Chapter 3

Research and development of new medicines
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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. 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

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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.
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. 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. 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.
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’. 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. 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. 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.

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.
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

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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. 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. 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. 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. 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

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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. 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. 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. Some researchers have suggested that the CYP2C9*2 and CYP2C9*3 variants are


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


\textsuperscript{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.
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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

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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.


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.\textsuperscript{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.\textsuperscript{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?


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. The paper emphasises the urgent need for harmonised terminology for protocols and guidelines including pharmacogenetic testing. 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

<table>
<thead>
<tr>
<th>Sample labelling code</th>
<th>Link between subject and data?</th>
<th>Records identifiable for clinical monitoring</th>
<th>Withdrawal of consent</th>
<th>Return of individual results?</th>
<th>Scope of subject’s privacy protection</th>
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<tr>
<td>Identified</td>
<td>Yes, directly</td>
<td>Yes</td>
<td>Sample can be withdrawn with immediate effect for any prospective use</td>
<td>Possible</td>
<td>Similar to general healthcare confidentiality</td>
</tr>
<tr>
<td>Single-coded</td>
<td>Indirectly via a code key</td>
<td>Yes, via protocol specified procedures</td>
<td>Sample can be withdrawn with immediate effect for any prospective use</td>
<td>Possible</td>
<td>Standard for clinical research</td>
</tr>
<tr>
<td>Double-coded</td>
<td>Indirectly, via two code keys</td>
<td>Yes, via protocol specified procedures</td>
<td>Sample can be withdrawn with immediate effect for any prospective use</td>
<td>Possible</td>
<td>Standard for clinical research</td>
</tr>
</tbody>
</table>


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).
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.’

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. 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

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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.


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

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


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.
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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.