

# 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).<sup>1</sup>

## 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

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<sup>1</sup> 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).<sup>2</sup> 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).<sup>3</sup> 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

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

<sup>3</sup> 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 (EMA) 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.<sup>4</sup> 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

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<sup>4</sup> 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.<sup>5</sup> 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.

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<sup>5</sup> 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-rationally 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.<sup>6</sup> **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

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<sup>6</sup> 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).**