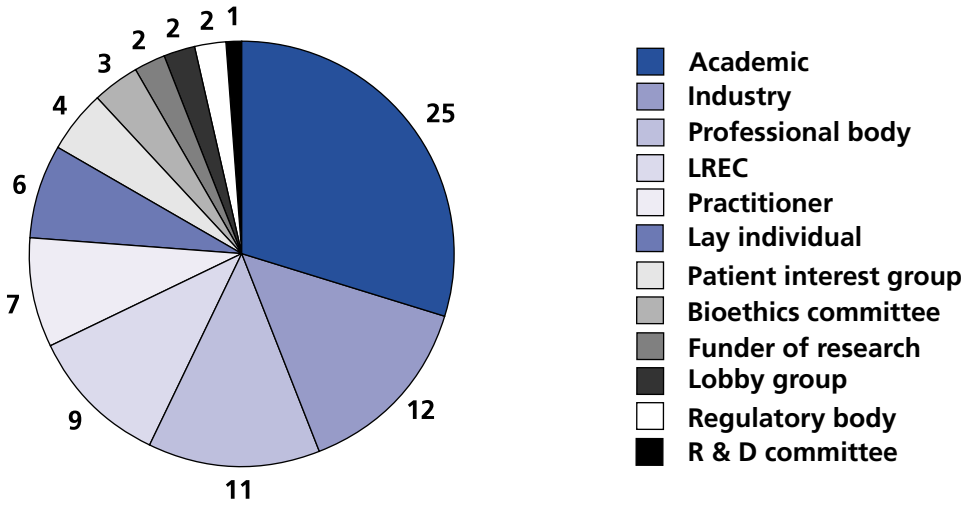


Table 1: **Country of origin of responses**

Country	Number of responses
UK	58
US	10
Australia	2
Ecuador	2
Estonia	1
Germany	1
Greece	1
Israel	1
Italy	1
Nigeria	1
Peru	1
Saudi Arabia	1
Spain	1
Sri Lanka	1
Sweden	1
The Netherlands	1

A summary of the responses to specific questions posed in the consultation paper is set out below. It aims to reflect the issues and concerns that were raised, rather than to constitute a quantitative analysis of the responses.

Economic and regulatory implications

The development and regulation of medicines

Q1. What do you think will be the likely economic impact of pharmacogenetics on the development of new medicines?

Most respondents expected that the economic impact of pharmacogenetics on the development of new medicines was likely to have two phases. It was suggested that the cost of the development of a medicine would increase in the short term as a result of a number of factors: new techniques would need to be developed; training and facilities would be required; segmentation of the market would result in a reduction in the revenue generated by the new medicine; and an extended period of post-marketing surveillance to capture rare adverse events would be required. However, a number of respondents suggested that the cost of developing a new medicine would decrease in the long term as a result of several factors. Trials would be guided by genomic knowledge rather than a trial and error approach. As a result, the success rates of new medicines would be likely to increase. Most significantly, the length of clinical trials would be reduced as a result of stratifying patients.

Other influences on the cost of medicines that were mentioned included: the possibility that medicines which had previously been withdrawn or shelved may be marketed; and the possibility that a reduction in adverse reactions might lead to fewer legal liability cases as well as fewer hospital admissions.

Q2. Do you think that further regulatory measures will be needed to encourage the development of clinically desirable but economically unprofitable medicines?

Most respondents recognised the need for some sort of incentive scheme for the development of medicines for small populations where market incentives did not already exist for the pharmaceutical industry. Orphan medicine regulations were generally seen as a suitable means of providing incentives for the pharmaceutical industry, although other suggestions such as extensions of the length of time for which patent protection was available were made. Several groups suggested that new regulatory measures for medicines were unnecessary.

Many respondents questioned whether pharmacogenetic medicines would be designated as orphan products, and suggested that a clarification of the regulations with regards to pharmacogenetics was necessary. It was suggested that whether or not achieving orphan medicine designation provided sufficient incentive to secure the development of clinically desirable but economically unprofitable medicines would need to be monitored over time.

One respondent suggested that sufficiently large pharmaceutical companies should be mandated by governments to allocate at least some of their research and development budget to the development of pharmacogenetic medicines. Another respondent took the opposite position, suggesting that forcing companies to develop unprofitable medicines would increase the cost of medicines for everyone and decrease the efficiency of the market system.

The provision of tests and medicines

Q3. In your view, should pharmacogenetic testing of participants in trials be a regulatory requirement for the development of medicines in the future?

Many respondents noted the desirability of undertaking pharmacogenetic testing of patients in the development of new medicines in the future. However, the majority suggested that a regulatory requirement for pharmacogenetic testing in all cases would not be appropriate. There were various reasons given for this: not all medicines would require pharmacogenetic testing; for those medicines that would benefit from pharmacogenetic testing, the additional costs this would impose may be unacceptable; a relevant test may not be available.

One respondent noted that when companies develop medicines designed to treat patients who have a particular genetic make-up, testing should be a regulatory requirement. Overall, it was suggested that the benefits of pharmacogenetic testing have not been sufficiently demonstrated for it to be a regulatory requirement. However, regulatory authorities may want to encourage pharmacogenetic testing.

> 'Given the potential benefits from pharmacogenetics, it would seem desirable to undertake pharmacogenetics testing of patients in the development of new medicines in the future. It is not clear to the [British Medical Association] from the evidence provided, however, that the benefits are sufficiently proven yet to make this a requirement in all cases.' *British Medical Association*

Q4. Who should be responsible for providing a pharmacogenetic test? For individual therapy, should tests be available directly to patients over the counter or on the internet, or should they only be available through medical practitioners as part of a decision about the use of a prescribed medicine?

Some respondents considered over-the-counter testing to be appropriate while others suggested that under no circumstances should a pharmacogenetic test be available over the counter or from the internet. Many suggested that the provision of a pharmacogenetic test should be within a medical setting, due to the difficulty of interpreting the complex information derived from it. Some considered a more important question to be whether the test in question met performance criteria, and suggested it should be left to market forces to determine who would be able to provide that testing service most efficiently, most conveniently and at the least cost to the consumer. One respondent suggested that the role of genetic counsellors could be extended to include discussion of the results of pharmacogenetic tests.

Q5. What will be the implications of pharmacogenetics for pharmaceutical companies and providers of healthcare regarding legal liability for adverse reactions?

The complexity of the situation with regards to legal liability was noted by some, while others suggested that they could see no reason why the use of pharmacogenetic testing would put healthcare providers, physicians or pharmaceutical companies at greater risk of legal liability.

The responsibilities of several parties were noted. When a medicine is licensed for use with a pharmacogenetic test, the failure to administer the test prior to prescription may result in a physician being found negligent. The responsibility of pharmacogenetic test providers lies in ensuring the sensitivity and accuracy of their tests. The need to obtain a patient's consent was pointed to, as was the need for the provision of appropriate guidance for medical professionals.

Q6. Should medicines which have been developed for administration in conjunction with a pharmacogenetic test be distributed to countries in which testing facilities are not available?

The majority of respondents recognised the difficulty in finding an absolute rule for this scenario and felt that decisions about distributing a medicine in a country with no capacity to use associated tests should be made on a case-by-case basis.

> 'Medicines should not necessarily be barred from distribution to countries in which pharmacogenetic testing facilities are not available… Distribution should take into consideration the severity of the disease, what the test is predicting (efficacy, safety), as well as the ability of each country to treat the adverse reactions associated with the medicine.' *Millennium Pharmaceuticals*

Many respondents suggested that medicines likely to cause severe adverse reactions in the absence of pharmacogenetic tests to guide prescribing probably should not be distributed to countries without testing facilities. However, in general, an assessment of the costs and benefits related to a medicine should be made by the regulatory authorities of that country, prior to approval.

Q7. How should predictions of efficacy and safety, as well as cost, be integrated in deciding whether to provide a particular treatment to patients in (a) a public healthcare system, and (b) a private healthcare system?

A number of respondents noted that:

> '[p]redictions of efficacy and safety as well as costs are already integrated into decision-making in prescribing in both public and private healthcare systems. The use of formularies and prescribing budgets, together with the rise in evidence-based medicine have simplified these decisions for some prescribing doctors.'
> *Pharmacogenetics Evaluation Policy, University of Cambridge*

Some respondents suggested that the use of a pharmacogenetic test might enable a greater degree of accuracy in targeting medicines to those patients who are likely to respond and therefore where cost-effectiveness is greatest. This was thought likely to have a significant impact on the public sector.

The Wellcome Trust noted that 'the provision of genetic services has serious resource implications for the NHS, and pharmacogenetics is just one component of this.'

The Royal Pharmaceutical Society of Great Britain detailed the impact that pharmacogenetics could have on private healthcare. It suggested that private insurance policies, like public healthcare systems, have defined benefits, and as such, they will determine which pharmacogenetic tests they are willing to pay for. Only under 'pay as you go' schemes will private patients truly have the freedom to access whatever treatments they wish, subject to their ability to pay for them.

Q8. Do you think the application of pharmacogenetics might exacerbate inequalities in the provision of healthcare? Is it likely to challenge the principle of solidarity that lies at the basis of the provision of national healthcare in the UK? Will the benefits of pharmacogenetics only be affordable or available to the wealthy?

Many respondents considered it likely that pharmacogenetics would exacerbate existing inequalities as they would only be available or affordable for the wealthy. Several noted that such inequality was not a new phenomenon, and that pharmacogenetics was unlikely to alter the present situation significantly.

> 'It is possible that the reimbursement agencies, such as [the National Institute for Clinical Excellence], would decide not to recommend reimbursing certain pharmaceuticals because the additional cost of testing would render them financially unattractive. However it is equally possible that such agencies would decide, on the grounds of cost-effectiveness, that such medicines should only be used in the NHS if pharmacogenetics testing can identify those who will most benefit and be at least risk... [I]n traditional prescribing patients are being excluded from treatments for their own safety as a result of family history, co-morbidity, concurrent medication, severity etc. Therefore there is no reason to believe, providing pharmacogenetics testing is integrated with prescribing decision-making, that it will exacerbate genuine inequalities.'
> *Pharmacogenetics Evaluation Policy, University of Cambridge*

One respondent noted that the NHS provides expensive medicines where they are considered to provide significant benefits. The use of an inexpensive test might prove financially attractive to providers and result in improved provision of such medicines.

Social and ethical issues

Confidentiality, consent and feedback in clinical trials

Q9. In your view, is the storage of genetic information for the purpose of pharmacogenetic analysis categorically distinct from storage of other kinds of genetic information, for example information about susceptibility to disease?

The majority of respondents did not consider the storage of genetic information relevant to pharmacogenetics to be distinct from the storage of other types of genetic information, and as a result, took the view that it should be subject to the same levels of security and confidentiality. Some considered that while storage systems should be the same, there could be differences in the impact of the different types of genetic information. Pharmacogenetic information was thought to have less impact psychologically and, according to one respondent, to be of less relevance to family members.

Some respondents suggested that while pharmacogenetic information might initially provide information about a person's response to a particular medicine, it might later provide information about disease susceptibility, and that there would be a significant overlap between the two types of information.

With regards to clinical research, one respondent did consider the storage of pharmacogenetic information to be distinct:

> 'In most genetic research in clinical trials…information is anonymised at an early stage and no feedback is offered... In the case of pharmacogenetic information, there is a direct therapeutic implication and the information must be available to individuals. To this degree, the storage of such information is distinct.' *Royal College of Physicians*

Q10. What level of anonymity should be accorded to genetic information stored as part of research in pharmacogenetics?

Overall, the responses to this question indicated that genetic information stored as part of research in pharmacogenetics should be anonymised as far as possible. For preliminary investigations, where the research aims to establish a relationship between a genetic variant and a response to a medicine, a link between genetic information and patient details may not be necessary and therefore anonymity may be possible. These studies were considered less likely to yield information which should be fed back to patients. For studies which were likely to yield

information of therapeutic utility, individual feedback would be important, and therefore full anonymisation would not be possible. Several respondents noted that anonymisation was often not possible during the development of a medicine as a result of regulatory requirements.

Q11. What kinds of consent should be required for the collection of samples for research in pharmacogenetics? Should pharmaceutical companies which collect samples in the course of research in pharmacogenetics be able to use such samples for any purpose, or should consent of the donor be restricted to allow usage only for specific kinds of research?

Most respondents considered that full and written informed consent should be required for the collection of samples for research in pharmacogenetics. It was also thought that researchers should not be able to use such samples for any purpose, but rather consent of the donor should be restricted to specific kinds of research. The consent could allow patients to donate their samples for other uses if they should so wish, or to stipulate that the sample be destroyed following testing.

> 'We feel that if the company wished to return to the samples in the light of new discoveries they would need to re-contact the patient and get new consent. This may encourage careful planning by researchers before embarking on their projects. Some participants may be prepared to give consent for any research but this would need to be made entirely explicit.' *Association of Genetic Nurses and Counsellors*

> '[B]road consent is acceptable for the use of anonymous samples but if there is any possibility of relevant genetic information being obtained about named individuals, prior explicit consent must be obtained from the donor. We can see no reasons for taking a different approach to pharmacogenetics. Drug companies should not be able to use identifiable genetic information for any purpose other than linking response to the drug and trial in question, unless further consent is obtained.'
> *British Medical Association*

Several respondents noted the importance of being able to follow up research:

> 'There certainly will be times a company will not know what adverse effect will show up in the population and it needs to be free to investigate genetic variations it may not have anticipated being involved in those adverse effects prior to beginning clinical studies.' *Dr Peter Wedlund*

> '[S]ome of the greatest gains in understanding may come from research avenues unanticipated at the time of consent… Thus the consent should be tailored to allow the widest freedom to operate, provided that the risks are clearly stated and the ethics committee approves.' *Millennium Pharmaceuticals*

Q12. Do you think that researchers should provide individual feedback about genetic information obtained from participants in research in pharmacogenetics?

The majority of respondents considered that individual feedback about genetic information should be provided to participants in research where the participant wishes this to occur. Some suggested that this information should only be provided by means of an additional test so as to enable anonymity in the research itself. Some added the caveat that individuals should only receive feedback where the genetic information had been validated, and where it was of clinical utility. A minority of respondents considered that there should be no requirement to provide individual feedback as they expected that most pharmacogenetic information would have little clinical value. GlaxoSmithKline noted: 'Under the provisions of the Data Protection Act there is a specific requirement to provide individuals, on request, with any personal data that is held on

them. The data returned has to be intelligible. Therefore for unverified research information a summary of the current status of the research may fulfil this requirement.'

Confidentiality, consent and decision-making in primary care

Q13. What, in your view, would be appropriate methods of regulating scope, storage and access with respect to pharmacogenetic information used in clinical practice?

A number of respondents suggested that there was no reason to treat pharmacogenetic information any differently than any other confidential medical information:

> 'Absent exceptional circumstances, the methods used should be the same as those used for regulating the scope, storage and access to any other confidential medical information use in clinical practice particularly with regard to consent, sample handling and database protection procedures.' *GlaxoSmithKline*

> '[In the US] there are extant laws and standards that already apply that protect genetic diagnoses and family history data. We see no reason why pharmacogenetics data should not be treated the same as any other medical information.'
> *Indiana University Centre for Bioethics*

Genewatch suggested that additional safeguards were required for genetic data in general, including:

> 'New legislation to prevent genetic discrimination, particularly by insurers and employers; a genetic privacy law, including legal clarification of when genetic information can be used without consent, particularly by family members, the police, courts or government; new legislation to regulate the commercial use of genetic databases and an end to the patenting of genes.'

The implications for providers of healthcare

Q14. Do you think that the ethical and legal issues raised by the use of pharmacogenetic tests in primary care differ from those raised by other forms of genetic testing? What about non-genetic tests, such as tests for cholesterol?

The majority of respondents did not consider that pharmacogenetics raised ethical and legal issues that were significantly different from those raised by other forms of genetic testing. A number of respondents noted that it was not possible to delineate between pharmacogenetic tests and tests for disease susceptibility, as there would be overlap between the two.

Some stressed the importance of not treating pharmacogenetic and genetic information as categorically distinct from other types of medical information

Issues particular to pharmacogenetics that were noted by respondents included:

- The potential for imposing a substantial burden on the healthcare system with the demand for pharmacogenetic tests.
- The training of health professionals and the provision of resources to ensure understanding of the complexities of pharmacogenetics, and in particular in interpreting and applying the results of pharmacogenetic tests.
- Requests for physicians to provide medicines for patients without the relevant pharmacogenetic test being performed.

Q15. What might be the psychological implications for individuals of pharmacogenetic tests? Are such tests likely to reveal information that is of relevance outside the context of testing for response to medicines?

Respondents discussed both positive and negative implications of the use of pharmacogenetics. It was considered that pharmacogenetics would be of benefit as it had the potential to determine the most effective medicine for a patient, who would then be spared a trial and error approach to the selection of treatment. A pharmacogenetic test which predicted adverse reactions might allow such a reaction to be avoided, or allow a patient to take a medicine which might not otherwise have been available to them. In contrast, however, many pointed to the potential negative psychological implications. Several respondents noted that pharmacogenetic tests might provide some information about their prognosis. Furthermore, the test may also provide disease susceptibility information about an unrelated condition.

Q16. What implications do you think pharmacogenetic tests might have for family members?

Most respondents recognised that pharmacogenetic tests would not only have implications for the patient but could also have an impact on family members. Family members might carry the same trait, and therefore might be interested in knowing their status, particularly if they were likely to use similar medicines at some point in their life. There could also be a psychological impact on family members. Questions about the responsibility of a patient or a physician to inform family members were raised.

Q17. In your view, are controversies likely to arise about who ultimately decides which treatment is prescribed in light of a pharmacogenetic test?

A number of different controversies were thought likely to arise as a result of pharmacogenetic testing. The primary concern was the possibility of disagreement between patients and physicians with regard to prescription. This might occur because a patient would like to be prescribed a medicine which the physician considers too dangerous or not effective enough. Several respondents noted that the decision to allow a treatment or not was ultimately the physician's decision and that physicians could not be obliged to act contrary to their clinical judgement.

> 'The Trust considers that there is some scope for controversies to arise if the tests are introduced without sufficient guidance for physicians and other healthcare professionals on how pharmacogenetic tests should be used in prescribing practice.' *Wellcome Trust*

Another area where controversy could arise was between healthcare providers and physicians. Physicians may, for example, consider a particular medicine and test appropriate for prescription, while bodies such as NICE did not recommend that the medicine or test was purchased by the NHS. In this situation, medicines could be available within the private healthcare system.

Several respondents, while noting the possibility that controversies might arise from pharmacogenetics, suggested that it would not result in any more conflict than existed at present and that it would not result in fundamental changes to the decision-making process.

Q18. Should patients be able to refuse a genetic test to determine response to medicines but still expect to receive a prescription?

The majority of respondents considered that a patient should, in principle, be able to refuse a genetic test and not be denied the related medicine as a result. Several respondents noted that the answer to this question would depend on the pharmacogenetic test in question:

> 'If the pharmacogenetic test has relatively poor power of prediction and the treatment has few serious adverse reactions, it may be relatively easy to accept a refusal of pharmacogenetic testing yet still prescribe the medicine. Other circumstances may make it more difficult to resolve this problem.' *Dr Abraham Rudnick*

Most considered that an assessment of the features of the disease, the associated test and the medicine, including whether it was licensed on the basis of a pharmacogenetic test and whether or not any alternatives were available would be appropriate in determining whether a patient could refuse a pharmacogenetic test and receive a medicine.

Q19. Do you think that the providers of health insurance should have access to pharmacogenetic information? What about other parts of the insurance industry, for example life insurance?

Respondents noted that pharmacogenetic information would be part of a patient's medical record. As such, the information was confidential and should only be disclosed with consent. Many respondents opposed the possibility that insurance companies could have access to pharmacogenetic information. Respondents pointed to the limited significance of pharmacogenetic information at present:

> 'Given current indications about the penetrance of genes associated with medicine metabolism it seems unlikely that the information revealed by pharmacogenetic testing will be of sufficient significance to alter the risk assessment made by underwriters…It is the risk of disease that is the principle determinant of insurability, at least at present.' *Genetics Interest Group*

The following response was received from *BUPA*:

> 'The former [Human Genetics Advisory Committee] took the view that while there was no reason in principle to refuse access to genetic information (as distinct from any other type of information that might be relevant to risk), such information should not in practice be made available to insurers until and unless the actuarial information linking the two was sound enough to provide a reliable assessment of risk. The same principle should apply to [pharmacogenetic] information… Insurers will have the right to ask for specific genetic information before agreeing to insure an individual or fixing the premium, in the way that they currently do with other information. It will then be up to the individual to decide whether or not to take out a policy and to supply the information as part of the agreement. If the insurer has already agreed to insure an individual there should be no subsequent right to demand genetic information that was not part of the original agreement.' *BUPA*

BUPA also noted the relevance of pharmacogenetics to the handling of claims within Private Medical Insurance (PMI):

> 'Pharmacogenetic information will be relevant to claims handling in PMI… We have already made decisions about funding care in oncology based on the receptors shown to be present in the members' tumours, and pharmacogenetics in relation to the metabolism of the non-cancerous cells of the body seems to us logically to be just an extension of that. The other relevant precedent is that we have the agreement of the [Department of Health] Genetics Unit that we may ask for the result of any BRCA1 or 2 gene test a member may have had, in connection with deciding whether we will make a discretionary payment to fund prophylactic mastectomy or oophorectomy in the light of their fears of cancer.'

The impact that the insurance industry could potentially have upon pharmacogenetics was discussed by several respondents:

> '[T]he perceived potential for misuse of pharmacogenetic information by insurance companies risks undermining the benefits of pharmacogenetic science as patients may be reluctant to consent to testing either in the clinic or in research.' *GlaxoSmithKline*

Race and ethnicity

Q20. Do you think that pharmacogenetics will increase the likelihood of the grouping of patients according to racial or ethnic groups for medical purposes? If so, what might be the ethical and social implications of such an outcome?

The responses to this question were mixed. Some suggested that pharmacogenetics might lead to increased grouping of patients according to ethnic groups. It was pointed out, however, that this was not a new phenomenon as many diseases were correlated with a particular ethnic group already (for example, Ashkenazi Jews and Tay Sachs disease). There was concern that in situations where a medicine was found to be less successful among a certain ethnic group, on average, clinicians may not treat any members of that ethnic group, even where particular individuals may still benefit.

> 'For example, a recent study of drugs used to treat heart disease demonstrated that a certain drug treatment was less successful among African-Americans than it was amongst Caucasians. On the basis of these results, some clinicians stopped prescribing the treatment for all African-American patients, even though some individuals could have benefited.' *Ms Katherine Morley and Professor Wayne Hall*

There was also concern that any increased grouping would result in fewer new medicines being developed for certain ethnic groups if they did not represent viable commercial targets.

Other respondents considered that pharmacogenetics was likely to reduce the grouping of patients according to their race or ethnic group, as they considered that race was likely to be less useful than the use of genotyping for predicting response to a medicine. The categories of ethnicity were thought likely to correlate poorly with predictions of response to medicines.

> 'Pharmacogenetics may reduce the grouping of patients according to their race or ethnic group for medical purposes as patient access would be on the basis of genotype rather than phenotype.' *GlaxoSmithKline*

Responses to the public consultation

The Working Party wishes to thank the following individuals and their organisations for their interesting and helpful responses:

Organisations

Anonymous (1)
Abbott Laboratories
Airedale Local Research Ethics Committee
Alzheimer's Society
American Society of Health-System Pharmacists
APRIL
Association of British Insurers
Association of Genetic Nurses and Counsellors
Australian Health Ethics Committee
BA Science and Public Affairs Forum
British Heart Foundation
British Medical Association
British Pharmacological Society
BUPA
Cambridge Genetics Knowledge Park
Cancer Research UK
European Federation of Pharmaceutical Industries and Association of the British Pharmaceutical Industry
Genetics Interest Group
Genewatch
GlaxoSmithKline
Hellenic National Bioethics Commission
Hereford & Worcester Local Research Ethics Committee
Indiana University Pharmacogenetics Discussion Group
Institute of Biology, Biomedical Sciences Committee
Institute of Clinical Research
Integrated Medicines Consulting
Life Sciences, LGC
London Ideas Genetics Knowledge Park
Lothian Research Ethical Committee
Mid Yorkshire Hospitals NHS Trust, Research & Development Committee
Millennium Pharmaceuticals
Pfizer
Pharmacogenetics Evaluation Policy, University of Cambridge
Royal College of General Practitioners, Committee on Medical Ethics
Royal College of Paediatrics and Child Health
Royal College of Physicians, Committee on Ethical Issues in Medicine
Royal College of Physicians, Joint Committee on Medical Genetics
Royal College of Radiologists
Royal Pharmaceutical Society of Great Britain
Scarborough and North East Yorkshire Local Research Ethics Committee
Southmead Local Research Ethics Committee
Variagenics, Inc

Wakefield District Research Ethics Committee
Wellcome Trust
West Birmingham Research Ethics Committee

Individuals

Anonymous (4)

Professor Lembit Allikmets
Department of Pharmacology, University of Tartu, Estonia

Kiain Balloch
Forth Valley Ethics of Research Committee

Dr Juan A Camacho & Dr. Francesc Abel

Dr Philip Cartwright
Consultant, Princess Royal Hospital NHS Trust

Dr J B Chapman

HH Judge Christopher Compston

Professor Angus Clarke
Department of Medical Genetics, Cardiff University

Dr Oonagh Corrigan
Centre for Family Research, University of Cambridge

Professor Gisela Dahlquist & Associate Professor Peter Hoglund
Working Group for Medical Research Ethics at the Swedish Research Council

Professor Stephen Denyer
Head, School of Pharmacy & Biomolecular Sciences, University of Brighton

Professor Karniyus Gamaniel
National Institute for Pharmaceutical Research and Development, Nigeria

Dr Seymour Garte
Genetics Research Institute, Italy

Dr Joseph Hackett
Office of In Vitro Diagnostic Device Evaluation and Safety, Food and Drug Administration

Dr Adam Hedgecoe
Department of Sociology, University of Sussex

Dr Andrew Herxheimer
Emeritus Fellow, UK Cochrane Centre

Mrs Valerie Inglis
Forth Valley Ethics of Research Committee

Dr Ian Jessiman
Mr Robert King
Broadmoor Local Research Ethics Committee

Professor K R Lees
University of Glasgow

Professor Roberto Llanos-Zuloaga
President, Peruvian Society of Bioethics

A.M. MacConnachie
Chair, Tayside Committee on Medical Research Ethics

Dr Juan Carlos Maldonado
Pharmacology Unit, Central University of Ecuador

Ms Katherine Morley & Professor Wayne Hall
Office of Public Policy and Ethics, University of Queensland

Mr Peter Nilsson
Peterborough and Fenland Local Research Ethics Committee

Ms Gail Pascoe
Director of Planning, Colchester Primary Care Trust

Mr Bob Pearson

Professor Munir Pirmohamed
University of Liverpool

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Glossary

Abacavir: A medicine used in the treatment of HIV/AIDS.

Adverse reaction: An untoward medical occurrence caused by and arising after the administration of a medicine under normal conditions of use.

Allele: A variant form of a *gene*, which differs in DNA sequence from alternative alleles of the same *gene*.

Amino acid: A molecule which serves as the building block of *proteins. Proteins* have different characteristics as determined by the sequence of *amino acids. Genes* specify this sequence.

Candidate gene: A *gene* suspected of contributing to a disease or trait by virtue of knowledge of its function and/or chromosomal position.

Chromosome: The thread-like *DNA* in a cell is divided into several separate lengths. Each length forms a structure called a chromosome. Most mammalian cells contain two copies of every chromosome, with the exception of sex chromosomes in males. Human cells contain 23 pairs of chromosomes.

DNA (deoxyribonucleic acid): The chemical substance of which a *gene* is made and which encodes genetic information.

Efficacy: The power of a treatment to have an effect.

Gene: The fundamental physical and functional unit of heredity consisting of a sequence of *DNA*, occupying a specific position within the *genome.*

Gene expression: The process by which information contained in a *gene* is transcribed to produce functional *RNA* molecules which are then translated to produce *proteins.*

Genetic exceptionalism: The view that genetic information is qualitatively distinct from other medical information.

Genetic marker: Any *locus* that, by virtue of allelic variation between individuals, serves to distinguish one group of *chromosomes* from another at a particular location. Depending on the context, *microsatellites, SNPs* and *polymorphisms* in *proteins* may all serve as genetic markers.

Genetic test: 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 *DNA* of an individual, or indirectly, by examining the products of their *DNA*, such as *RNA* or *proteins*. 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.

Genetic variation: The presence of different combinations of *alleles* in different individuals in a population.

Genome: The total genetic complement of an individual or of a species.

Genotype: An individual's genotype is their entire genetic constitution, as distinguished from their physical characteristics. See also *phenotype*.

Glivec (imatinib): A medicine used in the treatment of chronic myeloid leukaemia.

Haplotype: A specific combination of linked *alleles* in a cluster of related *genes*.

Herceptin (trastuzumab): A medicine used in the treatment of breast cancer.

Heterozygote: An individual is said to be a heterozygote when the two *alleles* at a particular *locus* are different.

Homozygote: An individual is said to be a homozygote when the two *alleles* at a particular *locus* are identical.

Locus: The site of a specific *gene* on a *chromosome*.

Metabolism: The process by which the body breaks down and converts medication into active chemical substances.

Metastasis: The spread of malignant cells from the original site of the cancer to another part of the body.

Molecular genetics: Molecular genetic methods involve studying genes at the level of the *nucleotide* sequence.

Mutation: The modification of a *DNA* sequence that can potentially result in a change in the function of a *gene*. Mutations may be caused by mistakes during cell division, or they may be caused by exposure to DNA-damaging agents in the environment. Mutations can be harmful, beneficial, or have no effect. If they occur in cells that make eggs or sperm, they can be inherited; if mutations occur in other types of cells, they are not inherited.

Nucleotide: Nucleotides are the subunits from which *DNA* and *RNA* molecules are assembled. A nucleotide is a base molecule (adenine, cytosine, guanine or thymine in DNA; adenine, cytosine, guanine or uracil in RNA), linked to a sugar molecule and phosphate groups. Nucleotides combine in groups of three to code for *amino acids.*

Orphan medicine: A medicine used to treat diseases that occur rarely and where there is no hope for recovery of development costs, so there is little financial incentive for industry to develop them.

Over-expression: Greater than normal production of a gene product, for example a *protein* or *RNA* molecule, from a *gene*. Many animal studies involve the over-expression of a *gene* in order to determine the function of its product. See also *under-expression.*

Pharmacodynamics: How a medicine works in the body.

Pharmacokinetics: The processes and rate at which a medicine passes through the body.

Pharmacogenetic test: A test to detect the presence or absence of, or change in, a particular gene or chromosome in order to predict response to a medicine. The test could examine inherited DNA or somatic mutations in DNA.

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. The research involves comparing the genotypes of individuals who have different responses to a medicine.

Pharmacogenomics: This term 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.

Pharmacology: The study of how a medicine acts in the body. It involves the consideration of both *pharmacokinetics* and *pharmacodynamics.*

Phenotype: The observable or measurable traits of an individual as produced by its *genotype* and the *environment.*

Polygenic: A disease or trait is said to be polygenic when it is influenced by more than one *gene*.

Polymorphism: Where two or more *alleles* exist for a *gene*, such that at least two of the *alleles* are present in more than 1% of the *chromosomes* in a population.

Protein: Proteins are biological molecules that are essential for all life processes and are encoded by an organism's *genome*. A protein consists of chains of *amino acid* subunits and its function depends on its three-dimensional structure, which is determined by its *amino acid* sequence.

RNA (ribonucleic acid): A single stranded nucleic acid molecule comprising a linear chain made from four *nucleotides,* whose sequence determines the informational content of the molecule. RNA is produced by *transcription* from *DNA* and may either be translated into *protein* or may itself play a functional role.

Quality Adjusted Life Years (QALYs): An arithmetic product of the number of life years gained by an intervention and the quality of life during these years. In effect the value of an added year is adjusted to take into account deterioration in the quality of life.

Single nucleotide polymorphism (SNP): SNPs are single DNA base pair variations. In genetic research they may be used as *genetic markers* to locate *genes* that cause disease or influence other traits. Most SNPs fall within the non-coding regions of human *DNA* and make no difference to the individual.

Transcription: The process by which a *gene's DNA* sequence is copied into *RNA*.

Translation: The process by which RNA directs the synthesis of a protein.

Under-expression: Lower than normal production of a *gene* product from a *gene*. See also *over-expression.*

Glossary of abbreviations and acronyms

ABPI	Association of the British Pharmaceutical Industry
ACGT	Advisory Committee on Genetic Testing
AIDS	Acquired Immunodeficiency Syndrome
ALDH	Aldehyde dehydrogenase
ALL	Acute lymphoblastic leukaemia
CML	Chronic myeloid leukaemia
CPMP	Committee for Proprietary Medicinal Products
CSM	Committee on the Safety of Medicines
DOH	Department of Health
DNA	Deoxyribonucleic acid
DPA	Data Protection Act 1998
EFPIA	European Federation of Pharmaceutical Industries and Associations
EMEA	European Medicines Evaluation Agency
EU	European Union
FDA	Food and Drug Administration (US)
GAIC	Genetics and Insurance Committee
GP	General practitioner
GSK	GlaxoSmithKline
HIV	Human immunodeficiency virus
HGAC	Human Genetics Advisory Commission
HGC	Human Genetics Commission
MCA	Medicines Control Agency
MDA	Medical Devices Agency
MHRA	Medicines and Healthcare products Regulatory Agency
MRC	Medical Research Council
NHS	National Health Service
NHSIA	NHS Information Authority
NAW	National Assemblies of Wales
NICE	National Institute for Clinical Excellence
ODA	Orphan Drug Act 1983 (US)
PHARMAC	Pharmaceutical Management Agency (New Zealand)
QALY	Quality-adjusted life year
RNA	Ribonucleic acid
SNP	Single nucleotide polymorphism
TPMT	Thiopurine methyltransferase
UK	United Kingdom
US	United States of America
VNTR	Variable number of tandem repeats

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