The Implications of Pharmacogenetics and Pharmacogenomics for Drug Development and Health Care

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Introduction

The completion of the first draft of the human genome project has raised enormous expectations, not only in terms of identifying genetic predisposition to disease, but also in improving drug therapy through the development and use of personalised medicines. This area of research, which is called pharmacogenetics or pharmacogenomics, is currently fashionable, and promises benefits for both the pharmaceutical industry and the patient. There are however many obstacles (technological, regulatory, social and ethical) that have to be overcome before (or if ever) the potential benefits are realised. The purpose of this chapter is to critically review this area, and the potential benefits that may accrue from it.

Definitions

Pharmacogenetics can be defined as the study of variability in drug response due to heredity. It is not a new term having been coined by Vogel in 1957 (see Pirmohamed, 2001). More recently, the term *pharmacogenomics* has also been introduced. The terms are often used interchangeably as there is no standard definition. However, for the purposes of this chapter, the term pharmacogenomics will be used in a wider sense to denote:

- all genes in the genome, and the variation within those genes, that may determine drug response; and
- the differential effects of different compounds on gene expression.

Therefore, pharmacogenomics, through examination of individual response profiles and elucidation of the differential effects of different compounds on gene expression, may ultimately lead to target identification, drug discovery and compound selection. Lindpaintner has suggested that pharmacogenetics should be used to refer to differences between patients, while pharmacogenomics should be used to refer to differences between compounds (Lindpaintner, 2002). This chapter mostly concentrates on pharmacogenetics, although where relevant, we also discuss relevant aspects which fall into the category of pharmacogenomics.

Current state of drug development and drug use

The whole process of drug development is extremely expensive. Industry-funded sources put the cost at approximately €500-800 million per marketed drug (Anon, 2001, DiMasi, 2002, DiMasi et al, 2003), although others suggest the figure is considerably lower (Henry et al, 2002; Public Citizen, 2001). It is time consuming, with each drug taking approximately 10-15 years to reach the market after discovery of the compound (Anon, 2001). In addition, there is a high attrition rate with only one out of every 5000 chemical compounds considered to have a therapeutic potential being successfully developed for clinical use. The number of new applications submitted to regulatory agencies for approval has shown a decrease almost every year over the last 5 years. For example, the US Food and Drug Administration (FDA) approved only 15 new drugs in 2002, compared with a 5-year annual average of 31.The trend is less noticeable in Europe, with the European Medicines Evaluation Agency (EMEA) approving 13 new products in 2002 compared with 14 in 2001 (5 year average 15.4) (Frantz and Smith, 2003). Nonetheless, data provided by the industry-funded Centre for Medicines Research suggests there was a steady decline in the number of new active substances submitted to the major regulatory authorities from 1997 to 2001, as well as a decline in the number approved between 1999 to 2001 (CMR, 2002). The incorporation of

pharmacogenomics into the drug development process has the potential to improve target identification, accelerate the development process and reduce the attrition rate.

The problems for both pharmaceutical companies and healthcare systems do not stop after a drug has been marketed. It is becoming increasingly clear that there is marked variability in the way individuals respond to drugs, in terms of both efficacy and toxicity (Evans and Johnson, 2001). For example, there is a 20-fold variation in the dose of warfarin required to achieve optimal anticoagulation across patients. Marked variability in efficacy has been demonstrated for compounds in almost every therapeutic class (Table 16.1). Adverse drug reactions are also a major problem (Pirmohamed and Park, 2001): almost 4 per cent of the compounds that were originally licensed by the UK Medicines Control Agency were later withdrawn because of safety problems (Jefferys et al, 1998), which has enormous financial implications for the industry and undermines public trust. EMEA figures show a similar picture, with 16 withdrawals from a total of 241 marketing authorisations since 1995 (EMEA 2003). Adverse drug reactions account for 5 per cent of all hospital admissions and increase the length of stay in hospital by 2 days at an increased cost of approximately US$2500 per patient (Pirmohamed et al, 1998). A meta-analysis in the US suggested that adverse drug reactions killed over 100,000 patients in 1994, making them the 4th most common cause of death (Lazarou et al., 1998). A recent systematic review attempted to quantitate the role of polymorphisms in drug metabolising enzyme genes in predisposing to adverse drug reactions (Phillips et al, 2001). Of the 27 drugs most frequently cited in adverse drug reaction studies, 59 per cent were metabolised by at least 1 enzyme with a variant allele associated with reduced activity, compared with 7-22 per cent of randomly selected drugs. This provides circumstantial evidence that dose alteration through a knowledge of the patient's genotype may have prevented some of these adverse reactions. However, it is important to note that the design of the study (relating published adverse drug reaction studies with review articles of drug metabolising enzyme gene polymorphisms) demonstrates an association and may not necessarily be causative. Furthermore, it does not take into account the fact that adverse drug reactions are likely to have more than one genetic predisposing factor.

It is difficult to calculate the likely cost savings in terms of reduced drug toxicity and/or improved efficacy because there are relatively few practical examples and little evidence based on actual clinical practice. Additionally, adverse reactions and efficacy are invariably the outcome of both genetic and non-genetic factors. Nonetheless, the potential benefits, in both health and economic terms, are considerable. However, therapeutic intervention based on individuals' genetic variation will not be applicable to all drugs and careful evaluation of cost effectiveness will be needed on a case-by-case basis (Veenstra et al 2000; Phillips et al 2001).

The incorporation of pharmacogenetics into clinical practice therefore has the potential to improve efficacy and reduce toxicity, by allowing the choice of the right drug for the right patient in the right disease at the right dose. This also represents a culture change in clinical practice: currently the practice of evidence based medicine is dependent on data from randomised controlled trials and meta-analyses, with the choice of appropriate treatment being dictated by an analysis of the whole population. Successful incorporation of pharmacogenetics will therefore lead to greater consideration of the individual rather than the whole population in the choice of drug. There are also many ethical issues that need to be considered, many of which are discussed in this chapter, and have also been addressed in the recent document from the Nuffield Council on Bioethics (2003).

Biological basis of pharmacogenetics and pharmacogenomics
Of the 3 billion base pairs in the human genome, 99.9 per cent are identical between different individuals. Variability that is observed in 0.1 per cent of the genome is thought to account for

this variability in drug responses.   Single nucleotide polymorphisms (SNPs) account for 90 per cent of the variability and are observed once every 500-1000 base pairs. The focus of pharmacogenetics has therefore largely been on SNPs, not only because they are the most common, but also because they are the most technically accessible class of genetic variant (Roses, 2000). By definition, a SNP occurs in at least 1 per cent of the population, and those which have been mapped are freely available on the worldwide web (http://snp.cshl.org). Combinations of SNPs on the same DNA strand can be inherited together to form a haplotype. It has been suggested that the haplotype pattern may be more important in determining drug response and disease predisposition than individual SNPs. For this reason, there is currently an on-going effort to map the haplotype structure of the human genome, which will also be freely available on the web. Looking further into the future, using whole genome scanning, it may be possible to correlate SNP and haplotype profiles in an unbiased fashion to drug response, but there is a need to develop cost-effective technologies to undertake this.

There have also been major advances in pharmacogenomic technologies, for example with microarrays (gene chips) and proteomics (the systematic study of protein expression within a whole organism). Drugs can have major effects on gene and protein expression, which may ultimately determine drug response. The ability to analyse changes in gene expression and protein profile on drug exposure in different tissues and in different patients, as well as the analysis and identification of disease categories, allied to the advances in bioinformatics, will provide us with unparalleled opportunities to identify new drug targets, novel candidate genes determining drug response, and allow the development of medicines targeted to individual disease subtypes. These technologies and developments therefore herald major potential changes for pharmaceutical companies, healthcare organisations and patients.

Pharmacogenomics and pharmacogenetics and the drug development process
Pharmacogenomics and pharmacogenetics may have a potentially beneficial effect on all aspects of the drug development process (Figure 16.1). These are considered in detail below.

*Target identification***:** Drugs currently on the market act on less than 450 of the estimated 10,000 targets in the human proteome (Norton, 2001). Target diversity is also limited, with 75 of the top 100 drugs acting on 4 families of molecular targets; G-protein coupled receptors are the commonest site of action. Proteomic and genomic technologies may increase the diversity of targets available for future medicinal products through:
- identification of novel proteins involved in disease processes;
- targeting of proteins with variant structure resulting from the presence of genetic polymorphisms;
- identification of mechanisms of action of currently used drugs and refinement of targeting to improve specificity of drug action;
- development of compounds with specific actions in disease sub-types; and
- increase specificity of drug action and thereby improvement in drug safety by reducing secondary targeting responsible for adverse effects.

It must be stressed however that these are theoretical possibilities and application on a large scale is eagerly awaited.

*Pre-clinical drug development***:** Pharmacogenetics has already had an impact on this phase of drug development – arguably this has been the major benefit to date of pharmacogenetics. It has been known for many years that individuals vary in their ability to metabolise certain drugs. The identification of the molecular defects underlying phenotypic variability has led to the development of *in vitro* screens. For example, a major advance has been the

development of cell lines expressing drug metabolising enzymes, such as the cytochrome P450 enzymes. These are the most versatile group of biological catalysts known to exist in nature and are involved in the metabolism of many of the currently used drugs. This allows assessment of the interaction of a drug with a particular enzyme such as a P450 enzyme at an early stage of development, and the subsequent prediction of polymorphic metabolism in man and the possibility of drug-drug interactions (Park and Pirmohamed, 2001). The finding that a drug is a substrate for a polymorphically expressed drug metabolising enzyme often leads to abandonment of further development. However, if the drug is developed, it also provides an opportunity to warn prescribers through appropriate warnings in the Summary of Product Characteristics (SPC). As our knowledge increases, such screens may be extended to the protein targets on which drugs act, such as ion channels and receptors.

A further development in pharmacogenomics has been the use of gene expression profiling in order to predict toxicity; indeed, a large amount of money is being spent on developing databases of gene expression profiles with known toxicants in the hope that this will allow future candidate selection and reduce attrition rates later in the development process. Although this may help in certain situations, where the adverse effect depends on an idiosyncratic feature found only in a small proportion of patients, it is unlikely that the gene profiling patterns developed through animal studies will be of use in humans. It is also important to note that such screens will not be absolutely predictive, and therefore will not replace animal experimentation (Lindpaintner, 2002). However, it is possible that these screens, because of their high throughput nature, will allow more focused animal experimentation, leading to a reduction in the total number of animals tested, and thereby savings in time and cost.

Phase I-III studies: These clinical studies, which provide the basis for regulatory approval, range from "first in man" kinetic and tolerability studies (phase I) in small numbers of healthy volunteers to the large randomised clinical trials designed to assess the efficacy of a compound (phase III). The typical cost of a phase I study is $7 million, but jumps to $43 million for a phase III study. Pharmacogenetics may lead to refinement of phase I studies by focusing on individuals with known genotypes defined through pre-clinical testing (Brazell et al, 2002). An earlier identification of problems may lead to the compound being dropped during phase I rather than in phase III, with considerable savings in development costs. In phase II, there may be further refinement of the pharmacogenetic determinants of drug response, which may provide information necessary for design of the phase III studies. The net effect may be a reduction in sample size for phase III studies, which may in turn result in more efficient and quicker drug development, and a net reduction in cost (Brazell et al, 2002). It must be stressed that although smaller numbers of patients will be required in phase III, there is a possibility that more individuals will need to be studied during phases I and II in order to provide adequate power to identify the pharmacogenetic determinants of drug response. The net effect may be a more streamlined drug development process whereby potentially toxic or inefficacious compounds are screened out and abandoned at an earlier stage, while compounds that make it to phase III studies are more likely to reach clinical use. However, the response of regulatory agencies to pharmacogenetics-based clinical trials remains unclear at this time, although they are increasingly supportive of the concept of personalised medicine.

Phase IV studies: Phase IV refers to the period after the drug is licensed; studies take several forms ranging from hypothesis-generating spontaneous reporting to hypothesis-testing pharmacoepidemiological studies, and can continue for the whole period the drug is on the market. Historically, less effort has been expended on improving post marketing surveillance than harmonisation of marketing authorisation procedures and creation of a single market

(Abraham and Lewis, 2000). For both therapeutic and social reasons, existing pharmacovigilance systems may need to be considerably strengthened in order to "fine tune" pharmacogenetics-based treatment regimes across different patient populations and encourage public acceptance.

Since phase IV involves exposure of large numbers of patients to the drug, detection of rare adverse events usually occurs in this phase. Storage of DNA samples from patients treated with the drug in this phase may allow pharmacogenetic testing and identification of genetic predisposing factors, which will further allow an improvement in the risk-benefit ratio. This is perhaps best exemplified by abacavir hypersensitivity, where studies post-marketing have identified a major genetic predisposing factor in the MHC locus (Mallal et al, 2002; Hetherington et al, 2002). However, a note of caution needs to be added here: since detection of adverse events is a function of the power of the studies, any reduction in the total number of patients studied in phase III may lead to the statistical need for larger, more structured phase IV studies in order to identify rare and long-term toxicities. Prospective collection of DNA samples is a possibility in phase IV (Roses, 2000), but would be expensive. The cost of this may have to be borne by the pharmaceutical industry, but whether this may result in a more expensive product, and hence a shift in cost to healthcare, is unclear at present.

Phase IV also involves assessment of alternative uses of the drug; these studies may, in fact, be more streamlined given that pharmacogenetic determinants of efficacy will already have been identified prior to marketing.

Nature of pharmacogenetic tests: The aim of pharmacogenetic studies will be to provide a DNA-based test that allows determination of efficacy or toxicity before the patient takes the drug with a high degree of sensitivity, specificity and accuracy. However, it is important to appreciate that it is unlikely that such a test will be absolutely predictive, and will provide probabilistic information; for example, there is a 70 per cent chance of developing a severe adverse reaction with drug A. Furthermore, pharmacogenetic testing is unlikely to be dependent on one gene that determines efficacy or toxicity. It is more likely that the response to a drug, either efficacy or toxicity, will be dependent upon a number of genes, and these genes in combination may provide adequate sensitivity and specificity and therefore accuracy in determining drug response (Pirmohamed and Park, 2000). The pharmacogenetic test may have been developed by the same company developing the drug, or in collaboration with a separate diagnostics or genomics company, and will require approval as part of the drug registration process. In other words, pharmacogenetic-based therapy is likely in some cases to take the form of a "kit" comprising the drug plus diagnostic test. There may well be a proprietary-driven "lock-in" with such an arrangement, with intellectual property rights surrounding not only the kit but the mechanism linking genotype/drug interaction. This may have important cost implications for reimbursement decisions and health care budgets generally.

It is usually assumed that pharmacogenetics will proceed from observation that exposure to a drug generates a differential response; identifying the predictive marker for that response; and then creating a diagnostic product that will then be co-marketed with the drug ('the right medicine for the right patient'). In contrast, others predict this process may well be reversed, with drug development based on diagnosis of new disease (sub) types, arising from improved knowledge of the molecular basis of diseases. Accordingly, the development and marketing of diagnostic tests becomes the 'driver', rather than such tests being seen as an "add-on" to the drug development process, and maintenance of the conventional practice of treatment based on differential diagnosis. (Lindpaintner (2002). Additionally, it appears that the same, or similar genetic pathways may be active in more than one disease state. Therefore, a wide

range of diagnostic products may be available in the future, some of which may have quite wide application, whilst others will be closely tied to a specific therapeutic product.

Any test developed after licensing, for example for an adverse reaction, will have to undergo a separate approval process, and a variation in licensing indications, the nature of which will depend on the accuracy of the test. The nature of the approval process for the pharmacogenetic test is unclear at present, but may well require a different set of standards which fall somewhere among a diagnostic device, a drug therapy and a clinical service. Responsibility for the regulation of genetic tests is in a state of flux. Although the FDA is responsible for regulating tests in the US, in Europe, this is not the responsibility of the EMEA, but this may well have to change for genotype-guided therapy. Presently, the regulation of in vitro tests in the European Union is the responsibility of member states, often through separate national device agencies, although some states have recently merged device regulation with the regulation of medicinal products.[1]

In Europe, the In-Vitro Diagnostic Medical Devices Directive regulates products used to examine substances derived from the human body, with the aim of achieving consistent interpretation and implementation across the EU. The Directive came into effect in June 2000, with a transition period until December 2003. There is pressure for harmonisation of device regulation at the European level, although some states, such as the UK, remain opposed to this step. There are also efforts to achieve global harmonisation across different regions, similar to that for medicinal products achieved through the International Conference on Harmonisation (ICH).

Salvaging of drugs: Another possible benefit, and therefore a positive economic impact, of pharmacogenetics will be the possible salvaging of beneficial drugs – so-called "drug rescue". Many drugs have been withdrawn from the market because of an unacceptable frequency of adverse drug reactions occurring in the minority of patients. For example, as noted earlier, it is stated that 4 per cent of all drugs licensed by the Medicines Control Agency in the U.K. were withdrawn because of adverse drug reactions (Jefferys et al, 1998), and a similar percentage have been withdrawn by the EMEA after approval via the centralised procedure. The withdrawal was to protect the minority who developed the adverse drug reaction, at the expense of the majority who benefit from the drug without developing any adverse drug reactions. Thus, pharmacogenetic testing gives us a possibility of rescuing drugs that are beneficial in a large percentage of the population and avoiding their use in those who had adverse reactions. This is an important aspect to consider given the paucity of new drugs in the drug development pipeline at present.

There is conflicting evidence as to whether major pharmaceutical companies will wish to engage in this type of pharmacogenetics product because of the perceived risks involved. However, if large companies decide against developing such products, smaller "niche" companies may well decide "drug rescue" is financially worthwhile. Drug companies withdraw drugs at two stages, during clinical trials and after approval and introduction to the market. Media attention surrounding withdrawals tends to focus on 'blockbuster drugs' already on the market. However, the majority of withdrawals occur during clinical trials – i.e. during the drug development process, rather than post-marketing - and this type of 'drug rescue' (i.e. reducing attrition) is perhaps likely to be most significant.

Economic impact of pharmacogenetics: The likely economic impact of pharmacogenetics upon the development of new medicines will depend on the disease being treated and whether other therapies are already available to treat that particular disease. Furthermore, the characteristics of the drug being developed, its therapeutic index and the characteristics of the

pharmacogenetic test (its sensitivity, specificity and accuracy) will also act as determinants of the economic impact of a particular medicine. On the positive side, pharmacogenetics may allow more efficient and quicker drug development by reducing the number of patients that require drug exposure during Phase III of the development process. Since a large percentage of the expenditure of new drug development goes in the clinical phases and particularly in Phase III, reduction in the number of patients in Phase III should allow a corresponding reduction in drug development costs. Furthermore, the demonstration of a homogenous therapeutic response with absence of (or reduction) of adverse reactions may increase the likelihood of the drug passing through the licensing process. It will also reduce the chances of the drug being withdrawn from the market since those individuals susceptible to developing adverse drug reactions, a major cause for drug withdrawal, should be excluded from drug exposure.

On the negative side, however, pharmacogenetic tests will almost certainly reduce the number of patients who are likely to receive the drug, as those with a different pharmacogenetic profile will be classed as non-responders. In others words, pharmacogenetics-based treatment is characterised by patient segmentation. This will therefore reduce the market uptake of the drug, and perhaps will end the era of blockbuster drugs. Whether a drug is developed for a particular condition will depend on a complex set of scientific, regulatory and commercial factors. For example, there are likely to be differences *within* pharma companies as regards the (commercial) merits of pharmacogenetics-based drug development. It is also important to note that the reduction in the number of patients exposed during Phase III studies will necessitate careful post marketing surveillance to ensure that serious idiosyncratic drug reactions are detected as early as possible after the drug goes onto the market, as discussed above.

Pharmacogenetics and regulatory issues
How regulatory agencies such as the EMEA and FDA will deal with the whole area of pharmacogenetics in terms of clinical trials, licensing and labelling is not clear at present. As the predictive power of pharmacogenetic testing increases, labelling is likely to become more prescriptive (Robertson et al, 2002). Many of the guidelines in place for drug development do not encompass the new technologies, and thus new guidelines will have to be developed, an issue acknowledged by both the FDA and EMEA. What is clear is that the FDA and, increasingly, the EMEA, are actively supporting introduction of pharmacogenetics-based therapy (Lesko and Woodcock 2002), with regular meetings with industry and discussion of 'safe harbour' type arrangements to encourage joint discussion of the 'meaning' and interpretation of pharmacogenetics data.

There are many drugs currently on the market that have information on their SPC relating to polymorphic drug metabolism, for example, when they are metabolised by CYP2D6, one of the cytochrome P450 metabolising enzymes. In the future, when a drug has been shown to be efficacious in patients with a certain genotype, the indication in the SPC will have to reflect this. Therefore, the drug will be licensed not only for a particular condition, but will also be recommended for use in patients with certain genotypes. This is exemplified by the SPC for trastuzumab (Herceptin) in breast cancer. Any prescribing for patients without the particular genotype will therefore have to be considered to be outside the licensed indication. Labelling will also have to disclose recommended dosage based on stratified patient groups according to genotype profiles. Clearly there are major issues here concerning how instructions for use will be encouraged or enforced (if, indeed, they should be enforced). Doctors currently have the right to prescribe "off-label" and it is difficult to see why this would change. Indeed, regulatory agencies increasingly recognise off-label use for patient groups not included in the original approval or to extend indications. How regulatory agencies will ensure appropriate

prescribing of medicines based on pharmacogenetic principles remains an outstanding question.

It is unlikely that pharmacogenetics testing will become part of regulatory requirements for all drugs. The need for pharmacogenetic testing for a particular drug will depend upon many factors, in particular on the genetic factors determining its disposition, pharmacodynamic characteristics, and its therapeutic index. Therefore, a drug that has a high degree of efficacy in a large percent of the population, shows little inter-individual variability in kinetics and dynamics and has a wide therapeutic index should not necessarily require pharmacogenetic testing, and indeed it would not be cost effective to test every patient prior to drug prescription. By contrast, a drug that is efficacious in 30 per cent of the population and has a narrow therapeutic index, as is found with some antipsychotics at present, should arguably be subject to pharmacogenetic testing prior to prescription. Pre-clinical studies should be able to identify the routes of metabolism and disposition of any particular drug, and its mechanism of action. If any of these parameters are subject to genetic polymorphism that could theoretically or in practice effect the response to the drug, then pharmacogenetic testing should be encouraged. Therefore, in terms of drug development constant dialogue between pharmaceutical companies and drug regulatory agencies will be important to ensure that the drug development process is as efficient as possible, but does not necessarily lead to cuts in standards.

Another issue to consider is that we may end up with some patients having an "orphan genotype", i.e. a genotype that cannot be treated with currently available drugs because those patients have been classed as non-responders or as susceptible to particular adverse reactions. This by definition will represent a small proportion of the population, and may lead to pharmaceutical companies being reluctant to develop new medicines because of their potential unprofitability. In such cases, further regulatory measures may be needed so that these orphan genotypes are treated in the same way as orphan diseases are treated at present (Motl et al, 2003). This may provide financial incentives for the pharmaceutical industry to develop medicines for small patient populations with these orphan genotypes. Alternatively, as already mentioned, smaller genomics/drug development companies may enter such markets, in a similar way to the orphan drug market. Since many more medicines could fall into the category of 'orphan' products because of a reduced market, pharmaceutical companies might seek extension of orphan drug legislation in order to obtain development subsidies. On the other hand, treatments that are not commercially viable at present may well become viable with reduced clinical trial costs through pharmacogenetics. In other words, 'orphan patients' could stimulate new drug development. To qualify for orphan drug status in the USA, companies must demonstrate that there are less than 200,000 potential users of the drug, and similar legislation exists in the EU. However, defining the prospective patient population is often not straight forward, and hence is a potential source of conflict between regulators and industry. This has already been observed in the case of Herceptin, where orphan drug status was refused by the FDA.

Pharmacogenetics and the health service
The development of genotype-guided therapies will potentially result in a shift in costs of drug development from the pharmaceutical sector to the healthcare sector. For example, while the costs of drug development to the pharmaceutical industry up to licensing will be reduced through a more efficient streamlined drug development process, the use of the drug after licensing will incur the combined cost of the drug and the pharmacogenetic test. There is therefore a danger that new drugs developed with the aim of being prescribed to certain genotypes will prove to be too expensive for healthcare systems to introduce.

Where the costs of healthcare are met by a state-funded national health service, introduction will require careful assessment by governments to evaluate the cost- and clinical-effectiveness of genotype-guided therapy. In the UK, for example, this may well fall under the aegis of the National Institute for Clinical Excellence (NICE). Unless national guidance is given in these cases, individual health authorities may make different assessments, with the possibility that the utilisation of genotype-guided therapies will be patchy akin to "postcode prescribing" which has been a major issue in the UK with expensive treatments such as the use of donepezil in Alzheimer's disease. There are also wider questions around whether Europe is willing to see the introduction of pharmacogenetics-based therapy in some member states and not others, particularly with the imminent expansion of the EU and the widely differing healthcare systems in the different member states. Similar considerations apply to private healthcare systems where insurer health management organisations (HMOs) paying for pharmacogenetic tests will require a rigorous evaluation of the cost- and clinical-effectiveness of genotype-guided therapies, in comparison to other therapies available to treat the same disease. There are also ethical and social issues around selective provision of such tests by health care systems of all types.

Given these considerations, there is a possibility that pharmacogenetics may exacerbate existing health inequalities, or initiate new ones. It may also lead to an even wider gulf in healthcare practices between the richer developed nations and poorer states, who cannot even afford the costs of drugs let alone the cost of pharmacogenetic testing. This has been acknowledged by the World Health Organization (WHO) which has strongly recommended that developing countries should not be deprived of potential healthcare gains afforded by genomic technologies (WHO, 2002).

The use of genotype-guided therapies requires that prescribers will have a level of knowledge sufficient to understand and interpret the rationale for prescribing for certain genotypes, but not for others (Robertson et al, 2002). This may be particularly important for primary care physicians, where the bulk of prescribing is performed. However, since most prescribers have only a limited knowledge of pharmacogenetics, training programmes will have to be put into place for existing prescribers and curricula altered to incorporated pharmacogenetics into undergraduate education (Gurwitz et al, 2003). Clearly controversies currently arise in relation to all prescribing issues, and this is going to be no different with respect to pharmacogenetics. Each clinician will have their own opinions about the relative merits of different treatments available and the incorporation of pharmacogenetics into the clinical care of their patient. Clinician acceptance is presently an unknown factor. It is possible that this may be a significant barrier to introduction of widespread genotype-based therapy. Anecdotal evidence suggests that many physicians are unimpressed with the projected benefits within the context of general practice. However, it is important that such opinions are based on a good understanding of the issues involved. Where a doctor is not confident about treating a particular condition, s/he is likely to refer to a specialist, which is the current clinical practice. It is possible therefore that pharmacogenetics may be considered a specialty in its own right in the future, or as a sub-specialty of clinical pharmacology.

The nature of the pharmacogenetic test results fed back to the prescribing physician also needs to be considered. If most clinicians do not have the appropriate training and knowledge to interpret individual genotypes and thereby determine whether the patient would benefit from a particular drug, perhaps the information relayed to the clinician should indicate whether or not the patient should be prescribed the drug, and indicate the probability of the patient responding (efficaciously or adversely) to the drug. Depending on the predictive power of tests, clinicians may or may not be able to view such tests as a strict 'gatekeeper' on prescribing behaviour (Robertson et al, 2002). Based on this information, the clinician would

be able to make an informed decision as to whether the patient should be prescribed the drug or whether they should get an alternative drug. But even with highly predictive tests, test information will need to be balanced against other clinical (and cost) considerations, and a modified rather than strict gatekeeper model may be most appropriate (Robertson et al, 2002). There may also be a role for pharmacists in interpreting genotypic information, as well as the provision of counselling and advice services (see below) and such services may complement the recent expansion of pharmacy practice. Not releasing individual genotypic information acts as another measure to enhance confidentiality and reduce any risks associated with secondary information contained within the test result.

There is also the question of test location. Will pharmacogenetic tests be conducted in doctors' surgeries – so called point of care testing (POCT) - or by commercial laboratories, much like existing diagnostic tests? Current pharmacogenetic tests (such as that used to determine whether to prescribe Herceptin for breast cancer, and the hypersensitivity test prior to use of the HIV drug, Abacavir) are conducted by specialist clinics. However, pharmacogenetic tests developed for other clinical situations, such as general practice, may in practice be less acceptable. Technologies for genetic POCT will eventually become available, but this will require considerable investment in infrastructure and training.

Whatever the test location, tests will need to be reproducible and reliable, and require validation, and clinicians will be faced with a range of quite complicated questions around which tests to conduct and how to interpret them (Manasco et al, 2002). Regulatory regimes for diagnostic tests are complex and vary across countries, and are also in a state of change. In the US, for example, tests developed by commercial testing labs – so-called "home-brew" tests – are exempt from regulations that apply to marketed tests, although the agency is expected to tighten controls in the future. In Europe, tests are governed by the In Vitro Diagnostic Medical Devices (IVD) Directive, implemented in December 2003.

Pharmacogenetic testing can be viewed as part of the wider use of molecular diagnostics in health care systems. According to Hall et al (2003), in state funded systems, the widespread introduction of molecular diagnostics in clinical practice has been hampered by a lack of funds for equipment and, more importantly, training for clinical and laboratory staff. Additionally, non-critical introduction will not necessarily lead to an improvement in clinical outcome if results do not affect clinical management, including ways of altering human behaviour as a method of disease prevention. As noted above, before introduction, genotype-based tests should be subject to a detailed cost-benefit analysis that includes a realistic assessment of likely improvements in clinical outcome.

Pharmacogenetics and the patient
Currently, we prescribe on the basis of population data that does not guarantee benefit for the individual. Prescribing by genotype offers the patient the potential benefit that they will be given the right drug at the right dose, which will maximise efficacy and minimise toxicity. Pharmacogenetic tests may predict not only improvements in short-term measures, but also in long-term mortality. For example, in hypertension, treatment with thiazide diuretics preferentially leads to falls in BP as well as in long-term measures such as myocardial infarction, cerebrovascular accidents and mortality in patients with certain adducin genotypes (Sciarrone et al, 2003). The possibility that we will be able to predict and prevent serious adverse reactions, which can be fatal, such as abacavir hypersensitivity (Mallal et al, 2002; Hetherington et al, 2002), will obviously be beneficial to patients.

Despite the potential benefits, there are other aspects of relevance to patients that have to be considered. First, given that these are going to be DNA-based tests, specific safeguards to

maintain confidentiality will have to be put into place. Laboratories carrying out such testing will need to undergo an accreditation process to ensure safe and secure storage of both samples and information. However, if pharmacogenetic information leads to prescription of a particular drug, the mere fact that the patient is on the drug will betray their genotype, even without direct knowledge of the results of their genetic test.

There is a strong argument for pharmacogenetic testing to be accompanied by counselling so that any psychological impact of a non-optimal genotype is minimised, and the patient given information as to whether alternative therapies are available. This will have major cost implications in that significant resources will have to be found for training counsellors. It is important to note however that even for genetic tests for disease susceptibility the psychological implications can vary enormously; for example, the implications of a test that indicates the possibility of Huntington's disease will be far greater than that which indicates susceptibility to haemachromatosis, because of the lower penetrance of the latter mutation. It has therefore been argued that by virtue of the fact that pharmacogenetic tests will provide probabilistic information, their psychological impact will be less than that of genetic tests used for Mendelian disorders. However, whether this turns out to be the case in practice needs further study.

There is a possibility that secondary information may be conferred by the pharmacogenetic test (Buchanan et al, 2002). The most important of this will be susceptibility to a disease process, which may share some (but unlikely to share all) of the same genes determining drug response. However, this is also likely to provide probabilistic information, which in most cases will be less accurate than the primary purpose of the test, i.e. to provide drug response data. Furthermore, it may be possible to minimise this secondary information to choose genetic markers more specific for drug response than for disease predisposition. Similar arguments will also apply in relation to other possible types of secondary information, for example, responses to other drug classes, or predisposition to addiction to cigarettes, alcohol or illicit drugs.

Pharmacogenetic tests may also have implications for family members. One issue that needs to be considered with all genetic tests is the possibility that non-paternity may be disclosed, particularly when other family members have been tested. The pharmacogenetic test may also indicate an increased predisposition to developing certain adverse effects. Where there are good data available, it may be necessary to undertake family screening, as is currently practiced for probabilistic tests such as the Factor V Leiden mutation. However, the implications for individual family members may vary from none at all (to those who will never be exposed to the drug) to the same as those for the index individual.

There may be implications for the patient having a pharmacogenetic test in obtaining life insurance. Life insurance companies routinely use phenotypic information to decide on insurance information. It is perhaps naïve to think that pharmacogenetic information will not be used in a similar manner eventually. It is likely therefore that in the future they will be given access to some information, but how this will affect insurance premiums and the ability to get insurance is difficult to predict. For example, an individual who has a high risk of developing a disease, but has a favourable response genotype may actually have to pay lower premiums than an individual with a low risk of disease but with a genotype that indicates poor response to the drug. Overall, pharmacogenetic information is likely to be less controversial in most cases than genetic information predicting disease, with the possible exception of the rare individuals who have a pharmacogenetic response profile that predicts non-response to any of the available drugs.

Nonetheless, one of the main challenges is addressing the ethical, privacy, and social concerns affecting the willingness and acceptance of persons to be genotyped. For example, reportedly nearly one-third of women offered a genetic test for breast cancer at the US National Institutes of Health declined, due to concerns about potential health insurance discrimination. The question of who has access to an individual's genetic information generated by such tests is crucial (Park 2003).

If a particular medicine has been licensed on the basis that it is only prescribed to certain genotypes, if a patient refuses the test, then the doctor does not have a legal duty to prescribe that particular medicine, and the patient should therefore not expect to receive that particular treatment. Obviously the patient has every right to expect some form of treatment (which is not dependent on pharmacogenetic testing). The clinician can prescribe a drug outside its licensing indication, but this will be an individual decision, and the legal implications of this will be different from that when the drug is prescribed within its licensed indications. Potentially there are also important legal and ethical implications arising when a doctor fails to offer a pharmacogenetic test when one exists. Health delivery systems of all types (state-funded, managed care organisations, and health insurance companies) are likely to play a significant role in determining whether a pharmacogenetic test is required and/or reimbursed. Targeted treatment is likely to lead to fewer adverse drug reactions and/or improved efficacy in the targeted group, and hence reduce overall health costs. Where they exist, such tests may in fact be made compulsory by such organisations in order to reduce the potential for litigation in the advent of serious adverse events.

Some commentators have also raised concerns about genetic self-testing, such as via the Internet, and some states have sought to investigate effective oversight of genetic tests supplied directly to the public (HGC, 2003).

Conclusions
Pharmacogenetics offers major potential benefits by allowing the use of the right drug at the right dose in the right patient. By virtue of this, it has many implications for all stakeholders, many of which are positive, although there are some negative implications as well, which will require consideration on a case-by-case basis. There has been a lot of hype about pharmacogenetics – this was particularly evident at the time of the first draft of human genome. The increasing realisation of the complex technical, ethical and social issues that will be needed in making pharmacogenetics a reality has rapidly led to a dissipation in the hype, and has given way to a much more pessimistic outlook. This, we are sure, will be replaced by a more realistic outlook. It is likely that pharmacogenetics will play a major role in healthcare in the future, but it is unlikely to be important for all drugs, and will be of greatest benefit for drugs with a narrow therapeutic index.

Notes
1. For example, the UK Medical Devices Agency merged with the Medicines Control Agency to form the Medicines Control and Healthcare products Agency (MCHA) in April 2003. Responsibility for medical devices in Sweden now resides with the Medical Products Agency (MPA); but in Germany it continues to reside with the Paul Erlich Institute.

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Table 16.1. Variable therapeutic responses to drugs for different conditions

Condition	Efficacy rate (per cent)
Alzheimer's disease	30
Asthma	60
Diabetes	57
HCV	47
Oncology	25
Osteoporosis	48
Rheumatoid arthritis	50
Schizophrenia	60

Adapted from Physicians' Desk Reference, 2000.

Figure 16.1. Possible implications of pharmacogenetics for drug development