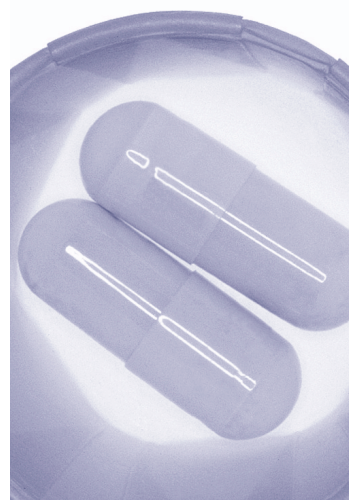
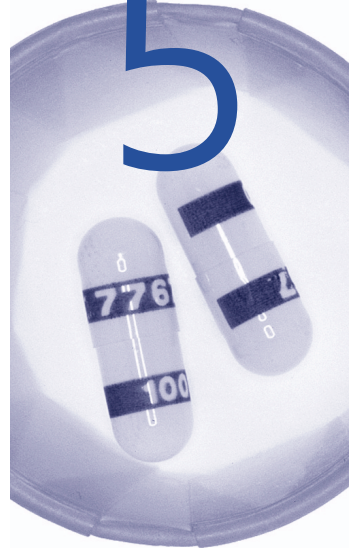
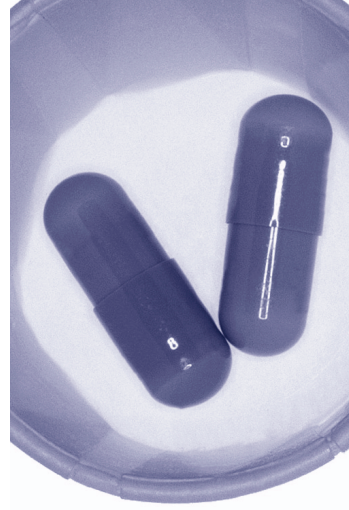


# Chapter

Ethical issues in  
treatment and  
clinical practice

5





# 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.<sup>1</sup> 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

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<sup>1</sup> 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.<sup>2</sup> 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.<sup>3</sup>
- 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.<sup>4</sup> **We recommend that initiatives to provide independent and impartial**

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

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

<sup>4</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.

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

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<sup>5</sup> Human Genetics Alert (2002) Evidence gathered as part of the Human Genetics Commission's consultation for Genes Direct. Available: [http://www.hgc.gov.uk/genedirect/evidence\\_hga.htm](http://www.hgc.gov.uk/genedirect/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.<sup>6</sup> 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.<sup>7</sup> 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-

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<sup>6</sup> 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](http://www.camh.net/research/research_ar2001/pharmacogenetics.html). Accessed on: 20 May 2003.

<sup>7</sup> 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.<sup>8</sup> 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.<sup>9</sup> 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.’<sup>10</sup>
- 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

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

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

<sup>10</sup> 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.<sup>11</sup> 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.’<sup>12</sup>

## ***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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<sup>11</sup> The lead researcher was Dr Darren Shickle, University of Sheffield. Further information about the survey is available at [www.shef.ac.uk](http://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.)

<sup>12</sup> 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.<sup>13</sup> 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.'<sup>14</sup>

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

<sup>13</sup> Nuffield Council on Bioethics (1993) *Genetic screening: ethical issues* (London: Nuffield Council on Bioethics); Human Genetics Advisory Commission (1997) *The 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.

<sup>14</sup> 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.**