THE ROYAL SOCIETY

Personalised medicines: hopes and realities

ISBN 0 85403 620 2

Typeset and image design by Franziska Hinz at the Royal Society.
Printed by OML 4–5 Warner Yard London EC1R 5EY

Personalised medicines: hopes and realities

Contents

Summary

One of the most important approaches towards more personalised medical care is the study of pharmacogenetics. This emerging science seeks to determine how people's genetic make-up affects their response to medicines. It offers the potential to develop a new generation of medicines, to help maximise their efficacy and enhance their safety, which could have implications for healthcare, both in the developed and developing world. The field of pharmacogenetics has been widely discussed by scientists and policy makers, and the pharmaceutical and diagnostic industry has been investing in exploring it for developing genetic technologies to enhance drug discovery and development. The advances in, and potential for, the application of pharmacogenetics are closely related to rapid advances in the underpinning genetic technologies. Hence it is now possible to foresee genetic testing on a very large scale and at a reasonable cost.

Currently, pharmacogenetics has very little impact on clinical practice. However, there are now a few products on the market, predominately in the field of cancer, for which there is good evidence for the benefit of pharmacogenetic testing.

Pharmacogenetics is unlikely to revolutionise or personalise medical practice in the immediate future. Rather, as related research identifies sub-groups of common diseases based on different genetic or environmental causes, and knowledge of pharmacogenetics advances, it should become possible to introduce genetic testing to predict people's response to at least some drugs. Appropriate trials and cost analyses will first have to be performed on a case-by-case basis.

Pharmacogenetics is likely to become increasingly important in drug discovery and development as knowledge of the relative importance of genetic factors helps to identify optimal populations for a particular medicine. Industry will continue to favour drug candidates that avoid the effect of genetic variation, but where that is not possible, the development of drugs with an associated diagnostic test is expected to become routine in the next ten to twenty years. It will be necessary to validate the clinical use of both the diagnostic test and the drug by large, controlled, clinical trials to enable new products to enter the clinic.

For new drugs, the clinical trials will be conducted by industry. However, information is also needed about the use of pharmacogenetic screening of existing medicines, including off-patent generic medicines, which constitute the bulk of those used in the National Health Service (NHS). Under the current arrangements industry has no obvious motive to investigate the pharmacogenetics of most of these products on its own. We recommend that public–private partnerships are established between the NHS, the Medical Research Council, research charities and the pharmaceutical and diagnostic industries to fund trials on existing medicines. All pharmacogenetic clinical trials should have the input of health economists to assess their clinical cost–effectiveness.

The future impact of pharmacogenetics will be linked to the continuing development of diagnostic tests that can deliver reliable and rapid diagnostic data to healthcare professionals. As this field evolves it will be necessary for regulation to follow the scientific developments and their applications closely. Regulatory authorities will have to establish standards of validity for the use of genetic tests if pharmacogenetic data are to be incorporated into licensing procedures. We recommend that regulators should incorporate some form of post-market monitoring, beyond phase III clinical trials, which links data on genetic variability to clinical outcomes in the healthcare system.

Education in genetics at undergraduate, postgraduate and continuing medical education levels has trailed behind the enormous scientific and technical advances in this field. In the future doctors, nurses and pharmacists will require a much stronger basic training in the fundamentals of human genetics. We recommend that training and education needs of these healthcare professionals are reviewed by the appropriate professional bodies.

Studies of pharmacogenetic variability will require the analysis of large repositories of clinical data during and after a clinical trial. Industrial and academic researchers undertaking such studies will require an ethical framework that provides guidance on how to collect and store information and samples with proper consent, while protecting the rights and confidentiality of the individual. This needs specific consideration by Government, the NHS, and the newly established Human Tissues Authority.

Public attitudes will play a crucial role in realising the potential of scientific and technological advances. Most participants engaged in the public dialogue commissioned as part of this study saw the potential development of pharmacogenetic testing as beneficial for helping people make informed choices. However, there were major concerns, including issues of consent and confidentiality in the handling of biological samples, and whether the Government and the healthcare system could successfully deliver genetic technology in the future. We recommend that the public should be regularly consulted about the applications of pharmacogenetics.

We endorse the recommendation of the World Health Organization that the introduction of simple DNA diagnostics for common genetic and infectious diseases in developing countries is vital. We recommend that the Medical Research Council and research charities commission more research into the cost effectiveness of the use of pharmacogenetics in developing countries, particularly for drugs for malaria, tuberculosis and HIV and for assessing drug resistance in common parasites.

Over the next ten to twenty years we expect to see several pharmacogenetic products enter mainstream healthcare, particularly in the field of oncology, although advances will be on a case-by-case basis. The major determinant of the rate of progress will be the clinical use and cost effectiveness of the new treatment regimes rather than development of the technology.

1 Introduction

1.1 Background

The term *pharmacogenetics* was first used in 1959 to describe a new discipline based on the observation that genetic factors, at that time variation in the function of a single gene, can modify drug action. More recently, and following the success of the human genome project, the term *pharmacogenomics* has come into common usage, being defined simply as how people's total genetic make-up affects their response to medicines. Although the two terms are often used synonymously this is not entirely correct. Although *pharmacogenetics* still retains its original meaning, *pharmacogenomics* is concerned with the genome-wide search for genes and their products (eg proteins) that may be involved in the complex interactions of genetic and environmental factors that underlie many common diseases, and hence which may provide new targets for therapy. In addition, *pharmacogenomics* aims to identify genes that may be involved in defining the action of therapeutic agents and how variations in their structure and function are related to differences in patient response.

In practice, the fields of pharmacogenetics and pharmacogenomics overlap. They cover the genetic basis for both variable therapeutic response and adverse reactions to drugs, drug discovery and development, more effective design of clinical trials, and most recently, the genetic basis for variable response of pathogens to therapeutic agents. Because the term pharmacogenomics reflects the potential of the new genetic and post-genome technologies to expand the field of pharmacogenetics, we use the latter term to describe this field throughout this report.

1.2 Overview of the report

This report comes at a time when an increased understanding of pharmacological and genetic principles has led many to hope that major advances in healthcare will be possible over the next decade by tailoring medicines to an individual's genetic profile. This is set against reservations by others that pharmacogenetics, in its current form, cannot fulfil these claims within this timescale. This issue is of particular importance, given the emphasis placed on the future application of pharmacogenetics within the National Health Service (NHS) by the Department of Health in its 2003 White Paper on genetics, entitled *Our inheritance, our future – realising the potential of genetics in the NHS (Department of Health 2003)*, and the recent report of the World Health Organization (WHO) Genomics and world health (World Heath Organization 2002). This study by the Royal Society was initiated to provide a balanced assessment of the future potential and limitations of pharmacogenetics.

The Royal Society has previously highlighted the potential for genomic technologies to improve human health (Royal Society 2002, 2003). In this report we summarise current scientific progress in pharmacogenetics and anticipate future developments in the field. The report discusses the potential role of pharmacogenetics in both clinical and public health practice, and drug development and genetic testing, and hence its likely impact on the provision of healthcare in the future. In addition, it considers some of the regulatory and ethical issues that may follow the development of this rapidly moving field.

This introduction provides an overview of the history of medical genetics and pharmacogenetics, leading to an outline of the factors, in addition to genetics, that can alter the effectiveness of a drug for a patient. Section 2 discusses the role of pharmacogenetics in the drug discovery process and the associated regulatory and monitoring requirements. Section 3 gives an overview of the current and future clinical applications of pharmacogenetic testing. Section 4 examines the implications of pharmacogenetics for industry, public and private research, and public health more generally. Section 5 discusses the social and ethical issues and summarises the results of the public dialogue exercise that was undertaken as part of this study. Finally, Section 6 lists our conclusions and recommendations.

We are grateful to those individuals and organisations that provided valuable input to this study. Our initial call for evidence was met with 36 responses. This was followed by three oral evidence sessions in December 2004 and January 2005. A full list of the contributors can be found in Annex 2. In many cases their comments have been reflected in our report.

1.3 A brief history of the development of medical genetics and pharmacogenetics

1.3.1 Medical genetics as a new field of medicine

Genetics was established as a major discipline at the end of the nineteenth and the first half of the twentieth centuries, though there was very little interest in the medical aspects of genetics at the time. The situation changed dramatically in the late 1950s, when genetics became an increasingly important part of medical research and practice. Initially, the field focused on diseases due to a single defective gene that could be traced through families in a way that followed Mendel's laws of inheritance (see Annex 3), or disorders due to defects in the structure or number of chromosomes. Remarkable progress was made in protein chemistry and biochemistry, making it possible to define the underlying cause of the disease in at least a few cases, although it

remained a mystery as to how this was mediated at the level of the gene. However, these advances led to major improvements in the diagnosis of genetic disease.

1.3.2 'New genetics' and the molecular era

From the mid-1970s advances in molecular biology progressed hand-in-hand with those in medical genetics (Peltonen & McKusick 2001). Techniques became available for analysing genes directly and, later, for isolating them and determining their structure. The first diseases to be investigated in this way were those for which the defective protein was already known. Examples include haemoglobin, in inherited blood diseases like sickle cell anaemia and thalassaemia, and one of the factors involved in blood clotting after injury in the case of haemophilia. However, at first it was not clear how it would be possible to find the defective gene for diseases for which there was no knowledge of the underlying defect.

The approach that finally solved the problem of finding genes for conditions of unknown cause was not new; rather, it was the availability of the new tools of molecular biology that made it possible. In a series of breeding experiments with fruit flies performed by Thomas Hunt Morgan and his colleagues in the USA at the beginning of the twentieth century, the mechanisms of inheritance that would eventually form the basis for major progress towards an understanding of the role of genetics in disease were defined. Whereas Mendel's laws described the inheritance of a particular gene, Morgan's group pointed out that if two genes are on the same chromosome, and especially if they are close together, they tend to be inherited together: the genes are said to be linked. Furthermore, when the germ cell (egg or sperm) chromosomes become closely opposed in a fertilised egg, during a process called meiosis, crossing over of genes can occur so that the two characters determined by the genes will part in some of the offspring. The closer together a pair of genes are on the same chromosome, the smaller the chance they will have to cross over. Hence, the number of crossovers is a measure of the distance between the genes.

As early as 1927 the British geneticist J B S Haldane suggested that an approach using genetic linkage would be valuable to human geneticists. By then it was already known that many human diseases follow a Mendelian recessive pattern of inheritance: that is, patients are only affected if they inherit a defective gene from both parents, both of whom, because they only carry one copy of the defective gene, are unaffected. Haldane suggested that it should be possible to tell whether children had inherited a gene for a recessive disease by finding a series of marker genes that could be easily identified, eye colour or a blood group, for example, and studying the pattern of inheritance of the two genes within families. If the two genes were always inherited together it would be more likely that they were linked, that is close together on the same chromosome; whereas, if they were some distance apart on the same chromosome, or on different chromosomes, they would be inherited independently. Clearly if one knew the chromosomal location of the marker gene, this would offer an approach to finding genes of unknown function that underlie genetic disease. The problem was that, until the molecular era, there were very few markers available for linkage studies of this type. The breakthrough came with the discovery of a family of enzymes called restriction enzymes that cut DNA at specific sites (see Annex 3). It soon became clear that there is considerable variation between individuals in the structure of their DNA (see Annex 3). These so-called restriction enzyme polymorphisms were used as markers in family studies to trace defective genes. But the discovery of a linkage of this type did not mean that the two genes were particularly close together. Genetic engineering, by chromosome walking, made it possible to move from the marker towards the gene of interest and, finally, to isolate it. This approach came to be called positional cloning.

1.3.3 Molecular genetics reveals new levels of complexity of disease mechanisms

Positional cloning led to the isolation of hundreds of different genes that underlie disorders inherited according to Mendel's laws and to the identification of the mutations involved, information that was invaluable for the diagnosis of genetic disease, even in early foetal life. Remarkably, it turned out that many single-gene disorders result from hundreds of different changes, or mutations, in the structure of the DNA of an individual gene. Some of these changes result in the production of an abnormal protein whereas others cause disease through reducing the rate of production of a normal protein product.

The partial completion of the human genome project in 2001, an international effort to map and sequence all the human genes, and subsequent research, has shown that the structure of our DNA is even more variable than was previously thought. There are now millions of known sites (Burchard et al 2003) in the genome that vary between different people and that provide linkage markers for extensive studies of families or populations. Because many of the common diseases of middle and old age, such as heart disease, stroke and diabetes, seem to reflect the action of environmental factors with varying susceptibility as the result of the action of many different genes, thoughts have turned to defining the different genes involved for a better understanding of the underlying cause of the disease (that is, why individuals behave differently with respect to environmental factors). Given the complexity of these diseases it is not surprising that progress has been slow, although a few of the genes that modify susceptibility to these complex conditions have now been defined.

In short, modern clinical genetics investigates rare disorders that are inherited according to Mendel's laws, and also covers every branch of medicine in an attempt to unravel the complex interactions between nature and nurture that underlie human diseases.

1.3.4 Genetics of somatic cells: cancer as a genetic disease

One of the most important discoveries of recent years is that genetic disease is not restricted to disorders that we inherit through our parents' germ cells. Rather, it appears that many forms of cancer result from changes in our genes that we acquire in our body's cells (somatic cells) during our lifetime. It is now clear that most cancers result from acquired mutations in families of genes called oncogenes and tumour-suppressor genes. Presumably these mutations occur because we are continuously encountering noxious chemicals from the environment and agents that we produce all the time through our metabolic pathways that damage our DNA. Although we have developed a highly sophisticated system for repairing damage to our DNA, this process gets less effective as we age. Oncogenes are part of our cells' normal machinery for ensuring that they divide only after damaged DNA been has repaired, interact with other cells appropriately and, in general, keep the cell functioning. The generation of many forms of cancer requires changes in several different oncogenes before the tumour becomes invasive. It is now clear that, even in what is apparently the same type of cancer in a particular tissue, there may be widely different changes in the pattern of oncogene mutations. In rare forms of cancer we may inherit a defective gene, a tumour-suppressor gene for example. While we retain one copy of the normal tumour-suppressor cancerous changes do not occur; but if we acquire a mutation of the unaffected gene then malignant change in the particular tissue ensues. Molecular mechanisms of this kind are well documented in the cases of common eye and kidney tumours in children.

1.3.5 Beginnings of pharmacogenetics

Pharmacogenetics was born during the period of intense interest in clinical genetics in the 1950s, after three quite independent discoveries (Meyer 2004). First, studies of the red blood cells of African–American soldiers who had developed severe anaemia after taking the anti-malarial drug primaquine were found to be deficient in the enzyme glucose-6-phosphate-dehydrogenase. This inherited error of metabolism was later found to affect 400 million people worldwide. Second, it was found that individuals who received the drug isoniazid for the treatment of tuberculosis could be clearly divided into slow and rapid metabolisers of the drug, and that this rate was genetically determined. Third, it was found that patients who had prolonged effects of the anaesthetic agent succinycholine, had an atypical enzyme, in this case a cholinesterase that was inherited. In 1957, based on these and related discoveries, the American geneticist Arno Motulsky wrote an article outlining the basic concepts of pharmacogenetics, but the word pharmacogenetics was not used until 1959 by the German geneticist Friedrich Vogel (Motulsky 1957; Vogel 1959).

During the 1960s and 1970s numerous other examples of unusual drug responses due to inherited enzyme defects were discovered. An important advance in understanding severe side effects was initiated by work directed at two drugs: debrisoquine, an agent used for treating hypertension, and sparteine, used for treating abnormal cardiac rhythm. Both drugs are metabolised in the liver by the same enzyme, a cytochrome P450 mono-oxygenase, later designated CYP2D6 (see Box 2, Section 2.4). This enzyme is involved in the metabolism of a wide range of other drugs, including anti-depressants and opioids such as morphine, hydromorphine and codeine (Meyer 2004).

Studies during the 1970s depended on identifying variable responses to drugs followed by an analysis of the enzymes responsible for their metabolism. But towards the end of the 1970s methods were becoming available for cloning and sequencing human genes and so pharmacogenetics, like the rest of human genetics, moved from the protein to the DNA era.

1.3.6 Molecular pharmacogenetics

From the 1980s onwards it was possible to isolate, clone and sequence many of the genes that had been found to be responsible for variation in drug metabolism (see Annex 3). For example, numerous additional alleles (alternative forms of the gene) of the CYP2D6 system were discovered; currently, nearly 80 distinct genetic variants of this metabolic system have been defined. Hundreds of variants of the glucose-6-phosphate-dehydrogenase gene have been found in different ethnic groups with a deficiency of this enzyme. Forty years after the discovery that variation of the metabolism of the anti-tuberculous agent isoniazid is under genetic control, the gene involved was isolated and, again, numerous different mutations were found. In addition it has been discovered that structural changes of genes that encode drug transporters and drug targets may also be involved in varying response to therapeutic agents.

1.3.7 Practical problems

An enormous amount of information had been obtained about the genetic basis for variable responses to and side effects of drugs by 2000. Yet its impact on day-to-day clinical practice had been negligible. In a few cases, for example glucose-6-phosphate-dehydrogenase deficiency, simple tests were developed for rapid identification of those at risk of side effects and they were applied before treating patients in countries in

which they could be afforded. But for the most part, information of this type had rarely been used in the clinic. Several reasons have been suggested, none entirely satisfactory: lack of awareness on the part of clinicians; the difficulty of performing complex and often expensive assays; and the fact that most of the well defined single-gene causes of variability in drug reaction are quite rare. For a commonly used drug like warfarin, it is surprising that there have been very few attempts to assess the benefit for patients of testing for the genetic polymorphism (variant) involved in its metabolism.

The pattern of response suggests that several different genes may be involved in the metabolism of the bulk of drugs that are used commonly in clinical practice. Furthermore, in many cases environmental factors will also be involved in variable response or side effects. Following the success of the human genome project, and the discovery that there are millions of genetic markers spread throughout our genomes, it was a natural progression to explore pharmacogenetics by the completely new technologies that were becoming available. In short, by 2000 classical pharmacogenetics, which was restricted largely to variation in the action of single genes, was about to be replaced by pharmacogenomics, which would take a much broader view of the relationship between drug action and human variability.

1.3.8 Post-genomics

It was soon clear that post-genomic technology might make it possible to obtain detailed profiles of the genes involved in drug action, and that this would ultimately lead to an understanding of individual variation in response to a wide range of therapeutic agents, or to the promise of 'personalised medicine'. The pharmaceutical industry also recognised that this technology offered a promising way of defining variable response to drugs at an early stage of their development and that this might greatly improve the efficiency of drug trials. Furthermore, genome searches for genes involved in complex multigenic diseases like heart disease, stroke and diabetes might well yield promising targets for drug development. Because many of the mutated oncogenes are potential drug targets, it was recognised that the concept of personalised medicine might also be applied to the cancer field.

1.3.9 Ethnic differences in drug response

It has been known for some time that there are ethnic differences in the response to drugs. More recently it has been found that at least some of these differences reflect genetic variation in drug-metabolising enzymes, transporters, receptors, and other factors that may be involved in variability of response to drugs and susceptibility to disease. The current international initiatives to try to determine the pattern of heterogeneity of the human genome will disclose many more examples, such as defining disease-susceptibility genes and the potential targets for pharmacogenetics arising from these genes. The Human Genome Organisation (HUGO) Pacific Pan-Asian Single Nucleotide Polymorphism (SNP: see Section 2.3) Initiative is planned to begin in 2005 (Science 2004). Several countries, including the United Kingdom, are developing large DNA databases for long term studies relating disease phenotype to the pattern of genetic variation; it is possible that further ethnic pharmacogenetic information may stem from these sources. However, it should be remembered that recent studies of human evolution have shown that there is far more genetic variability within than between different ethnic groups. Hence, except in a few exceptional cases, it is unlikely that the ethnic background of a patient will be of value in determining variability of response to therapy (see section 1.3.5).

1.4 Pharmacology and the variability of drug response

The aim of drug therapy is to administer the appropriate drug in the correct dose to produce the desired effect with a minimum of toxicity. Currently the 'trial and error' approach is used to guide the choice of drug and dose, and hence there is a wide range of efficacy and side effects. The result is that whereas in one patient the desired therapeutic effect may be achieved, in another no response of any kind may be seen, while yet another patient may suffer an adverse effect with little or no benefit.

Factors influencing drug response include the age, weight, sex and ethnicity of the patient, the nature of the disease, the patient's diet, which other drugs and remedies the patient is taking, the time of day that the response is studied, and many others. Among the most important factors, however, are the dose of the medicine prescribed, whether the patient takes the medicine as prescribed, and possible genetic variation in response to the drug.

1.4.1 Dosage

There is usually a relationship between the dose of a drug administered and the patient response. This relationship may be steep, in which instance a small increase in dose will produce a marked increase in effect (beneficial or otherwise), or flat, where increasing the dose does not produce a commensurate increase in effect. It should be noted that the dose–response relationship for a beneficial or an adverse effect may not be the same. For example, in the case of thiazide diuretics, which are used to decrease blood pressure, increasing the dose does not produce a notable

decrease in blood pressure (hypotensive effect), but it can lead to a decrease of potassium and an increase in uric acid in the blood, both potentially adverse side effects.

1.4.2 Patient compliance

Compliance is still used as a technical term to describe the extent to which a patient follows a prescribed routine. However, since the word has developed unfortunate overtones, implying orders that a patient is expected to obey, the words 'concordance' or 'adherence' have been used more recently to reflect the fact that methods of treatment are best arrived at jointly by a doctor and patient. There is no doubt that non-compliance is a major factor in variation in drug response; different studies have found its frequency to be as low 10% and as high as 90% for certain drugs. Although the reasons for lack of compliance are still not well understood, several factors appear to be of considerable importance (Herxmeimer 2003). Apart from the cost of drugs, which is an important factor in some countries, the two major issues are the complexity of the routine and the adverse effects of a particular drug. Apart from simple forgetfulness, the complexity of a drug regime becomes particularly important when the agent has to be taken at several times during the day, particularly if more than one drug is prescribed and it is not possible to synchronise the dose timing. The other major factor is undoubtedly adverse drug effects, which occur with most drugs at one time or another; compliance then depends on whether the patient can be persuaded that the likely benefits of treatment outweigh its disadvantages. In addition, certain illnesses, particularly psychiatric disorders, may make it difficult for patients to adhere to a drug routine. Similarly, in diseases that may be symptomless, high blood pressure for example, patients may simply not feel that it is worth continuing with an agent because they perceive no benefit from it.

As well as monitoring therapeutic response, a variety of ingenious methods have been developed to assess compliance. However, many of them are expensive and time consuming and therefore restricted to use in formal clinical trials. Compliance remains a major problem, and one has to take it into careful consideration in assessing the results of clinical trials as well as therapeutic efficacy in practice.

Finally, it should be emphasised that the blame for poor compliance should not be laid entirely on patients; many busy doctors and primary healthcare workers do not have time to spend providing the detailed instructions required for complex drug regimens; the same applies to hospital practice, particularly when patients are being discharged from wards with prescriptions for complex, and often multiple, drug treatments.

1.4.3 Genetic factors

Genetic influences on drug response are mediated through both pharmacokinetic and pharmacodynamic processes. Pharmacokinetics examines the fate of drugs in the body: absorption, distribution, metabolism and excretion (ADME). Pharmacodynamics is the study of reactions between drugs and living structures, that is what drugs do to bodily processes such as metabolism.

The ADME properties of drugs are all subject to genetic as well as environmental influences. This has best been studied for drug metabolism, and specifically the superfamily of cytochrome P450 enzymes (for more information see Box 2 in Section 2.4), which act to break down certain drugs. Polymorphisms (common variations in DNA) in the cytochrome P450 genes are major causes of inter-individual variation in response to drugs. Genetic influences on pharmacodynamics, that is, on receptors and other response mechanisms, are less well understood, but polymorphisms of the β–adrenoreceptor and protein kinase receptors such as the human epidermal growth factor receptor are known to account for both beneficial drug action and the basis for potentially adverse effects.

1.4.4 Other factors influencing drug response

Many other diverse factors can have a varying effect on the response to different drugs, but probably the most important are:

- Environmental influences such as diet, alcohol consumption and cigarette smoking.
- Disease, especially liver and kidney disorders, which effect the metabolism of drugs.
- Interactions with other drugs, which can influence rates of drug metabolism.

A 20- to 30-fold variation is commonly seen in the response to drugs. The contribution of genetic factors must be considered, with the factors listed above, on a case-by-case basis. Each factor is like to contribute differently to each drug response.

2 Drug development and pharmacogenetics

2.1 Introduction

This section summarises the drug discovery process and discusses the current and future impact of pharmacogenetics on drug design and development. The potential for pharmacogenetic analysis to address existing challenges in medicine and healthcare, such as decreasing adverse drug reactions (ADRs), increasing drug efficacy, the development of diagnostics, and how advances in pharmacogenetics may impact on the regulation and licensing of medicines in the future is illustrated. This section is based on evidence from scientists and clinicians in the pharmaceutical industry and academia, and provides a background to later sections on the clinical applications of pharmacogenetics and the implications of this technology for the health service.

2.2 Drug discovery and development

Drug discovery and development is a long and expensive process. Recent benchmarking data (provided to the working group) suggest that the average time from project inception to new drug launch is approximately 13–14 years and the average total investment required can be in excess of US$1 billion (£555 million). Projects can encounter many technical difficulties and ultimately fail for many different reasons at different stages of this development process. Average attrition data suggest that there is a 1–3% chance of project survival at inception, rising to about a 7–8% chance when it reaches pre-clinical testing some five to six years later. To compensate for this extreme scientific and commercial uncertainty, pharmaceutical companies are forced to run many parallel projects and to make difficult 'go'/'no-go' portfolio decisions throughout the research and development process.

Box 1 The process of drug discovery and development

The process of discovering and developing a new, safe and efficacious drug consists of seven steps outlined below:

(A) Generating and validating a new hypothesis; by modulating the function of a chosen protein target, a related disease pathology could be symptomatically relieved, modified or prevented.

(B) Identifying chemical 'lead' compounds that modulate the function of the chosen target and have the general physico-chemical and toxicological properties needed for them to become drugs.

(C) Chemically optimising a chosen series of lead compounds to be selectively unique for the target and to have the appropriate pharmacokinetic, metabolic and safety properties.

At the completion of this stage a preferred compound is selected and after careful pre-clinical safety testing using animal models, it is administered to human patients in clinical trials.

(D) **Phase I** clinical trials are conducted with a few healthy subjects (up to 100) to determine the early safety profile, maximum tolerated dose and the pharmacokinetics of the candidate drug. In parallel, manufacturing processes and product formulations are optimised so that the drug can be produced to high standards of purity and reproducibility.

(E) **Phase II** clinical trials are conducted with groups of several hundred patients with the target disease to gather safety data, a preliminary test of efficacy, and optimal dosages and dosing routines.

(F) Large **phase III** trials are conducted with patients with the target disease to provide enough data to demonstrate statistically the efficacy and safety of the compound. Usually these trials involve several thousand patients spread across multiple locations and are conducted to allow comparison to already-approved therapies for the disease and/or 'best standards' of current care.

(G) The entire package of discovery, development, clinical and manufacturing data is presented for regulatory approval. After approval, **phase IV** studies are conducted to continue the evaluation of the new drug and to collect information about its effect in various trial populations and any rare side effects associated with long-term use.

Before the rapid expansion of knowledge of human DNA sequence variation, the application of genetics research in industry described in Box 1, step (A), focused on attempting to discover novel disease genes that could become the targets for new drug discovery programmes. Over the past decade many companies have invested in such susceptibility-gene hunting using large family-based human DNA collections to gain insight into the underlying genetic component in major multifactorial diseases. However, it is becoming clear that this approach is more challenging than first thought and frequently leads to susceptibility genes that are not directly amenable to drug discovery and which require significant further biological, functional and pathway analysis to understand their relationship to the overall disease pathology. Consequently, the focus is shifting towards the use of population-based genetic association studies as a means of using genetics to increase confidence in potential disease intervention targets, and towards the application of pharmacogenetics.

The following sections describe how the science of pharmacogenetics is changing (and might change) the different steps in the drug development and discovery process. It is most important to distinguish between the effects of genetic variation as it relates to the biological definition of disease, relevant to defining sub-sets of patients, and steps (A), (E) and (F) in the drug discovery and development process (Box 1); and separately how genetic variation affects patient response to the drug itself. This latter application of pharmacogenetics focuses on the secondary pharmacology of the drug and its pharmacokinetic and metabolic properties. In drug design terms, steps (B) to (D) (Box 1) tend to be highly interactive so that negative feedback on the new drug, particularly from *in vivo* tests (tests in animals or humans) of potential drugs, is used for redesign and optimisation of the properties of subsequent compounds.

2.3 Discovery of polymorphisms, haplotypes and their ethnic distribution

As discussed in Section 1.3.2, the concept of genetic linkage and its application to discovering genes associated with disease has been one of the major technical advances in modern molecular genetics. Fundamental to this concept is the identification of sites of variation in the sequence of the genome. These variations in the sequence are known as single nucleotide polymorphisms (SNPs). Each individual has many SNPs that together create a unique DNA pattern. This section explains how SNP analysis is being used to investigate the genetic basis for variation in drug metabolism. Readers who are unfamiliar with this complex field are referred to Annex 3.

SNPs are the most abundant and the simplest form of DNA variation. Only an SNP that falls in a protein-coding region of a gene, or within control regions of DNA that govern the gene's activity, are likely to make a difference to the gene product. Knowledge about the number and genomic location of polymorphisms has risen rapidly in the past ten years, catalysed by the creation of the joint public–private SNP Consortium Initiative set up by the Wellcome Trust, international pharmaceutical companies and leading academic centres in the UK and USA to participate in the identification and analysis of SNPs. The total number of common SNPs in the human genome is now estimated at over ten million (Entrez SNP database 2005).

This explosion in the amount of genetic data is such that it is possible to examine sequences from published data so decreasing rapidly the practical requirement to re-sequence DNA samples to discover SNPs experimentally. Individual SNPs are grouped into DNA sequences in the same gene in which they tend to vary together through a phenomenon called linkage disequilibrium. These groups of SNPs are called haplotypes and form common patterns of human DNA sequence variation (see Annex 3). Their ethnic distribution is a natural representation of the genetic evolution of humans. Current data suggest that the median difference in allele frequency between major ethnic groups is between 15% and 20%. This means that very common alleles (those present more than 20% of the population) tend to be shared, whereas rarer alleles may be specific to an ethnic sub-set of the population (Burchard et al 2003).

Genetic data for haplotype analysis are available from the HapMap project (HapMap database 2005). The goal of the project is to develop a haplotype map of the human genome that will describe the common patterns of human DNA sequence variation, including haplotype frequencies among population samples from Nigeria, Japan, China and the USA. An important objective of haplotype mapping is to identify those SNPs that 'tag' or identify SNP variation in haplotype blocks (tag SNPs). This could reduce genotyping costs by several fold and enable large-scale genotyping projects that would otherwise be too expensive. The number of tag SNPs needed will vary with the amount of linkage disequilibrium in a region and the required statistical power for the study (Hinds et al 2005; Kamatani et al 2004). The optimal strategies for using sets of tag SNPs are currently under development and are the subject of much debate.

It has been suggested that a 100 000 SNP single microarray might predict accurately each individual's drug response, and that the test might only need to be done once in a patient's life time. However, more work is required to assess whether this approach will be feasible and, in particular, the number of SNPs that will be required to determine the spectrum of common and rare variations that underlies individual drug response. At present, there are commercially available prototype chips for 100 000 SNPs; the cost is about one US cent per SNP. However, costs are decreasing rapidly.

At present new technologies for sequencing are being developed that combine the accuracy of current sequencing techniques with lower costs. Overall, these approaches should be able to improve today's sequencing methods by several orders of magnitude.

Although this technology is improving there are still many difficulties to be overcome in matching phenotypes, disease susceptibility or variations in drug response, to SNP haplotypes. It will be necessary to establish an all-inclusive SNP database in which phenotype (efficacy, therapeutic failure, toxicity of the drug) is associated with a given genotype. This is a challenge in data processing as well as in data collection and will require new skills, systems and databases that may take up to a decade to complete. However, it is likely that an increasing number of diagnostics aimed at supporting specific prescription decisions will be available over the next five years.

Box 2 Cytochrome P450 enzymes (CYP450)

The cytochrome P450 *(CYP450)* genes are a family of genes whose products are active in the liver to break down certain chemicals including many drugs. There are many different P450 genes, each of which makes a protein that modifies a different sub-set of drugs. Different polymorphisms have been implicated in increased, decreased or completely absent levels of metabolism. Both the use of the drug and the dose that is administered may be affected by the individual's genotype.

Studies have identified several examples of functional genetic polymorphisms in the CYP450 enzymes that metabolise approximately 25–30% of currently available drugs, including commonly used agents such as antidepressants, anticonvulsants and anticoagulants. Amongst the diverse range of genes that make up the CYP450 family, several have been identified as being particularly important in oxidative metabolism including *CYP2D6*, *CYP2C9* and *CYP2C19*.

The CYP2D6 enzyme is involved in the metabolism of around a quarter of all prescribed medicines, including some beta-blockers used in the treatment of heart disease and high blood pressure, some tricyclic anti-depressants, and anti-psychotic medicines. A gene-based microarray test has recently been launched by Roche Diagnostics for the detection of poor, intermediate, extensive or ultra-rapid metabolisers according to variants in the *CYP2D6* gene. It is envisaged that one of the first clinical uses of this test would be in hospital-based psychiatry. A report from the Department of Health suggested that genetic testing for *CYP2D6* gene variants could be cost effective in identifying psychiatric in-patients who would be prone to severe side effects from anti-psychotic drugs (Department of Health 2003) allowing better tailoring of drug dose. Prescribing doctors (and nurses) would also test patient compliance and drug efficacy in the clinical areas relevant to CYP450 isoenzymes.

Below is an example of how a polymorphism in a specific CYP450 isoenzyme affects the use of codeine, a commonly used analgesic:

Codeine is a drug that must be converted from an inactive form to the active form (morphine) by the CYP2D6 enzyme for a therapeutic effect to occur. Patients with a polymorphism of the CYP2D6 gene which results in increased production of the enzyme are ultra-rapid metabolisers of codeine and are more likely to develop adverse effects and toxicity when taking a standard dose of codeine, including impaired breathing and sedation. In contrast, patients with decreased CYP2D6 production are poor metabolisers and will show little or no conversion of codeine to morphine; they will not experience any pain relief, but will become nauseated due to the higher amounts of codeine in their body (see Figure 1).

Genetic studies have demonstrated that individuals from different ethnic groups exhibit considerable variability in the functional capacities of their expressed CYP2D6 enzymes. It is estimated that as many as 7% of Caucasians may have a defective CYP2D6 gene, resulting in reduced pain relief due to poor metabolism of the drug. The genotyping of this enzyme has permitted adverse effects to be predicted in sensitive patients, leading to the publication of dosage recommendations by the Medicines and Healthcare products Regulatory Agency for codeine in this sub-set of patients.

2.4 Application of pharmacogenetics to drug metabolism and pharmacokinetic properties of drugs

Functional polymorphisms in the most important class of drug metabolising enzymes, the cytochrome P450 family (CYP450), are well established, and genotyping assays are frequently used to inform drug development projects and for submission to regulatory authorities (see Box 2). Typically, modern drug design protocols in the pharmaceutical industry include *in vitro* screens that guide medicinal chemists away from molecular features that are susceptible to CYP450 oxidation. If this proves difficult, variation in pharmacokinetic properties may be evaluated experimentally in human volunteers pre-selected for the respective common CYP450 genotypes. Drug candidates with a wide therapeutic and safety margin may be able to accommodate wider pharmacokinetic variation whereas those with a narrow margin might not progress to full patient trials. Ethnic variations within CYP450 are also well documented and hence related pharmacokinetic consequences in different populations can be predicted.

Despite this sophisticated state of development, according to a recent survey only thirteen US drug package inserts had wording related to drug metabolising enzyme (DME) genotype, of which only seven were recommended for guiding therapy (see Table 1).

Figure 1 The distribution of different forms of drug-metabolising enzymes in the population. (Adapted from Service 2005)

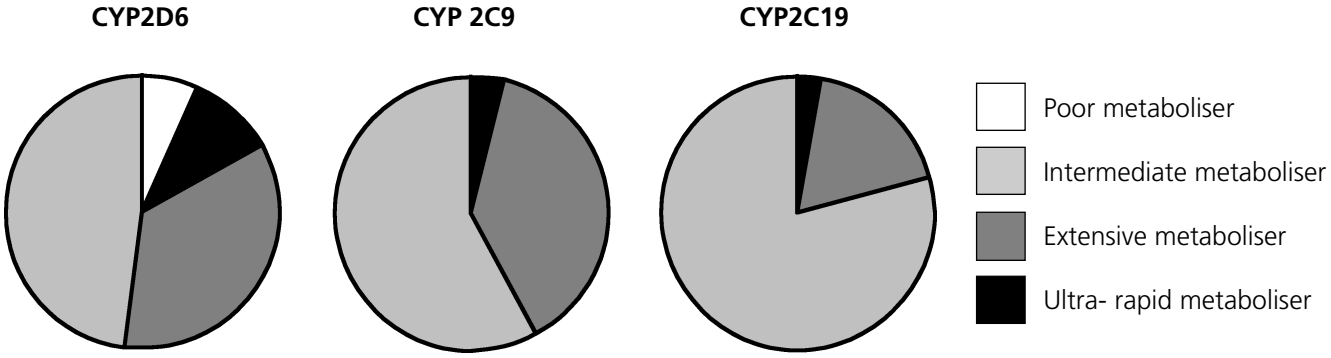

Table 1 Drugs for which wording relating to a drug-metabolising enzyme genotype is being used to guide therapy in US prescribing information (Adapted from Zineh et al 2004).

Gene	Enzyme family	Drug	Drug action/class	Note
CYP2D6	Cytochrome P450 (Oxidation)	Aripiprazole Atomoxetine Modafinil Thioridazine	Dopamine agonist Psychotropic Psychostimulant Antipsychotic	Thioridazine is the only example of a drug label stating specific contra-indication in a genetic sub-group in the label ('patients, comprising about 7% of the normal population, who are known to have a genetic defect leading to reduced levels of activity of CYP2D6').
CYP2C9	Cytochrome P450 (Oxidation)	Celecoxib	Non-steroidal anti-inflammatory	
CYP1A2	Cytochrome P450 (Oxidation)	Theophylline	Inhaled steroid (asthma)	
TPMT	Thiopurine methyl transferase	Mercaptopurine	Antimetabolite (cancer)	See Box 6

The lack of examples in Table 1 demonstrates that despite the weight of evidence that links DME gene polymorphism to variability in drug response, comparatively little of this has been translated into clinical practice. Even in leukaemia treatment by mercaptopurine, it appears not to be common practice to genotype new patients prospectively (see Section 3.3, Box 6).

A recent guidance document for industry on the submission of genotyping data for drug metabolising enzyme (DME) has been published by the US Food and Drug Administration (FDA) (FDA 2005). Test kits for genotyping are available from a wide variety of sources, including DNA microarrays that can simultaneously test for the presence of some commonly occurring DME gene variations (see Annex 3).

Other genes involved in drug action include those encoding rarer drug transporter or metabolising enzymes. Currently there is less known about these genes or the functional significance of their polymorphisms. Although this is an area of increasing research interest it is likely that progress will be relatively slow because of the need to understand more about the complexity of the biology involved in drug action.

2.5 Prospect for pharmacogenetics to explain and predict adverse drug reactions

Pharmacogenetics and related new technologies may offer unique opportunities for the better understanding of ADRs (see Section 3.2.2). Information gained about genetic components of ADRs may be used to aid molecular design strategies for subsequent drugs and hence develop those that avoid ADRs linked to genetic variation.

An obvious example discussed in the previous section is the preclinical screening of drugs for interaction with the common CYP450 gene products so that drugs that are not metabolised by CYP450 can be selected. Historically, several ADRs have been found to be associated with a sub-group of patients who have transiently high plasma drug concentrations associated with poor CYP450 metabolism. A more recent example concerns the pre-clinical screening of compounds for interaction with the Human Ether-a-go-go Related Gene (HERG) ion channel in heart muscle. Certain mutations in the *HERG* gene are the cause of familial 'long QT' syndrome and the initiation of potentially fatal changes to the normal heart rate or rhythm.

Overall, the use of pharmacogenetics to explain ADRs is still relatively new, but the technology has begun to be applied in exploratory investigations and in carefully controlled clinical trials. However, there is little evidence at present to aid these studies from either phase III clinical trials or the use of a drug after it has been approved. Collecting these data poses considerable logistical challenges. By their very nature, ADR cases are rare; it is often difficult to obtain an accurate description of the phenotype of the affected patients and the cases do not occur in sufficient numbers to be of statistical significance in an investigation. In addition, unless proper informed consent was given by the affected patient as part of a controlled clinical trial, it will be necessary to track back to the patient and obtain consent to take a DNA sample for pharmacogenetic analysis.

Even when there are a reasonable number of cases and good patient records and properly consented blood samples are available, it is still necessary to construct a hypothesis for the cause of the ADR and an associated candidate gene list, before conducting the genetic research. Candidate genes are those whose expression may impact on the drug action, for example metabolic pathways, molecular targets or biological response pathways. Generally, the genes are ranked, based on their perceived likelihood of being involved in the ADR, and the stronger candidates are tested first. However, as genotyping costs reduce and a core haplotype SNP tag list is agreed (see Section 2.3), it will become progressively more feasible to search for a genetic explanation of ADRs through a 'hypothesis-free' analysis approach in which scientists attempt to test the whole genome.

Association studies of SNPs or haplotypes and either disease outcomes or suspected adverse events associated with drug therapies are prone to both false-positive and false-negative results. To overcome these problems, unless the pharmacogenetic effect is big, studies will need to be large (typically thousands or tens of thousands of people), particularly if associations are to be examined for sub-strata of the population, for example by age, gender, ethnicity, disease group or lifestyle characteristics (such as smoking or social class). Particular problems arise with false-positive findings, as some associations are bound to arise by chance given the multiplicity of tests that might be done in gene-association studies. To protect against this, it has been suggested that the threshold for statistical significance should be set as low as $p < 10^{-7}$; this will especially be the case when genome-wide scans are performed (Lander & Kruglyak 1995). Problems can also arise if the population sample includes people from different ethnic groups with different population structures (Marchini et al 2004). Usually replication will be required, either in a different study, population or sub-strata.

Although the technological prospects are positive, pharmacogenetic 'explanations' of rare ADRs in phase III clinical trials of new drugs are always going to be problematic due to the small number of adverse events observed. However, the application of this approach to more widespread drug-related morbidity for commonly used generic therapies is realisable today. A good example is the project funded by the Department of Health on the use of warfarin in the UK (see Box 3).

Box 3 Warfarin

Warfarin is an effective and routinely used oral anticoagulant, given to prevent blood clot formation in people who have coronary artery disease, or venous thrombosis, particularly after surgery and periods of immobility. Warfarin is metabolised in the liver by a member of the cytochrome P450 family CYP2C9 (see Box 2), but a variant *CYP2C9* gene alters the rate of its metabolism. People with the variant gene break the drug down more slowly than usual, so requiring lower doses to achieve the same anticoagulant effect. Having too much anticoagulant can lead to potentially dangerous bleeding and increased susceptibility to some drug interactions. The frequency of these variant genes differs among various ethnic populations, with the variant occurring at a higher frequency within Caucasians than Afro-Caribbeans or Asians.

Doctors routinely start patients on low doses of warfarin, monitor their blood clotting, and increase the dose gradually until the appropriate level is reached—a sort of biological assay of drug effectiveness in the individual being treated. Most people take warfarin in a dose of about five milligrams a day, but people who have low levels of CYP2C9 activity normally require a dose of only one to five milligrams a week.

There are around 750000 patients in the UK receiving warfarin; this number increases annually by about 10%. It is estimated that serious side effects such as haemorrhage may be experienced by between 8% and 26% of patients treated for at least one year (Petty et al 1999). It has been suggested that pharmacogenetic testing for *CYP2C9* alleles may identify people at risk of warfarin-associated bleeding (Higashi et al 2002) and certain drug interactions. Potentially such tests are close to clinical application although rigorous data showing clinical use and cost effectiveness are not yet available. Furthermore, the recent discovery of the warfarin target gene, *VKORC1*, and the fact that different haplotypes can stratify patients into low, intermediate or high warfarin groups based on maintenance dosage (Reider et al 2005) indicates the likely complexity of studies needed to obtain such data.

Although it would appear obvious that a gene test would be useful in determining drug dose, the information required before a pharmacogenetic discovery is clinically validated can be complex. People vary quite widely in their response to warfarin, based on factors such as age, presence of other illnesses and use of other drugs, as well as the genetic component.

Because most variation is due to factors other than genetics, the current dose titration strategy would still need to be practised, even after a test for CYP2C9 activity. Furthermore, some argue that many of the episodes of dangerous bleeding that occur are later on when treatment is well established, frequent monitoring has stopped, but for some reason the patient's drug requirement alters. It remains to be seen whether such late alterations in drug responses can be usefully predicted by genotyping.

An investigation of the genetic and environmental factors underlying warfarin-associated bleeding is one of six projects recently funded by the UK Government's £4 million programme on pharmacogenetics, which is focussing on developing genetic tests to identify patients at risk from therapies currently in use. The remaining studies are examining pharmacogenetic variation of commonly used medicines such as anaesthetic agents, azathioprine for use in inflammatory disease, the risk of liver injury in patients taking penicillin or anti-tuberculosis medicines, patients' response to the anti-epileptic drug clobazam, and the risk of heart damage in patients who received anthracyclines for cancer treatment.

Ongoing pharmacogenetic research could result in the development of a simple blood test to pre-select those patients likely to experience intolerance to a drug, although other factors such as environmental effects, concurrent drug treatments and the extent to which the patient adheres to their treatment may be equally, or more, important.

2.6 Prospect for pharmacogenetics to explain and predict variation in drug efficacy

There is a clear prospect for pharmacogenetics to explain and predict some of the variation in drug efficacy. Currently there are 22 approved drugs where reference to genetic testing is made in the drug labelling or package insert as a guide to how the drug should be used. Some important examples are described in Table 2.

Table 2 Examples of drugs for which the target patient population may be determined by predictive pharmacogenetic testing (US prescribing information) (adapted from Zineh et al 2004).

Drug/Manufacturer	Disease	Biomarker	Label description
Somatotropin **(several)**	Prader Willi Syndrome	Chromosome 15 aberration	Use of drug is indicated for patients with the presence of the biomarker
Retinoid (Vesanoid) **Roche**	Acute promyelocytic leukaemia	*PML/RAR* gene	Use of drug is indicated for patients with the presence of the biomarker
Cetuximab (Erbitux) **Imclone/BMS**	Colorectal cancer	EGFR	Use of drug is indicated for patients with the presence of the biomarker
Trastuzumab (Herceptin) **Roche/Genentech**	Breast cancer	HER 2 protein	Use of drug is indicated for patients over-expressing the biomarker
Alpha1-proteinase inhibitor (Prolastin) **Bayer**	Congenital alpha$_1$-proteinase inhibitor deficiency	PiMS or PiMZ alpha$_1$-antitrypsin deficiency phenotypes	Use of drug is not indicated for patients with these phenotypes
Imatinib (Gleevec/Glivec) **Novartis**	Chronic myeloid leukaemia	Philadelphia Chromosome positive	Use of drug is indicated for patients with the presence of the biomarker
See Box 4	Gastrointestinal stromal tumours	CD117 (*c-kit*) positive	

The data in the Table 2 demonstrate that most current examples of a drug linked to a genetic test are anti-cancer therapies, whereas the functional variation is acquired during the lifetime of the patient and is restricted to the tumour rather than being inherited.

Cancer is particularly amenable both for predictive pharmacogenetic testing and for the development of new drugs because the disease arises as a consequence of acquired somatic cell mutations that allow cancer cells to escape normal growth control, but which also provide obvious gene and protein targets.

Detailed knowledge of these changes is growing rapidly, and has already been used to develop novel medicines such as Glivec (see Box 4) and Herceptin (see Table 2 and Box 5) specifically targeted against tumours that carry genetic changes.

Box 4 Glivec

Chronic myeloid leukaemia (CML) is a slowly progressing cancer of the blood and bone marrow characterised by the production of too many white blood cells. There are three phases of CML: the chronic phase, the accelerated phase, and the blast crisis phase. As patients move through these phases their disease progresses and their condition deteriorates.

Healthy cells require an activation signal to start growing and dividing. This is done by specific signalling molecules called tyrosine kinases. Once tyrosine kinases are activated, the signals they generate begin a cascade of events which result in cell division. When the activation signals stop, so too does cell division.

There is a specific chromosomal defect called the Philadelphia chromosome that is found in 95 out of every 100 people with CML. It carries a mutated gene (called *bcr/abl*) which is produced by a rearrangement of two of the cells' chromosomes which carry the *bcr* and *abl* genes separately. The *bcr/abl* fusion gene encodes for a tyrosine kinase that is permanently activated, and this results in rapid cell division typical of cancer. The diagnosis of CML is confirmed by genetic analysis to identify the Philadelphia chromosome.

The drug Glivec (imatinib), or Gleevec in the USA, is a signal transduction inhibitor that interferes with the pathways that signal cell replication by targeting the activity of the tyrosine kinase (BCR/ABL) to block cell division. In patients with chronic-phase CML, Glivec induces complete remission in more than 80% of patients with the Philadelphia chromosome. There are relatively few reported side effects although problems of 'residual disease' and the development of resistance are an issue in its clinical effectiveness. Despite this, most researchers believe that this drug (and the biological rationale behind its development) paves the way forward for a significant improvement in cancer therapy.

In other situations (for example thiopurine S-methyl-transferase (TPMT): see Section 3.3, Box 6) inherited genetic variation influences the sensitivity to a drug. Cancer drugs are unusual in that they are often very toxic at levels not much higher than those needed for effective treatment. This is because the doses necessary for optimal eradication of malignant cells are often close to those that damage normal cells. Even a small amount of extra precision in achieving the correct dose can be critically important. Therefore pharmacogenetics has great potential in improving treatment outcomes by either increasing efficacy or decreasing toxicity through optimal treatment selection, dose individualisation and discovery of new drugs.

Genetic or protein profiling of tumour and normal tissues can facilitate the individualisation and optimisation of cancer treatment. DNA microarray technology can be used to identify polymorphisms in genes that encode enzymes such as drug transporters or drug metabolising enzymes, which limit the exposure of tumour cells to drugs (see Annex 3). Proteomics identifies patterns of proteins in both healthy and cancerous tissue. In the future, routine tissue biopsies taken before, during and after therapy may be used to modify treatment based on the patterns of the proteins expressed in response to therapy.

It is anticipated that examples of the application of pharmacogenetics to oncology and acute-care therapy (see Section 3.4) will continue to rise over the next 10 years, partly because of the intensive pace of research but also by the improved logistics of obtaining patient consent, DNA samples and validated analysis in a hospital setting.

Scientific evidence for cases of pharmacogenetic markers being associated with variation in drug efficacy outside oncology is also increasing. However, this is only the first step to developing a predictive test that will be clinically useful to guide therapy. Many pharmacogenetic associations will not be clinically useful, either because the predictive power of the test is too low, or because the logistics of therapy make testing impractical, especially in the broader context of medical practice.

Most pharmaceutical companies have taken active steps to try to determine possible genetic factors that might affect both the efficacy and safety of potential drug candidates before they proceed to late stage clinical evaluation. In ideal circumstances, this information feeds back directly into the revision of molecular design in a similar manner to that already adopted for CYP450 variation (see Box 2). When this is combined with the practical issues referred to above, a gradual rather than 'revolutionary' expansion of the use of genetic factors into new chronic care drugs is likely.

A different argument pertains to potential pharmacogenetic understanding of efficacy variation in already marketed or generic drugs. Here, there appears to be considerable potential for retrospective analysis of large patient populations and the possibility of discovering information that could lead to a battery of pre-selection 'best' therapy tests.

2.7 Diagnostics

The primary role of the diagnostics industry in the context of pharmacogenetics is to translate predictive biomarkers into reliable, rapid and low-cost clinical tests that are logistically simple enough to provide useful information to the healthcare services. The future impact of pharmacogenetics is therefore inextricably linked to diagnostics. Much of the underlying technology is already in place and it is anticipated that growth in the diagnostics industry will occur over the next five to twenty years to meet pharmacogenetic-inspired demands. The latter will arise not only from an increase in the number of drugs that carry a pharmacogenetic label but also from an increasingly knowledgeable public, keen to self-assess their predisposition to serious diseases and their treatment regime. The degree of expansion will depend on many of the factors discussed in Sections 2.8, 3 and 4.4 of this report (for example the logistics of co-developing novel drugs and diagnostics, uptake by healthcare providers of pharmacogenetic technologies, and cost–benefit assessments). This view of an increasingly important role for the diagnostics industry is reflected both in the existing literature and through submissions received by the working group from industry and the British In Vitro Diagnostics Association. It should be noted that although just under half of participants in the public dialogue supplemented professional advice with their own research on medicines, they were, in general, against the idea of pharmacogenetic tests being freely available 'over the counter' or through the Internet, and felt strongly that professional advice would be needed to support patient choice about the use of such tests (see Section 5 for further details).

Examples of relatively simple pharmacogenetics diagnostic tests already exist, including TPMT polymorphisms (Clinical Laboratory Improvement Amendments (CLIA)–certified molecular diagnostic from Prometheus, San Diego, see Box 6) and COBAS TaqMan analysers from Roche Diagnostics approved by the FDA for analysis of CYP2C19 and CYP2C9 (see Box 2). In cases where many predictive biomarkers are associated with a given drug response, automated multiplex detection formats must be used. The pharmacogenetic analysis of the highly polymorphic gene CYP2D6 has been achieved using an oligonucleotide microarray (see Box 2). A key advantage to these arrays is their ability to detect diverse forms of genetic variation (for example SNPs, insertions and deletions, gene conversions, complete gene deletion and gene-duplication events) in a single test. It is likely that proteomics-based technologies will also be incorporated into novel pharmacogenetic diagnostics.

As with many aspects of pharmacogenetics, most of the current and many of the foreseeable applications of diagnostics are in the field of cancer. Diagnostics are predominantly used to classify tumour types. For example a diagnostic to detect HER2 over-expression in breast cancer patients is used to guide therapy decisions for Herceptin (see Box 5). In addition, cancer diagnostics aid the design of clinical trials by enabling pre-selection of trial populations, potentially accelerating drug approval. They will also play a role in identification of risks associated with novel (and existing) drugs that can be identified by post-approval monitoring.

Box 5 Herceptin

In the UK Herceptin (trastuzumab) is licensed for and used in the treatment of breast cancer that has spread beyond the breast. Clinical trials have shown that Herceptin administered either in combination with chemotherapy or alone may significantly reduce tumour size, increase median time to disease progression, and increase one-year survival rates. Herceptin is not licensed for use in early stage breast cancer although clinical trails are currently being conducted on women with this condition.

Herceptin is an antibody-based treatment for a sub-group of breast cancer patients who have a genetic mutation resulting in multiple copies of a gene that causes the overproduction of a tumour growth factor receptor, HER2. When these receptors are present in large numbers they can result in the growth of tumours. Around 25–30% of breast tumours have high levels of HER2 and these may respond to treatment with Herceptin, which acts by effectively blocking the action of the receptor and selectively killing cancer cells that carry it, slowing the growth of tumours. Herceptin is directed specifically at the receptors—and so it can only help women who have the relevant gene. In other women this highly specific drug is much less effective. Accordingly, Herceptin can only be prescribed in conjunction with the relevant genetic test to ensure the optimum outcome for the patient.

The frequently used testing methods to determine HER2 status are immunohistochemistry (IHC) and fluorescence in-situ hybridisation (FISH: see Annex 3). Both methods are reliable, robust and highly specific when performed using standardised and validated testing protocols, and both are globally accepted as the established standard for HER2 testing. The IHC test is used to measure HER2 receptor overexpression in the tumour sample; the results of the test are graded from 0 to 3+. Herceptin is only prescribed if the result is 3+, when the cancer is considered HER2-positive. The FISH test uses fluorescent probes to 'paint' the *HER2* genes in a tumour cell, to see if the number of gene copies is normal or not. A normal cell has two copies of the *HER2* gene. If a FISH test detects more than two copies of the *HER2* gene, it means that the cell is abnormal and is HER2-positive. Patients with either a positive IHC or FISH test result should respond well to Herceptin. The development of Herceptin would not have been possible without specific diagnostic tests that identify HER-2 positive patients.

2.8 Current exploitation of pharmacogenetics in the pharmaceutical industry

The pharmaceutical industry recognises that the science of pharmacogenetics offers the promise of improving healthcare by helping to identify the optimal population for particular medical therapies. This will benefit individual patients and societies seeking more efficient use of healthcare resources. As discussed in the previous sub-sections, the pharmaceutical industry foresees a gradual rather than revolutionary movement towards implementing pharmacogenetic science, with certain therapeutic areas such as oncology taking the lead. Maximum use of the new science will only be achieved if work on the relevant ethical, regulatory and legal framework is fully aligned and keeps pace with rapid expansion of scientific understanding. It will also be critical to maintain public confidence in the technology and its potential to improve the average outcomes of prescription medication. This was shown very clearly in the public dialogue (outlined in Section 5.2.1), where concerns were expressed about whether the accompanying institutional arrangements could successfully deliver the technology. Concerns ranged from issues of consent to how information was shared with third parties such as insurers.

Although practices vary, many pharmaceutical companies are now collecting DNA samples from their clinical-trial patient populations when they can obtain appropriate informed consent. In the early phases of clinical development, pharmacogenetic analysis of these samples can act as pilot experiments to test hypotheses about the relative importance of genetic variation. It is estimated that this type of clinical research is being conducted in 20–30% of current early-stage programmes of drug development, with a higher proportion in oncology.

A proportion of these early-stage pharmacogenetic experiments will progress to phase III clinical trials, where the therapy is tested with an associated diagnostic. Some companies have estimated that within five years this will be the case for up to 10% of their late-stage portfolio, perhaps rising to 20% in the next ten years. Again, the proportion will tend to be higher for companies with a stronger portfolio in oncology.

It is important to recognise that pharmaceutical companies constantly evolve their processes for drug discovery and development as science progresses. As knowledge of the relative importance of genetic factors as a cause of drug safety and efficacy increases, industry will absorb this information into their processes for improving the prospective design and selection of new candidates. Where possible, this will favour the selection of candidates that avoid the effect of genetic variation; where it is not possible, and especially when genetic

factors contribute to segmentation of the disease pathology, the development of candidates with an appropriate diagnostic is expected to be routine practice in the next ten to twenty years.

The age of the blockbuster drug (one that generates more than US$1 billion (£550 million) of revenue each year) may be past if the application of pharmacogenetics reduces their target population. New medicines, such as Glivec (see Box 4) and Herceptin (see Box 5) have been successfully developed as a result of the segmentation of the disease pathology based on genetic variation. This process identified sub-groups of the population in which the medicine is effective. However, there is the danger that a market may be segmented into parts too small to provide a financial incentive for the development of appropriate therapies by the pharmaceutical industry. In this situation, incentives may be needed to promote the research and development of medicines for rare diseases or 'non-responders' to existing medicines identified by pharmacogenetic testing.

Medicines that are developed for the treatment of very uncommon diseases are known as 'orphan medicines'. The EU defines an orphan medicine as one that could treat a disease with a prevalence of less than 5 per 10 000 of the population, which approximates to 185 000 cases across the European Union (EU). As the number of patients who would benefit is too small to be profitable for the pharmaceutical industry, regulatory incentives such as a period of market exclusivity and research grants, currently exist for orphan medicines in the EU, along with tax incentives developed by individual member states. Advances in pharmacogenetics may result in the need for regulatory agencies to reconsider the definition of orphan medicines. The provision of European-wide tax incentives for such developments is important.

It is a considerable challenge to develop a genetic-based diagnostic in parallel with the development of a novel drug. Sufficient experimental evidence to demonstrate a statistically significant advantage in outcome for the diagnostically defined sub-group will have to be accumulated before pivotal phase III efficacy and safety trials. Both the positive and negative predictive value of the test must be known in order to design the phase III trial. Hence, the clinical utility of the biomarker must be assessed to be statistically sound; not only must the biomarker be measured in a well-defined analytical system but also there must be an established scientific framework that supports the physiological, toxicological and clinical significance of the results. This may require larger phase II trials and/or a greater degree of technical and commercial risk.

There is an even greater challenge in considering safety biomarkers because rare adverse reactions are not normally observed before the pivotal phase III programme. One implication of these statistical and logistic challenges is that pharmacogenetic safety and efficacy markers will continue to be discovered after a new drug is on the market, when evidence can be accumulated from many patients. This highlights the vital importance of a close and supportive ongoing dialogue with the regulatory authorities through both the development of a new drug and its post-marketing support phase (see Sections 2.9 and 2.10).

A further statistical challenge is the variation of polymorphism frequencies between different populations and the relative representation of these populations in the prospective clinical trial group. A notable example is the dramatic variation in the frequency of the epidermal growth factor receptor (EGFR) gene mutation between US, Japanese and European populations. Currently, most countries have individual laws, regulations and guidelines for conducting genetic research that hinder essential pharmacogenetic studies across populations. The rapid and efficient progress of international drug development relies on harmonious regulatory, legal and clinical frameworks across different countries. Progress should be made in this area and we recommend that the UK Government, with the International Conference on Harmonisation (ICH) (see Section 2.9), should review current guidelines and regulations for the conduct of genetic research across international borders.

2.9 Regulation and licensing

There are several functions of the regulation of medicines: first, to protect public health by allowing only medicines with a satisfactory risk-benefit profile on to the market; second, to provide adequate information to those who prescribe medicines and patients who take them so that they are taken safely and effectively; and third to encourage the development of innovative medicinal products by not raising unnecessary regulatory difficulties. In the UK these functions are performed by the Medicines and Healthcare products Regulatory Agency (MHRA), with the European Medicines Agency (EMEA).

Regulatory authorities grant marketing authorisation for medicines on the basis of clinical trial data for efficacy, safety and quality. As we have illustrated previously, many patients respond to a drug satisfactorily and without problems, some fail to show any response whatsoever and others may experience adverse reactions. The prescriber cannot reliably predict which of these responses an individual patient will demonstrate, and thus prescribing remains a relatively empirical process. Part of the reason for this is that the dose schedules recommended are often inflexible and do not take into account inter-individual variability in response to drugs. This is partly because the design of clinical trials on which marketing authorisation is granted usually use fixed-dose regimes that are defined by small

studies in early clinical development and which may not reflect the range of clinical variability in a larger population.

Most major regulatory authorities, such as the FDA and EMEA, as well as the ICH, recognise the importance of taking pharmacogenetic variability into account when regulating the development of new medicines, especially when considering their approval for marketing. The ICH brings together the regulatory authorities of Europe, Japan and the USA and experts from the pharmaceutical industry in the three regions to discuss scientific and technical aspects of product registration. All three bodies have issued guidelines for the sponsors of new medicines on how the genetic differences that may influence not only the efficacy and safety of medicines, but also drug interactions, may be addressed in regulatory submissions.

Regulatory submissions that include pharmacogenetic data must be compliant with the rules applicable to the usual requirements of that regulatory authority. At present, many pharmacogenetic data sets are not scientifically established to a sufficient extent to be appropriate for regulatory decision making. In many instances the pharmacogenetic test in question may not have been established as a valid biomarker. So far, relatively few biomarkers used in pharmacogenetic studies satisfy these requirements and more rigorous validation and establishment of standards are required.

Most major regulatory authorities currently encourage the voluntary submission of pharmacogenetic data by the sponsors of new medicines. For example both the FDA and EMEA took a significant step in March 2005 in issuing guidelines to encourage pharmaceutical companies to submit information about how genetic variations affect the way people respond to drugs (FDA 2005; EMEA 2005). Regulatory agencies wish to encourage the production of pharmacogenetic data that are reproducible and predictive of drug response before including such information in the evaluation, approval and labelling of medicine. However, there has been some reluctance by companies to submit such data for fear of the information being used to limit the market for their drugs. Sponsors are in fact being encouraged to submit their preliminary pharmacogenetic data for consideration, without prejudice for their overall development programme, into so called 'safe harbours' whereby companies discuss exploratory data with regulators on a confidential basis. This should help to expand the evidence base for the application of pharmacogenetics, which is an important requirement to encourage the development of the field. Building a better mutual understanding of the data will also provide additional impetus for the development of cheaper and more accessible testing.

Regulatory scientists need to develop a better understanding of the gene expression profiles and genotype/phenotype correlations being explored by the pharmaceutical industry for pharmacogenetic testing, and the test systems and techniques need to be better defined. Regulators also need to address the problems associated with the transmission, storage and processing of large amounts of complex pharmacogenetic data. This must be done as a priority before complex pharmacogenetic data becomes a routine part of the drug regulatory process.

2.10 Post-market monitoring

At the time of licensing, the amount of clinical information on patient safety is limited to data derived from clinical trials. The purpose of post-market monitoring is twofold. First, to gain information on the potential frequency of adverse reactions when the drug is more widely used in clinical practice, and, second, to identify rare adverse reactions which did not emerge during clinical trials because of the limited size of the population studied.

Post-marketing safety monitoring relies on several systems. Spontaneous reports of suspected adverse reactions from doctors, nurses, pharmacists and patients to regulatory authorities, either directly using systems such as the UK Yellow Card scheme or through industry, are a valuable source of safety signals. The Yellow Card scheme was introduced in 1964 to provide a straightforward route for a doctor or dentist to report a suspicion that a medicine could have harmed a patient. Nurses, pharmacists and the public (in a pilot scheme) can now also contribute reports. In 2004, the scheme was reviewed in response to an increase in requests for access to Yellow Card data, which raised major issues in relation to public health. Following the recommendations of the review, three categories of data were introduced:

1 Aggregated anonymous data collated from individual Yellow Cards. The recommendation was that these data should be proactively published on a regular basis.

2 Data that include details from individual Yellow Cards, but without any information that identifies a reporter or patient or provides any opportunity for the recipient to contact a reporter. The recommendation was that applications for such data should be reviewed by independent scientific and ethics committees.

3 Data similar to category 2, but where the intention is to conduct research that would involve contact with the reporter and/or patient. As in category 2, the recommendation was that applications for such data should be reviewed by independent scientific and ethic committees.

Clinical databases can also be used for observational studies comparing the frequency of adverse reactions in a drug under question with a control population. Finally, prospective randomised controlled studies are sometimes used to answer important questions about drug safety, although these are expensive to mount and are usually of considerable duration.

If all the challenges discussed above could be addressed together there is a major opportunity for pharmacogenetic analysis to be applied to the explanation and ultimately prevention of some rare adverse events by better targeting of therapies. This opportunity applies not only to new drug developments but also to improving the safe use of existing widely prescribed medicines.

2.11 Conclusion

Application of pharmacogenetics. The pharmaceutical industry foresees a gradual rather than revolutionary movement towards implementing pharmacogenetic science, with certain therapeutic areas such as oncology taking the lead. Cancer therapy is particularly amenable to both pharmacogenetic testing and development of new drugs because the diseases arise as a consequence of acquired mutations to somatic cells, which provide obvious gene and protein targets. The pace of advance will rely on relevant ethical, regulatory and legal frameworks keeping pace with technological and scientific developments, as well as the increasing availability of large and reproducible sets of data.

Industrial research. The current industrial drug discovery process has moved away from susceptible-gene hunting using large family-based DNA collections, and towards the use of population-based genetic association studies as a means of using genetics to increase confidence in potential drug targets. Technology has advanced enabling both industry and academia to genotype large numbers of samples easily and cheaply. Haplotype maps will make this process easier and further reduce the cost.

The age of the blockbuster drug (one that generates more than US$1 billion (£550 million) of revenue each year) may be past if the application of pharmacogenetics reduces its target population. Industry sources predict that within the next five years, up to 10% of the late stage portfolio progressing through major phase III trials will be a therapy with an associated diagnostic test. This may rise to 20% in the next ten years, although the proportion will be higher in companies with a large oncology portfolio. Advances in diagnostic technology are unlikely to be the rate-limiting step in the introduction of pharmacogenetics into clinical use.

The pharmaceutical industry has little motivation to fund research into the pharmacogenetic factors that might affect the response to generic drugs that are already on the market. Over half of the medicines dispensed in the NHS are generic drugs, whose patents have expired. Research on these medicines must be done by publicly funded researchers, either alone or in partnership with the pharmaceutical or diagnostic industries.

Sample size. Each pharmacogenetic test must be evaluated statistically on a case-by-case basis. To ensure the validity of evaluations of new pharmacogenetic tests, prospective trials will frequently require many patients.

Using pharmacogenetics to explain adverse drug reactions or to increase drug efficacy. With the exception of oncology, there are few current examples of how pharmacogenetic testing can improve drug targeting in routine clinical practice. Using pharmacogenetics to explain rare ADRs in phase III clinical trials of new drugs is not straightforward because it is often difficult to obtain sufficient statistical power and accurate phenotypic description of affected patients. In addition, it may be necessary to track back to the patient and obtain informed consent for DNA analysis, unless this was previously given as part of a controlled clinical trial or epidemiological study. Application of pharmacogenetics to more widespread drug-related morbidity for commonly used generic therapies may be realisable, but is unlikely to be conducted by industry. An example may be in the use of warfarin (as outlined in Box 3). There is potential for partnerships between industry and academia to conduct retrospective analysis of large populations of patients who have been treated with existing drugs to explain the variation in efficacy.

Regulation and ethics. The full potential of pharmacogenetics will only be achieved if work on the relevant ethical, regulatory and legal frameworks are fully aligned and keep pace with the rapid increase in scientific understanding. At present, many pharmacogenetic data sets are not well enough established scientifically to be appropriate for regulatory decision making. Most major regulatory authorities currently encourage the voluntary submission of pharmacogenetic data by sponsors of new medicines. Regulatory authorities wish to encourage the production of pharmacogenetic data that are reproducible and predictive of drug response before using such information in the evaluation, approval and labelling of medicines. Pharmacogenetic testing will require increased post-market monitoring. However, linking post-market monitoring with genetic data will be associated with practical and ethical problems such as confidentiality, consent and cost (see Section 5).

International harmonisation. Rapid and efficient progress of international drug development relies on harmonising regulatory, legal and clinical frameworks across different countries. Currently most countries have individual laws, regulations and guidelines for conducting genetic research that hinder essential pharmacogenetic trial work across populations. Progress must be made in this area if large-scale trials across different countries are going to be possible.

3 Clinical applications of pharmacogenetic tests

3.1 Introduction

This section outlines the translation of pharmacogenetic tests from regulatory approval into routine clinical practice. It builds on the potential of pharmacogenetics in research and development outlined in the previous section and expands on many of the issues raised in the drug development process and the subsequent value of the technology in the clinic. The use of a test in routine clinical practice is based on the fundamental pharmacological principles, outlined in Section 1.4, that an appropriate drug is delivered in the correct dose to produce the desired effect with a minimum of toxicity. The clinical use of the test is central to the process that will determine the impact of the pharmacogenetic test on mainstream healthcare. Consideration is also given to the current use of pharmacogenetics in the developing world and its potential in the future. The clinical use provides background to the subsequent section, where the implications of pharmacogenetic tests for a variety of end users are discussed.

3.2 Pharmacogenetic testing in the clinic

A pharmacogenetic test is a genetic test with the objective of influencing the choice of drug or dose used in the treatment of an individual patient. Such tests may be conducted on the person (to test for inherited variation) or on the disease tissue (currently confined to oncology). The test conducted would usually be an examination of genomic sequence looking for specific variants, but could include expression analysis – a quantitative or qualitative determination of the messenger RNA transcribed in a tissue or organ (see Annex 3). Pharmacogenetic tests may also include the examination of protein products, or functional tests, also designed to reveal genetic differences in the target individual or tissue. Some important examples are shown in Table 3.

Table 3 Partial spectrum with examples of different mechanisms involved in genetic variation to drug therapies. (Based in part on Evans & Relling (1999); Evans & McLeod (2003); WHO (2002)).

Mechanism of gene variation	Gene or gene product	Drug	Clinical consequence on drug efficacy (E) or adverse effect (A)
Drug metabolism	*MDR1*	Protease inhibitors, others	HIV response (E)
	NAT-2	Isoniazid, Hydralazine, others	Neuropathy (A), lupus erythematosus (A)
	CYP2D6	Codeine, antidepressants, anti-psychotics, others (see Box 2)	Changes in efficacy (E), Dyskinesia (A), narcotic effects (A)
	CYP2C9	Warfarin, others	Changes in efficacy (E), haemorrhage (A)
	VKORC1	Warfarin, others	Changes in efficacy (E), haemorrhage (A)
	RYR-1	Halothane, other anaesthetic agents	Malignant hyperthermia (A)
Protection against oxidants	G6PD	Primaquine, Acetanilide, others	Haemolytic anaemia (A)
Drug target	Angiotensin converting enzyme	Captopril, Enalapril	Treatment of hypertension or cardiac failure (E)
	HERG	Quinidine	Cardiac arrhythmia (A)
	HKCNE2	Clarithromycin	Cardiac arrhythmia (A)
	Oestrogen receptor	Hormone replacement therapy	Effects on bone mineral density and HDL cholesterol (A)

Table continues overleaf

Mechanism of gene variation	Gene or gene product	Drug	Clinical consequence on drug efficacy (E) or adverse effect (A)
Drug targets for cancer treatments (see Table 2, Boxes 4 and 5)	*bcr/abl*	Glivec	Chronic myeloid leukaemia (E)
	EGFR	Cetuximab	Colorectal cancer (E)
	HER2	Herceptin	Breast cancer (E)
Genetic polymorphisms related indirectly to therapy	Apolipoprotein	Tacrine, statins	Alzheimer's disease (E)
	Factor V Leidan	Oral contraceptives	Risk of venous thrombosis (A)
	Haemoglobin S	Anti-malarials	Protection against malaria may confound trials (E)
	pfcrt	Chloroquine	Mutations of this gene in the malarial parasite *Plasmodium falciparum* results in resistance to chloroquine (E)

The examples shown are as follows: *MDR1*: multidrug resistance; *NAT-2*: N-acetyltransferase; *CYP*: cytochrome P450; *VKORC1*: vitamin K epoxide reductase complex; *RYR-1*: ryanidine receptor; G6PD: glucose-6-phosphate dehydrogenase; *HERG* and *HKCNE2* are potassium channels; *bcr/abl* is a tyrosine kinase; EGFR: epidermal growth factor receptor; HER2: human epidermal growth factor receptor; *pfcrt*: *Plasmodium falciparum* chloroquine resistance transporter.

With the range of tests available it is possible to identify several potential goals for clinical pharmacogenetic testing:

- The sub-division of common diseases into different molecular sub-types which may be more or less susceptible to specific treatments.
- To evolve more logical approaches to dosage, efficacy and the prevention of adverse reactions by analysing the genetic basis for differences in the pharmacodynamic or pharmacokinetic properties of drugs.
- To identify genetic susceptibility to various common diseases that, although not directly related to drug metabolism, offer targets for pharmacological intervention.

These goals for clinical pharmacogenetics testing are discussed further in the following sections.

3.2.1 Molecular heterogeneity of common disease

So far, by far the most progress in relating molecular heterogeneity of common diseases to potential drug targets has been made in the field of cancer. It is now clear that what used to be thought of as single entities, similar histological tumours of the bowel or lung, for example, show considerable heterogeneity in the patterns of oncogene mutations. As described in Section 2.7, there is already clear evidence that by sub-dividing these different genetic entities it is possible to develop chemotherapy related against specific varieties. However, like all forms of cancer therapy, even these individualised approaches will be associated with the problems of new mutations and drug resistance. There are already microarray data to suggest that complex patterns of expression of oncogenes may be involved in determining the prognosis and response to treatment for certain cancers. Although it is too early to be certain about the full extent to which the molecular dissection of common cancers will become part of clinical practice in the future, there is no doubt that it is already changing our approach to the management of many forms of the disease.

At present, much less progress has been made towards defining the molecular heterogeneity of other common diseases in a way that might have pharmacological implications. However, a start has been made. Although type I diabetes, that is insulin-responsive diabetes, is very rare in infancy, several babies have been reported with this condition in whom blood tests have shown a complete absence of C peptide, which is a marker for the presence of insulin. Hitherto, these babies have been treated with insulin with varying control of their diabetes. Recently, it has been found that a sub-set of these infants carry mutations in the gene for the *KATP* gene, which is involved in insulin secretion. It turns out that these children are fully responsive to the oral agent sulphonylurea, and it has been possible to stop the insulin treatment and maintain them on this drug with complete control of their diabetes (Slingerland & Hattersley 2005).

Type II diabetes, which is the form that is not responsive to insulin, is one of the commonest diseases of mankind, predicted to affect over 300 million of the world's population by 2020. It is associated with obesity, high blood pressure and an increased risk of heart disease. Although there is growing evidence that it results from complex interactions between changes in foetal growth and diet, it is also clear that it has a strong genetic component and varies widely in its frequency among different ethnic groups. There is already evidence for genetic heterogeneity of this disorder. For example, the form associated with mutations of the hepatocyte nuclear factor gene *(HNF-1)* turns out to be particularly sensitive to the sulphonylureas (Stride & Hattersley 2002). It seems very likely that this condition, like many other common multigenic diseases, will show further molecular heterogeneity, which may have important implications for more precise therapy.

3.2.2 Dosage, efficacy and adverse reactions

There are now numerous examples of genetic variation in the pharmacodynamics and pharmacokinetics of drug response that encompass the full spectrum of drug disposition, including metabolism and transporters that influence absorption, distribution and excretion. Similarly, there is an equally wide variety of genetic variability in the targets for drug action (Evans et al 2003) (Table 3).

There are more than 30 families of drug-metabolising enzymes in humans. The CYP450 family of genes, which is involved in drug metabolism, is described in Box 2. Many genetic variants involving one of these genes have been described as the basis for varying response to drugs. There is increasing evidence that more than one gene may be involved in some cases. For example, about three-quarters of Caucasians and about half of Blacks have a genetic inability to express functional CYP3A5, but this may not be evident because many medications metabolised by this enzyme are also metabolised by another enzyme, CYP3A4. For drugs that are equally metabolised by both enzymes, the natural rate of metabolism is the sum of the two; interactions of different variants of these two enzymes produce a complex series of differences in response to a variety of drugs.

Several important variations in genes encoding drug transporters have also been identified. For example, there is a large family of genes involved in adenosine triphosphate (ATP) binding of membrane transporters. A principal member of this family, P-glycoprotein, is encoded by a gene called *MDR1*. P-glycoprotein is involved in the energy-dependent efflux of a variety of substrates, including several anti-cancer drugs, cardiac glycosides, immunosuppressive agents and protease inhibitors that are used for the treatment of HIV/AIDS. The importance of genetic variation in the function of P-glycoprotein in the management of HIV is discussed later in this section. Several other genetic systems involving transporters have been found to be associated with variation in drug response.

There is also a growing list of genetic polymorphisms involving drug targets that can influence drug response. For example, variations at the locus that controls angiotensin-converting enzyme have shown reproducible effects on the action of ACE inhibitors on blood pressure reduction and cardiovascular function. Similarly, polymorphisms involving the gene for the bradykinin B2 receptor appear to be involved in determining the frequency of the distressing cough induced in some patients by ACE inhibitors. And variation at the locus that controls oestrogen receptor modifies the response to hormone-replacement therapy. There are now many other examples of target-gene polymorphisms that are likely to be of clinical relevance.

All this genetic variability has potential implications for improving the efficacy of drug treatment and for the avoidance of adverse effects.

3.2.3 Genetic variation with indirect effects on drug response

A variety of mutations have been discovered in blood-clotting factors that pre-dispose towards venous thrombosis and cerebral vein thrombosis. One of the commonest is called blood Factor V Leiden. Individuals with this mutation are more likely to develop venous thrombosis when taking oral contraceptives and, under certain circumstances, may require treatment with anti-coagulant drugs. Individuals with particular genetic varieties of the apolipoproteins, notably apolipoprotein E (APOE), seem more likely to respond to tacrine, given for Alzheimer's disease, and appear to have an enhanced survival when giving statins to prevent the progression of atherosclerosis. A variety of other interactions of this type have been reported. And, as discussed in Section 3.7, genetic variability in response to infections may be of increasing importance in designing trials of drugs or vaccines directed at their control.

3.2.4 Overall impact

There is now an extensive literature on genetic variability in response to different pharmaceutical agents. However, many of these studies have been quite small and there have been virtually no attempts made to expand them to see whether they would be efficacious and cost effective in a broader clinical setting. Even in cases in which the efficacy has been clearly proved (see Box 6), use of genetic variability to a given pharmaceutical agent has not yet been widely adopted by the medical profession. And, as outlined below, there are many difficulties to be overcome before this is achieved.

3.3 Potential problems in the investigation and application of pharmacogenetics in the clinic

Throughout this report it has been emphasised that, with the possible exception of certain forms of cancer, many of the better-defined genetic modifiers of drug response that result from mutations in single genes are quite uncommon and, in such cases, it may not be cost effective to screen for them.

Even more importantly, it is becoming clear that the action of many drugs is under the control of more than one gene and hence there may be considerable phenotypic variability in response, depending on which combination of the particular genes carry functional polymorphisms. Indeed, it is already apparent that the problems of defining the genes involved in the complex multigenic systems that may underlie variability of drug response are very similar to those encountered in genome searches for the genetic component of common diseases. In both cases it has often been difficult to replicate the findings in different studies, at least in part because some of the genes involved have a very small phenotypic effect.

Although, as technology improves, there will undoubtedly be further progress in genome searching for both disease and drug-response associations, for a successful outcome there are two critical issues. First, it will be vital to obtain a clear definition of the pharmacogenetic phenotype that is under investigation. As discussed recently, it is all too rarely appreciated that the appropriate definition of drug response, in terms of both safety and efficacy, is often not obvious and considerable exploration of clinical data is required to guide genetic studies (Need et al 2005). The second problem is population size. Already there are several examples of apparent associations between variability in drug response and particular genes which, when larger populations have been analysed, have not been confirmed. While the use of better tagging resources such as HapMap (see Section 2.3) to represent common variants, with complementary methods appropriate for defining rare variation, will lead to more rapid and precise methods for gene hunting, the importance of phenotypic definition and population size and composition cannot be over-emphasised.

These problems may be compounded as attempts are made to apply this type of genetic information in the clinic and community. As in all modern population screening techniques, one of the key issues is the 'numbers needed to screen'. To assess the role of complex gene-environment interactions and screening in a population, it is vital to know the penetrance of the genetic trait, that is how often the phenotype is expressed in individuals with the variant gene, and its frequency, that is how often the variant gene occurs in the population. An example of these problems is posed by Vineis et al (2001) in relation to the *BRCA1* gene. Mutations of this gene increase the risk of breast cancer to about 80% in mutation-positive relatives of a person with breast cancer with a BRCA1 mutation. Although there has been some lack of agreement between the results of different trials, it has been suggested that the drug Tamoxifen might reduce the risk of developing breast cancer with these genotypes by approximately half giving an absolute risk of 40%. If this were so, to prevent one case of breast cancer in an individual family it would be necessary, statistically speaking, to screen five family members and to treat 2.5 mutation carriers. However, if the general population is screened rather than an individual family, the numbers needed to be screened changes greatly because of different penetrances of the same mutation in differing genetic/environmental backgrounds, and the fact that population screening may pick up novel mutations in BRCA1 of unknown (and often reduced) penetrance. So now, the cumulative risk in mutation carriers might be 40%, not 80%, with an absolute risk reduction by Tamoxifen of 20% rather than 40%, which means to prevent one case of breast cancer five mutation carriers must be treated. However, because only 0.2% of the general population are mutation carriers, the numbers needed to screen is 2500 to prevent one breast cancer; this very large number needed to screen makes BRCA1 an unrealistic marker for use in general population screening. The phenotype of BRCA1 mutations is expressed in a reasonably high proportion of those who carry the variant gene; for a gene of lower penetrance the numbers that would be needed to be screened would be even higher.

Granted that difficulties of this kind will undoubtedly have to be faced, there is still room for optimism. For example, it is already clear that some of the genetic variants which modify drug response, alleles of the CYP450 system for example (see Box 2) occur at reasonably high frequencies and have a high level of penetrance. Similarly, the effect of different *VKORC1* haplotypes on the regulation of warfarin levels (see Box 3) is a good example of the action of common genetic variants of high penetrance that might be eminently suitable for pharmacogenetic testing in populations (Rieder et al 2005).

Even this very brief review of these complexities suggests that each genetic variant will have to be tested on an individual basis by large-scale population studies, after a precise definition of the pharmacogenetic phenotype.

Box 6 Thiopurine S-methyl-transferase

The thiopurine drugs mercaptopurine and azathioprine are used clinically as immunosuppressants for Crohn's disease, systemic lupus erythematosus, dermatomyositis, and severe psoriasis, in renal transplantation and to treat neoplasias, such as acute lymphoblastic leukaemia. The predominant metabolic pathway for these medications is by thiopurine S-methyl-transferase (TPMT). A mutation in the *TPMT* gene can result in decreased levels of enzyme production and therefore a decreased rate of breakdown of the thiopurine drugs.

When treated with mercaptopurine or azathioprine, patients who inherit a TPMT deficiency accumulate excessive concentrations of the active thioguanine nucleotides in blood cells. This can lead to severe and potentially life-threatening problems with the formation of blood cells (haematopoietic toxicity). About 1 in 300 individuals carries two mutant *TPMT* alleles (that is, they are homozygous for the polymorphism), and do not express functional TPMT. These individuals require doses to be reduced to as little as 5–10% of the conventional dose to tolerate therapy. About 10% of the population are heterozygous (they have one mutant allele) for this polymorphism and have intermediate levels of TPMT activity requiring only modest dosage reductions. The remaining 90% of the population carry two normal alleles (wild type) and have full TPMT activity. Acute lymphoblastic leukaemia patients with one or both mutant *TPMT* alleles tend to have an improved response to mercaptopurine therapy and better chances of being cured, compared with patients who have two normal alleles.

Currently, prescribing is monitored by a regime of laboratory tests every two weeks including full blood count and liver function. Clinical diagnostic tests are now available for the detection of inactivating SNPs in the human *TPMT* gene, and TMPT genotyping may potentially reduce the requirement for the monitoring regime, which is onerous for patients and health professionals. However, the routine use of TPMT genotyping to make treatment decisions is still limited. To some extent, this is related to the perceived high cost of genotyping, even though this process has been shown to be cost effective. In the USA, the FDA recently revised mercaptopurine drug labelling to include the mention of TPMT testing, although, after much debate, it decided against requiring such testing. The drug label includes information on the prevalence of patients with reduced TPMT activity and states that genotypic and phenotypic testing is available to determine if a patient has homozygous, heterozygous or wild-type TPMT deficiency/activity.

3.4 Type of conditions being considered

The potential benefits of pharmacogenetics may vary according to the type of conditions being considered.

Common/chronic conditions. The potential for public health benefit could be considerable, reflecting a high morbidity from side effects of treatment in the population, or high wastage from patients treated with drugs of low or no clinical efficacy. In these situations the costs of testing would be high, even if genetic screening per person were relatively cheap, as large numbers would need to be screened, and there would need to be wide availability of the genetic test from general practitioners or pharmacists. Examples include maturity onset diabetes, high blood pressure, disorders of lipid metabolism, cardiovascular disease, and asthma.

Rare conditions. Availability of tests for these conditions could be restricted, for example to a hospital setting. The cost of screening per individual might be high, but total cost in terms of avoiding adverse drug reactions might be relatively low. Individual benefit might also be high: for example *TMPT* gene screening in the treatment of childhood leukaemia (see Box 6).

Acute conditions. In this situation individual benefit could be potentially high if efficacy is a major consideration. For example the choice of antibiotic in infection or anti-depressant therapy for severe depression where there is risk of suicide if effective treatment is delayed.

All of these classes of usage are theoretically possible. A few examples of most of them already exist, particularly in the field of oncology (see Section 2.6) and many examples of each will doubtless eventually be discovered. Progress towards implementable tests is likely to be fairly gradual, rather than a precipitate change in practice, because each test/drug combination needs to be identified separately and validated with extensive clinical and economic data.

3.5 Questions for clinical application

Moving from theoretical value to practical implementation requires demonstration of clinical efficacy. In addition to scientific validity, this implies examination of factors such as cost, the speed with which results would be available, the urgency of getting the dose right and the consequences of delay in finding

the best drug/dose for the patient, and the penalty for choosing a sub-optimal treatment. Doctors and other prescribing professionals faced with a patient, a choice of drug, and the option of testing, will want to know:

- How substantial is the advantage of one drug over the alternative?
- How soon will the test result be available?
- What is the therapeutic, economic or medico-legal consequence for prescribing the less advantageous drug?
- What is the cost of the test?
- Is a pharmacogenetic test more effective than careful monitoring of response as currently practised?
- How robust are the data on which the answers to the foregoing questions are based?

Similarly, in testing for susceptibility to adverse events, the questions will be:

- How common is the adverse event?
- How severe is it?
- How effective, and how costly, is treatment of the adverse event if it does occur?
- What proportion of cases is attributable to (and avoidable by testing for) the susceptible genotype?
- Is a pharmacogenetic test more effective than careful monitoring?
- What is the cost of testing: not just the individual test, but the whole programme, for example for common conditions, or routinely testing very large numbers of people to detect small numbers of susceptible individuals?

These questions give an indication of the factors that must be taken into account when deciding on the clinical application of a test. Warfarin (see Box 3) can be used to illustrate this point. As described in Section 2.3, it is possible to genotype an individual before starting treatment to provide some background information, but whether, in routine clinical practice, it actually makes a difference to the outcome of treatment sufficient to justify the cost and effort involved is not easy to predict. It will require large prospective controlled trials of patients treated with and without genotyping, comparing long-term outcomes, to be fully convincing. This is just one example of the complexity of factors that must be taken into account, when deciding whether a pharmacogenetic discovery will make a real difference to clinical outcomes and should be adopted into routine practice.

3.6 Current situation in clinical practice

The NHS in England is expected to spend around £11 billion on drugs in 2005–6. According to the Audit Commission, deaths in England and Wales from prescription errors and ADRs have increased 500% over the past ten years, resulting in 1100 deaths in 2002 (Audit Commission 2002). Adverse drug reactions are estimated to affect around 7% of patients or hospital admissions at an annual cost of around £466 million in England (Pirmohamed et al 2004). These figures do not take account of the increase in primary care consultation time, the loss of patient confidence and non-compliance, resulting in wasted resources associated with ADRs.

Many of these costs are not amenable to reduction through pharmacogenetic approaches, as they are the result of factors such as prescription errors or poor patient adherence to treatment. Nonetheless, pharmacogenetics could theoretically reduce some of the burden of ADRs in the community by identifying patients at high risk, leading either to reduced dose or use of alternative treatments. This might include the identification of people at risk of long-term adverse effects from a particular class of drugs. For example, COX-2 inhibitors are widely prescribed for rheumatoid and osteoarthritis, but may disappear entirely as a class of drugs because of the associated risk of adverse cardiovascular events, including heart attacks. It is possible that genetic testing might in the future allow such preparations to be used among a sub-set of patients who can be identified as not being susceptible to the associated risk. In addition, pharmacogenetics could be used to identify only those people likely to benefit from treatment, that is, where there is clinical efficacy. Patients could therefore be prescribed clinically relevant treatments, with expected reductions in morbidity and gains in health and quality of life, while the numbers of wasted prescriptions would be reduced.

The 2004 General Practitioner contract links remuneration with clinical outcomes in the areas of cardiovascular disease, stroke, asthma, diabetes and epilepsy. These targets are difficult to achieve and may sometimes require the administration of many drugs concurrently, with frequent manipulations and additions to medication regimes. This involves inconvenience for the patient and possible drug toxicity. Both patient and practitioner would therefore welcome the promise of better targeted medicines in the future, one of the key goals of pharmacogenetics. However, there may be possible medico-legal implications for the prescriber if a

patient requests a pharmaceutical but refuses genotyping or is found on testing to be a non-responder or at risk of adverse reaction. Duty of care could be compromised and further legal and regulatory advice on this issue would be helpful. This was discussed by the participants of the public dialogue exercise, who were supportive of the right of an individual to have access to drugs even if test results were unfavourable, if they decided that on balance they were willing to accept the risks of a course of treatment and the potential benefits outweighed the risks. For medical negligence liability, the need for some form of disclaimer or waiver was discussed in some groups. Only a few participants thought that, all things being equal, the decision should be left up to the professional as to whether the drug should be offered (see Section 5.2.1).

Problems of drug efficacy were recognised by members of the public in the dialogue workshops, with around half of participants having experienced an untoward reaction to a drug in the past. For many participants genetic tests were seen to be empowering and a way of informing patient choice. It should be noted that a significant minority had reservations about the growing use of genetic tests in society. This is explored further in Section 5.2.1.

However, current pharmacogenetic testing is largely restricted to the field of cancer. Until studies of the clinical and cost effectiveness of its value on a drug-by-drug basis have been carried out, its role in clinical practice will remain uncertain.

3.7 Delivering pharmacogenetic tests in the future

It is not yet clear whether pharmacogenetic tests will be ordered and implemented by doctors, pharmacists or prescribing nurses, and all may have a role in different situations (see Box 7). Pharmacists could, for example, provide basic information, collect some sample types (for example buccal swabs), convey results of simple tests to patients, and, within agreed limits, be responsible for prescribing and advising, monitoring and reviewing the treatment prescribed, recording results and educating the public and healthcare professionals. The Royal Pharmaceutical Society is preparing guidelines for such practice to pharmacists who plan to set up such services. As an example of a test that has been developed for routine delivery over the past ten years once the market was defined, the market for diagnostic tests on samples taken from the human body (*in vivo* diagnostics) such as INR monitoring (INR stands for international normalised ratio and is a test used to monitor the effects of anticoagulant drugs like warfarin) has moved from a laboratory-based test to a simple desktop test. It is entirely possible that some pharmacogenetic testing will follow a similar course. However, the public dialogue exercise that was undertaken as part of this study suggested that doctors were preferred over pharmacists for anything other than minor medical advice (see Section 5.2.1).

Doctors, pharmacists and prescribing nurses, as well the recipient patients, will need to understand the basis, reliability, sensitivity and specificity of the tests and the information they provide, which will require an educational programme. If tests give simple, highly discriminatory results with considerable reliability, prescribers will not require extensive prior education to enable them to act appropriately on the results. It seems likely that the role of both pharmacists and nurses will evolve further and this will have implications for current and future training in basic genetics and pharmacogenetics.

Use of genetic test results will be heavily influenced by the advice and actions of pharmaceutical regulators. As we have outlined previously (see Section 2.9), it is critically important to have appropriate regulation and national advisory mechanisms in place before clinical applicability becomes widespread.

Because pharmacogenetic information may have a considerable effect on the cost–benefit factors involved in drug treatment, it will also be necessary for Governmental control bodies, including the National Institute for Health and Clinical Excellence (NICE) to become acquainted with the likely complexities of these new developments.

Box 7: Other health professionals with responsibility for prescribing

Community pharmacists
The 2004 Community Pharmacy contract significantly changes the role and responsibilities of community pharmacists. The contract sets out to use fully the skills and knowledge of pharmacists and to extend their role to improve public health. It aims to integrate pharmacy more fully into primary healthcare services. Key roles of community pharmacists that in the future may have implications for pharmacogenetic testing are:

- To advise patients and other health professionals on the safe and effective use of medicines and to be a point of first contact with healthcare services for patients in the community.
- To provide medicine management services, especially for people with chronic illness. Pilot projects are currently devolving responsibility for repeat prescribing to community pharmacists assisted by electronic transfer of scripts.
- To promote patient safety by preventing, detecting and reporting adverse drug reactions and prescribing errors. Pharmacists can offer a Prescription Intervention Service to optimise dosage and to promote adherence to prescribing guidelines.
- To prescribe medicines and to monitor clinical outcomes.
- Supplementary services provided by community pharmacy will include diabetes and coronary heart disease screening, substance misuse, and prescribing for self-limiting minor illness.

Nurse prescribing
The nurse prescribing scheme for district nurses and health visitors was piloted in 1994 and extended in England over the next six years. By September 2001 more than 22000 district nurses and health visitors, including 1000 practice nurses, were qualified to prescribe from the Nurse Prescribers Formulary, which provides up-to-date guidance for nurses on prescribing, dispensing and administering medicines. In May 2001 the Government announced that nurse prescribing would be extended to a wider range of medicines, to cover four broad areas of practice: minor ailments, minor injuries, health promotion and palliative care. Supplementary prescribing by nurses allows them, after initial assessment of a patient by a doctor, to prescribe for a patient in accordance with a clinical management plan. Relevant clinical areas include asthma, diabetes, heart disease and mental illness. The Extended Independent Nurse Prescribing role is dependent on extensive training and continuous clinical supervision.

3.8 Ethnic considerations

There have been some concerns about the use of drugs directed only at particular population groups. For example, the recent decision to licence the drug BiDil for the treatment of heart failure only in African–Americans has caused considerable concern in the media over the possibility that ethnicity rather genetics would be used for prescribing. However, as discussed in Section 1.3.9, there is vastly more genetic variation within than between ethnic groups and hence an ethnic basis for variable response to therapy is unlikely to be common. There will, of course, be exceptional cases. For example, glucose-6-phosphate-dehydrogenase deficiency occurs throughout the tropical world because, as well as causing anaemia in response to certain drugs, it has also afforded protection in the past to infection by severe malaria and hence its frequency has increased. Undoubtedly there will be other examples of genetic polymorphisms that have come under selection like this or have reached higher frequencies in particular population groups owing to founder effects and the like. But, like glucose-6-phosphate-dehydrogenase deficiency, many of these polymorphisms will not be completely confined to one particular ethnic group and hence, ethnicity itself is unlikely to be a major guide to the control of drug therapy in the future.

3.9 Developing countries

As emphasised by the World Health Organization (WHO 2002), pharmacogenetics undoubtedly has a potential role to play in the diseases that are still decimating large populations in developing countries, particularly communicable disorders. In discussing the role of pharmacogenetics in developing countries it is necessary to take a broader view of genomics research. The human genome project was accompanied by similar initiatives to sequence the genomes of viruses, bacteria and parasites that affect human health. This work holds considerable promise for discovering a wide variety of new drug targets and ways of developing vaccines.

There are already examples of single-gene variants that have potentially important implications for the treatment of infectious disease. The inherited deficiency of the red blood cell enzyme, glucose-6-phosphate dehydrogenase (G6PD), affects hundreds of thousands of people in tropical countries. This condition causes a severe form of anaemia after the ingestion of several drugs, among which is the anti-malarial agent primaquine. This is the only easily available drug for the complete eradication of infections due to Plasmodium vivax, a particularly common form of malaria in many developing countries. There are many different molecular forms of G6PD deficiency, some of which result in a short, self-limiting bout of anaemia after primaquine therapy, whereas others are associated with profound and life-threatening anaemia. Although there are simple, enzyme-based tests available to identify this condition, they have not been widely applied in practice as it is still far from clear whether it will be cost effective to introduce genetic testing, given the enormous difficulties in the provision of basic healthcare in the developing world. Even simpler rapid stick tests are being developed but they are still not available. This problem is likely to be intensified in the near future because of partial resistance by the parasite to primaquine and hence the need to give the drug in larger or more prolonged dosage. The further development of rapid stick tests for G6PD should be pursued, the effectiveness and accuracy of the test assessed in populations with different molecular forms of the enzyme deficiency, and the results applied in public health measures towards the prevention and management of malaria in tropical countries.

Another variant gene, *MDR1* (see Section 3.2.2), which is much more common in West African populations than in those of European or Japanese background, is probably involved in defence mechanisms against potentially toxic agents ingested in the diet. Variation in *MDR1* also appears to reduce the efficacy of protease inhibitors and related drugs which are now widely used in the treatment of HIV infections. No doubt more genetic variation of this kind will be found for the drugs that are used for the management of common infectious diseases. But, just as in the case of the variation in the metabolism of the anti-tuberculous agent isoniazid (cited in the introduction) and the use of tests for G6PD deficiency (outlined above), it is unclear whether it will be cost effective to introduce genetic testing for these drugs.

There is also increasing evidence that a better understanding of the genomes of infectious agents may have important implications for therapeutics in the future. For example chloroquine, which was one of the mainstays of treatment for severe malaria caused by *Plasmodium falciparum*, is now scarcely effective in many populations because of resistance of the parasite. Preliminary studies have shown that it is possible to identify drug-resistant parasites by using DNA tests but further information is needed to determine whether this approach will be as cost effective as more lengthy culture techniques in the population control of malaria. The same applies to the increasing variety of antibiotic-resistance genes that can be identified using DNA technology. Further research is urgently required to determine the cost effectiveness of the use of DNA tests for determining the emergence of resistant forms of the viruses, bacteria and parasites compared with standard techniques, particularly for common communicable diseases in developing countries.

It is also possible that genetic testing of humans for genetic resistance to pathogens for communicable diseases may become part of pharmacogenetics in developing countries. There is a wide range of different genetic polymorphisms that must have come under intense selection in countries in which there was, or is, a high frequency of malaria. Among the best documented are inherited abnormalities of haemoglobin, notably sickle cell anaemia and thalassaemia. Recent studies suggest that individuals who are carriers for the sickle cell trait enjoy between 60% and 80% protection against the severe complications of malaria; carriers for some forms of thalassaemia achieve at least 60% protection. And there are several other genetic variants that seem to afford considerable protection to carriers. As new drugs are produced for the control of malaria, and particularly if attenuating vaccines are developed, it may be necessary to incorporate genetic testing for these protective polymorphisms as part of preliminary trials on the efficacy of these agents. If a range of innate protection occurs in frequencies ranging from 5% to more than 60% of the population, and if this level of protection is not known ahead of time, the results of these trials could be very difficult to interpret.

Although these examples suggest that pharmacogenetics could have broad implications for the developing world, there are many problems to be overcome before this is possible. Because of dire poverty and ineffective healthcare delivery systems, many countries have not even reached the stage at which appropriate drugs are available. Although the situation is improving in many South American and Asian countries, the laboratory services to do these tests are not available to many of the poorer countries. And even if they were, each of these genetic tests would have to be studied to assess the cost effectiveness of its application.

Currently, a great deal of work is being directed at finding cheaper, phenotypic tests for genetic traits that can be used in developing countries. However, as described in the World Health Organization report (WHO 2002), genetic testing for very common genetic diseases and the use of DNA diagnostics for infectious disease is likely to increase slowly in developing countries. Hence, provided it turns out to be cost effective, pharmacogenetics may begin to have a role, albeit limited in their healthcare.

3.10 Conclusion

Future clinical role of pharmacogenetics. It is unlikely that there will be a radical change in clinical practice based on pharmacogenetics in the near future. Both the academic and the industrial sectors are cautious about the potential for the clinical application of pharmacogenetics in the short term (five years) and there is still much work to be done. But it shows greater potential to be beneficial in the medium term (15–20 years). The rate-limiting step in its application in the medium term is not seen to be technology required to deliver the results, but the need for proper validation of the effect of pharmacogenetic testing in improving patient treatment compared with current practice. Genetic typing of cancer is already an area of promise where several examples exist of typing improving the treatment of patients, by the use of drugs developed specifically against particular genetic changes in cancer cells.

Although some have suggested that pharmacogenetics holds the promise of revolutionising therapeutics over the next decade, there are several reasons to be guarded in this prediction. First, unless the dose of a drug is carefully selected to lie within the safe margin designed to achieve efficacy, even in a sub-group of subjects with well characterised drug metabolising capacity, the advantages of pharmacogenetic tailoring would be lost. Second, possible drug interactions represent a major risk; concurrent administration of an inhibitor of drug metabolism can convert a subject with an extensive metaboliser genotype into a poor metaboliser phenotype. The third risk is co-morbidity. Liver and kidney dysfunction can heavily influence drug disposition, irrespective of genotype. So unless prescribers take careful notice of prescribing information and advice, the advantages of pharmacogenetics in therapy may be lost.

Evaluation. There has been little systematic evaluation so far of the clinical application of pharmacogenetic testing and until such assessments are completed it is unclear whether testing will improve treatment for patients. Each pharmacogenetic test must be evaluated on a case-by-case basis. Clinical trials involving pharmacogenetic testing will require many patients studied over prolonged periods to ensure validity, together with a precise definition of the particular phenotypes under evaluation.

Complexity. As well as genetic complexity, adherence to drug regimes, the age of the patient, other medication taken and diet are important determinants of drug efficacy and safety. Even when the efficacy of a drug is under significant genetic influence, it is often unclear how this translates into improving clinical care.

Pharmacogenetic testing. Most examples of pharmacogenetic testing outside the field of oncology centre on reducing the prevalence of adverse drug reactions. There are as yet only a few important examples of how pharmacogenetic testing is in practice increasing the effective use of a drug.

Role of pharmacogenetics in developing countries. Although pharmacogenetics undoubtedly has a role to play in treating the common diseases of developing countries, progress in its application in clinical practice is likely to be slow. In the case of very common genetic variants that may result in severe drug reactions, G6PD deficiency for example, there is an urgent need to develop simple phenotypic tests that can be applied widely in the community. For the increasing number of genes that have been identified as the cause of resistance to therapy in infectious agents, there is an urgent need to analyse cost–benefits to compare the use of DNA analysis compared with standard culture methods for identifying resistant organisms. The DNA technology required for pharmacogenetics can be established as part of cost effectiveness programmes directed at the diagnosis of common genetic and infectious diseases, and pharmacogenetics added to these programmes, if appropriate.

4 Implications of the use of pharmacogenetics

4.1 Introduction

In this section we examine the implications of the widespread introduction of genetic testing into the UK health service and the management and delivery of the tests, including the associated training and staffing issues. This builds on discussions in the previous two sections and examines the current implications for the few applications that are already used in the clinic, and, more importantly the issues that need to be considered if this technology is established in the medium to long term. In addition to use in the clinic, the requirements for the provision of information technology (IT), data storage and access are outlined. As emphasised throughout this report, there is still virtually no information about the cost effectiveness of pharmacogenetic testing in clinical practice. Hence, it is difficult to offer advice on the future organisational and educational changes that would be required if, as seems likely, the field slowly develops over the next 20 years. However, because the application of pharmacogenetics would raise issues of use in the clinic that have not been addressed hitherto in the organisation of healthcare provision, it is important that a start is made in defining the complex questions involved.

4.2 Implications for the National Health Service

As we will outline in this section, advances in genetics must be matched by parallel developments in information technology to deal with increasing volumes of data. The newly established NHS Connecting for Health agency, responsible for development of IT in the NHS has recently commissioned the construction of the genetic section of the IT programme. Patients and clinicians will need reassurance that access and data storage for sensitive information are secure. This was a key concern of the public dialogue (see Section 5.2.1).

Genetic profiling could provide vast quantities of data, much of it unintelligible to the primary- (general practitioner) and secondary- (hospital-based) care clinician. Genetic testing differs from most other laboratory tests as it potentially gives a result that can last a lifetime, which will need to be recorded and stored in an electronic healthcare record. Interpretation and use of pharmacogenetic testing will be facilitated by computer programs that combine morbidity, information on medications, age, gender and lifestyle such as occupation and smoking, to provide a risk analysis. It is likely that a variety of SNPs will be involved, so dedicated computer programs may be needed for the clinician to aid interpretation of the results of tests. The results, with interpretation, will need to be available to all clinicians, including nurses and pharmacists (community and hospital) who are prescribing (see Box 7), so the ability to access rapidly up-to-date data in primary-, secondary- and tertiary-care settings will be required. Patient-held records allow patients to take more responsibility for their healthcare and to share in decision making. In general terms, participants in the public dialogue were keen to have access to information that helped in making choices over their healthcare. The role of the professional was to help interpret data rather than make decisions.

The availability of electronic data about patients in the health service, linking prescription data for individual patients with clinical outcomes, will enable new uses to be made of the data for research and audit. One important area is in post-market monitoring of the safety of drugs. This monitoring currently relies on several systems and is usually of considerable duration (see Section 2.10). In the future there will be the potential to use the NHS electronic database of patient records for the monitoring of drug safety and the detection of ADRs. This will be especially useful for rare ADRs of commonly prescribed drugs, or more common ADRs of less commonly prescribed or 'niche' drugs. It may also pick up less severe ADRs which might not be detected by other monitoring systems such as the Yellow Card system (see Section 2.10). The use of the NHS electronic database of patient records for post-market monitoring would therefore complement the existing Yellow Card system and could very rapidly be used to research the signals generated by the Yellow Cards.

As mentioned in Section 3.5.1, the cost–benefit implications of the introduction of pharmacogenetics into NHS practice will also need to be understood and evaluated by the National Institute for Health and Clinical Excellence (NICE).

Relating findings from the NHS electronic database of patient records back to genotypic data will require access to biological samples (for example blood or saliva) from individual patients, or stored genetic data, and the identification of a representative control group within the database. The ethical aspects need to be carefully considered to enable this to be done, while protecting the rights and confidentiality of the individual. However, it could be considered unethical not to undertake such surveillance in the public good, given the huge expenditure by the health service on drugs and the high cost and morbidity associated with ADRs and inappropriate prescribing. Large databases containing information on individual patients and genetic data (for example UK Biobank, which will collect such data on 500000 individuals) may also be valuable for pharmacogenetic research.

Concerns about the implications for personal insurance have so far been allayed by the recent announcement of

an extension of the moratorium on the use of the results of gene testing for setting premiums to 2011 (excepting life policies over £500 000 and critical illness policies over £300 000). Currently Huntington's chorea is the only genetic test approved by the Department of Health's Genetics and Insurance Committee.

4.3 Education and training

In any field that is moving as rapidly as pharmacogenetics, and with considerable uncertainties about its future clinical application, it is difficult to be certain at this stage about training requirements. However, there seems little doubt that genetics will play an increasingly important part in clinical practice. Therefore doctors, nurses, and pharmacists of the future will require a much stronger basic training in the fundamentals of human genetics than they have received hitherto. Regardless of the role of pharmacogenetics, this will prepare them for many other aspects of medical practice in the future.

Education in genetics at undergraduate, postgraduate and continuing medical education levels has trailed behind the enormous scientific and technical advances in this field. Knowledge about simple inherited conditions, such as cystic fibrosis or Duchenne muscular dystrophy, has improved diagnosis for patients and their families and provided them with alternative options for reproduction. Clinical genetics promotes non-directive consulting and addresses consent and confidentiality for patients. Pharmacogenetics will need a model similar to that in place for several current therapies: lipid profile and liver function tests for statins, renal function tests with ACE inhibitors and thyroid function testing for patients prescribed lithium. Providing information on reasons for and choice of therapy, and giving explanations of side-effect profiles are part of good medical practice. Pharmacogenetic testing should integrate within this consultation in the future, but GPs and pharmacists will need training to be able to offer and interpret such tests. Participants in the public dialogue questioned whether professionals would be sufficiently up to date with the new technology and have time to advise upon and support patient choice.

One area of urgent need is for a renewed focus on training in clinical pharmacology. In the 1940s and 1950s many drugs were discovered that are still the basis for much of our current prescribing. Because of the need to study their effects in humans, the discipline of clinical pharmacology emerged, both in academia and industry. Although therapeutics, or prescribing, had previously been taught in most medical schools, it had little scientific basis and the emergence of clinical pharmacology provided the necessary scientific rigour and increased our understanding of how drugs exert their effects in humans.

As a discipline, clinical pharmacology flourished in the 1970s and 1980s, but as the curriculum for educating students in medical schools changed to a problem-based learning approach, academic departments in many disciplines merged and even disappeared. Clinical pharmacology was no exception, and not having a clear 'organ base', or direct link to a clinical speciality such as cardiology or gastroenterology, its role in the NHS also suffered. Paradoxically, this was happening at a time of great activity in drug discovery with corresponding need for innovative clinical pharmacology, and at a time when educational needs in the use of new medicines were greater than ever.

One of the main contributions of clinical pharmacology is to increase our understanding of why people differ in their response to drugs and the clinical consequences of these differences. Genetic influences on both drug handling and drug response are increasingly important in achieving this goal. Several of the institutions in UK and Europe where clinical pharmacology still flourishes have built up important programmes in pharmacogenetics; the problem is that there are not enough of these centres of excellence.

With the vast amounts of genetic, prescribing and clinical data becoming available, there are important training needs for non-clinical scientists in areas that are short of expertise such as population genetics, biostatistics and IT, in addition to clinical pharmacology.

4.4 Health economics

The aim of any evaluation of health economics is to determine how healthcare resources can be used most prudently. Using the tools of health economics, the analysis of cost effectiveness in pharmacogenetics can be used to examine the clinical and economic impact of pharmacogenetic interventions. In pharmacogenetics, many of the new technologies will be competing with existing methods of diagnosis and treatment. As such, they will need to undergo rigorous evaluation in large-scale trials. Although the introduction of pharmacogenetic testing has the potential to reduce costs through improved interventions, greater efficacy, less inappropriate prescribing and fewer ADRs, it is not clear whether or not the tests will increase or decrease overall health costs. This is because of the costs of developing, evaluating and implementing pharmacogenetic testing; associated costs of training and clinical time needed to administer and interpret the tests effectively; and auditing their use in a health service setting.

4.4.1 Determining cost effectiveness

The assessment of cost effectiveness is relatively well developed in the healthcare system. However, its application to pharmacogenetics is far less developed.

It is important that a pharmacogenetic intervention is always compared with another option, which normally is the current treatment practice without a genetic test. Studies therefore need to answer the question of whether it is worthwhile to add a genetic test to current pharmacological treatment so as to target it better, or to improve its efficacy, or both. However, it is difficult to determine the extent to which this question can be answered given the few examples in the field so far. The recently funded Department of Health initiative in pharmacogenetics should generate some useful initial data in the six clinical areas under study, though ultimately large-scale trials will be required, covering both the long and short term, as prolonged periods may be necessary before true costs and benefits are apparent. Refinement and development of the criteria used for modelling cost effectiveness as it applies to pharmacogenetic studies are also needed and should be built into future studies.

4.4.2 Assessing potential impact

A recent review of the cost effectiveness of pharmacogenetics interventions (Phillips & Van Bebber 2004) highlighted the limited number of conditions to which cost–benefit analysis had been applied. There were limited data for deep vein thrombosis, cancer and viral infections. In these examples it was suggested that pharmacogenetic interventions would be cost effective. The small number and range of studies included examples where the benefits have been known for some time but also highlighted obvious gaps in information. It is certainly too soon to make any broad conclusions or recommendations about pharmacogenetic interventions.

4.5 Conclusions

Healthcare structures. At the structural level, a much stronger partnership will have to be developed between the healthcare providers, the regulatory agencies and the pharmaceutical industry to enable emerging issues and new scientific understanding to be progressed in an effective manner. It will also be necessary to address the difficult questions of liability and responsibility. It will be necessary to prescribe consistent reporting formats and to have a sufficiently good doctor–patient relationship to facilitate follow-up and consented access to key clinical samples. With the development of IT systems holding individual patient data on drug prescriptions linked to data on clinical outcome, there will be important new opportunities for post-marketing surveillance of drug safety. As the value of individual pharmacogenetic tests becomes established, it will be necessary to organise both the site (hospital, general practice and pharmacy) and the professional level of those who are to provide advice to patients and to take the necessary action in assuring that this information is used correctly in clinical practice. As we outline in the next section, the public will have its own views on this which should be taken into account.

Information technology. IT underpins the scientific and practical aspects of pharmacogenetics, which generates a large amount of data that must be analysed and turned into useful information. Pharmacogenetic testing for specific polymorphisms produces a lifetime result, which must be stored on the patient's electronic health record. Advances in genetics must therefore be matched by parallel developments in IT whereby the rapid development of systems for electronic patient records can be coupled with proper confidentiality protocols. The ability to access key up-to-date data rapidly in primary-, secondary- and tertiary-care settings will also be required. The use of pharmacogenetic testing will be enhanced by the development of computer programs that facilitate the interpretation of risk data by professionals who are not experts in pharmacogenetics, such as prescribing nurses. These programs will help to provide a risk analysis by combining data on SNPs, lifestyle and socio-demographics. Public confidence in the new technology must be maintained to address concerns over the capacity of the healthcare system, and particularly GPs, to be able to manage such information effectively and securely. In July 2005 the Royal Society launched a policy study investigating the potential impact of developments in information and communication technologies on health and healthcare.

Education and training. Education in genetics at the undergraduate and continuing medical education levels has failed to keep up with scientific advances in this field. GPs, nurses and pharmacists will need training to be able to offer and interpret the tests, which may sometimes involve the need for quite extensive and complex information, although the most difficult cases are likely to be referred on to a specialist genetic or other centre.

The importance of clinical pharmacology in increasing our understanding of the basis of inter-individual variability in drug response and clinical consequence is central to research into the genetic aspects of drug effectiveness. Over recent years there has been a decrease in the teaching of, and research into, clinical pharmacology; the prevalence of vital skills is therefore reduced in the UK. Training must also be addressed in other areas of shortage such as population genetics and biostatistics.

Health economics. The annual NHS drugs bill is £11 billion. Pharmacogenetic testing may reduce this by predicting which patients may develop ADRs and increasing drug efficacy; however, it is currently not possible to predict if pharmacogenetics will increase or decrease overall health costs. Further evaluation of the cost effectiveness of pharmacogenetics must precede the introduction of individual pharmacogenetic tests.

5 Ethical issues and public dialogue

Previous sections have concluded that the implementation of pharmacogenetic technology will be a gradual rather than revolutionary process, and that it is unlikely to result in a widespread change in clinical practice in the short to medium term. There is already a growing body of literature on the ethical implications of this technology. Hence this section summarises the main concerns surrounding the use of pharmacogenetic testing. In addition it explores these issues through a public dialogue exercise, commissioned as part of this study to investigate public expectation of the technology and the associated ethical questions.

5.1 Ethical issues

Several reports have considered ethical and social issues surrounding the translation of pharmacogenetic research into practice. They include: the Nuffield Council on Bioethics *Pharmacogenetics: ethical issues* (2003); the Wellcome Trust *Translating pharmacogenetics research into practice: ethical and policy issues* (2003); the report of the Society of Pharmaceutical Medicine's Working Party on Pharmacogenetics (2001), and the Human Genetics Commission discussion document entitled *Whose hands on your genes? A discussion document on the storage protection and use of personal genetic information* (2000).

In the most recent of these reports, the Nuffield Council on Bioethics describes the current ethical debate, which has centred on the principles of consent, privacy and confidentiality. In addition it also explores ethical issues in the areas of information management, and the implications of differentiating individuals into groups based on their likely response to a drug. The implications of the main ethical and social concerns that may arise, if and when pharmacogenetics starts to appear in everyday medical practice, identified in the reports from the Nuffield Council on Bioethics and from other organisations, are listed below.

- The use of pharmacogenetic information collected in research relies on the voluntary nature of the consent but concerns arise about the privacy of the information that is obtained and stored.

- Genuine voluntary consent may be difficult to obtain in clinical trials or in clinical practice when, for example, routine genotyping from DNA is part of the trial or clinical process which may be difficult to refuse.

- Privacy and confidentiality measures must be in place to protect participants in research. However, concerns about the anonymity of samples and its compatibility with fulfilling the objectives of the research remain to be addressed.

- Pharmacogenetic stratification of disease may prove to be an economic disincentive for those developing new medicines. This may require the adaptation of existing orphan medicine legislation.

- Pharmacogenetics and ethnic groups requires further scrutiny as there is a danger that ethnicity, rather than genetic profiling, may be used in the allocation of pharmacogenetic tests and medicines.

- The need for health professionals to be provided with education and training to communicate pharmacogenetic information and the associated risks to patients.

- Responsibility for test and treatment. Questions arise about whether patients will have the option to receive treatment without taking the appropriate test.

- Privacy and confidentiality of pharmacogenetic information could have implications for family members. This could lead to circumstances in which the obligation of health professionals to their individual patients comes into conflict with their obligations to others, which may lead to encouraging patients to share pharmacogenetic information with family members.

These reports have made a significant contribution to the wider public and academic debate around the application of new technologies in the clinical and biomedical research.

5.2 Outcomes of the public dialogue

There remains an identifiable gap in the engagement of the UK public with pharmacogenetic technologies and with genetic testing in general which has not been addressed by any other public consultation. To address the broader issue of public debate, the Science in Society secretariat at the Royal Society organised three workshops that engaged 76 members of the public, recruited according to specific socio-economic characteristics, in a discussion with specialists on potential developments in pharmacogenetic testing. The workshops were held in London, Manchester and Oxford and were stratified by ethnicity, socio-economic status and age respectively. Full details of the methodologies and participants can be found in Annex 4. A full report of the public dialogue is also published by the Royal Society concurrently with this one, and is available on the Royal Society website (Royal Society 2005).

5.2.1 Key findings from public dialogue

Key findings from the workshop are summarised below in the following nine themes: health advice and trust; drug effectiveness and genetic make-up; genetic tests; genetic exceptionalism; patient sovereignty and the role of professionals; delivery, capacity and control; limits to patient choice; ethnicity; cost and orphan medicines.

Health advice and trust. Health professionals, particularly doctors, were seen as the main source of trusted medical advice. However, many participants supplemented such information on diagnosis and treatment through their own research (for example by using the Internet). Trust in professionals was highest in workshops with participants aged over 55 years and lowest (though still predominant) in those with participants from Black and minority ethnic backgrounds. While competency and expertise were major criteria for trust in medical advice, the responsiveness of professionals to individual concerns was also very important (relative to other experiences including adverse drug reactions). Drug companies were not trusted to give impartial advice about drugs.

Drug effectiveness and genetic make-up. In general, drug and medical development was viewed by participants as fundamentally beneficial and as having transformed society over the past century. However, there were concerns that drugs were currently dispensed far too easily in society, and social and institutional norms such as the excessive work pressures under which GPs were placed, and their relationship with the pharmaceutical industry, facilitated this process. For drug effectiveness, people's predominant view was that it was related to an individual's genetic make up. It was the main reason people cited for null or side effects to medicines, as opposed to misdiagnosis and poor patient compliance. A substantial number of participants in each workshop group (typically around a half) had experienced an untoward reaction to a medicine in the past, but only in a few cases did such an experience have a major impact on trust in conventional healthcare. The groups had a fairly accurate understanding of current drug effectiveness and some had knowledge that different classes of drugs, such as those for cancer treatments, were less effective.

Genetic tests. The use of genetic tests to understand predisposition to diseases was explored and participants were generally familiar with, and understood the concept of, this type of genetic test. The most cited examples by the groups included sickle cell anaemia and cancer tests. In most cases, genetic tests were seen to be empowering, particularly if lifestyle changes could be made or drug treatments were available that would improve the prognosis. Where changes in lifestyle were not likely to improve prognosis, around half of participants still preferred to have a test if there was a strong likelihood of them having a serious hereditary disease, particularly when considering whether or not to raise a family. A significant number of participants (around a third) were unsure what they would do in such circumstances and highlighted the complex issues raised by genetic testing, particularly relating to other family members. There was a significant minority who had reservations about the growing use of genetic tests in society. Participants examined the predictive accuracy of genetic tests for diseases, for instance for monogenic disorders such as Huntington's disease compared with conditions such as bowel cancer where lifestyle factors are important. There was good awareness of the scope and limitations of genetic tests in this context. The use of pharmacogenetic tests was also explored, and although only a minority (typically one person per group) had heard of this application, participants were able to easily understand the basic principles of such testing and its distinction from other genetic tests.

Genetic exceptionalism. On balance, participants did not feel that genetic tests were distinct from other medical tests. A minority of participants expressed the view that genetic tests provided highly predictive or diagnostic health information in relation to other tests. A similarly small number thought that the very personal nature of the test and the relevance of information to other family members meant there were some differences. In general, upon reflection, other participants thought there was no fundamental reason for genetic exceptionalism other than the fact that genetic testing is a relatively uncommon technology.

Patient sovereignty and role of professionals. The key theme to emerge across all groups concerning pharmacogenetic testing was the importance of patient sovereignty and the role of the professional to offer impartial advice to enable people to make informed choices. Hypothetically, if test results were unfavourable, participants were supportive of the right of an individual to have access to drugs if they decided that on balance they were willing to accept the risks of a course of treatment and that the potential benefits outweighed the risks. This was particularly the case if there were few treatment options available and the increased risks were seen as marginal. For medical negligence liability, the need for some form of disclaimer or waiver for healthcare professionals was discussed in some groups. Only a few participants thought that, all things being equal, the decision should be left up to the professional as to whether the drug should be offered.

Delivery, capacity and control. There were major concerns as to whether the accompanying institutional arrangements (for example the NHS) could successfully deliver the technology associated with pharmacogenetic testing. This ranged from issues of consent and confidentiality in the handling of biological samples, data security, how information was shared with third parties such as insurers (a relatively large factor), the transparency of relationships between public and private

organisations involved in delivery, handling or potential use of genetic information, to pragmatic questions of whether GPs would be sufficiently up to date with the new technology to support the effective use of tests in surgeries, and their capacity to advise upon and support patient choice. Concern was raised that a different test might be available for each pharmaceutical company's product to treat a particular condition. It was unclear how this would be dealt with in practice, and how (close) links between doctors and companies impact on trust.

Limits to patient choice. The NHS was seen as the most appropriate institution to control access to pharmacogenetic testing. Despite the strong consensus on patient sovereignty, participants were concerned at the potential for 'over the counter' access to pharmacogenetics tests in pharmacies or through the Internet (the problems in effectively regulating the latter were noted) because of the need for trusted expert advice to support patient choice in the use of such test. On the issue of whether patients should have the right to ask for a particular drug treatment without taking the associated pharmacogenetic test, on the whole participants were not supportive of this position if there was a likelihood of an adverse reaction, irrespective of an individual's reason for not taking the test (including, for instance, issues of confidentiality and who might gain access to the information). This was mainly because in these circumstances patient choice would no longer be informed by appropriate medical evidence, something that participants felt was important. It was recognised that people could effectively be excluded from a treatment if they were not willing to have a pharmacogenetic test accompanying a medicine.

Ethnicity. The issues of genetic tests in relation to ethnic origin were explored, along with the potential for racial stratification in relation to drug metabolism. In general, people thought that genetic variants that affect disease, sickle cell anaemia or diabetes for example, were likely to be more common in some ethnic groups than in others. However, they also recognised variation between and within ethnic groups. In general, the use of genetic tests to provide medical information to help manage disease within minority communities was welcomed. Groups were wary of using race as a proxy for genotype.

Cost and orphan medicines. For potential 'orphans' created through classifications of 'poor metabolisers', initial discussion on this issue centred on the principle that all members of society should be afforded a certain level of health provision by the state, irrespective of the cost implications. In general, the participants thought it was unrealistic to expect the costs for orphan medicines to be subsidised by pharmaceutical companies' profits, rather than being met by the state or charities. The enormous costs of drug development were discussed, and its potential impact on diseases of developed countries. After discussion, while recognising the principle of providing members of society with a satisfactory level of healthcare, a range of views were expressed about the extent to which financial support should be given by the state to provide research into groups of people with relatively rare, unresponsive, pharmacogenetic variants of a disease.

5.3 Conclusion

Ethics. Several reports have considered ethical and social issues surrounding the translation of pharmacogenetic research into practice. Current debate has centred on the principles of consent, privacy and confidentiality, and the ethical issues in the areas of information management and the implications of differentiating individuals into groups based on response likelihood. Large repositories of pharmacogenetic data are vital for ongoing research in this field. An adequate consent and global ethics structure is needed to couple research and the healthcare record to allow the continuous assessment of clinical records linked with genetic data, and the ability to return to individual records.

Public dialogue. Participants engaged in the public dialogue had good awareness of genetic science and the complex issues forged by genetic tests, both for the individual and society. Pharmacogenetic tests were not viewed as providing highly predictive healthcare information, but rather illustrated potential likelihoods of good, null or adverse reactions to particular types of drug. On balance, most participants saw the potential development of pharmacogenetic testing as beneficial in providing information to make choices about diseases affecting them and treatments available. However, a significant minority of participants were concerned about the increasing use of genetic tests in society. The importance of patient sovereignty and the role of the professional to offer impartial advice and to enable people to make informed choices was a major issue. Of great concern for participants was the practical issue of whether the accompanying institutional arrangements could successfully deliver the technology associated with pharmacogenetics. Although the NHS was seen as the most appropriate organisation to control access to testing, concerns were raised about whether appropriate safeguards could be given to ensure the accurate, reliable and confidential use of pharmacogenetic tests. The capacity of GPs to be sufficiently up to date with the technology to support widespread use was questioned, together with their ability to advise upon and support patient choice. In some cases the view of the participants differed from those of this report's working group: for example, where future expectations about the delivery of genetic tests by pharmacists conflict with the preferences of the public. These issues will need to be explored further.

6 Conclusions and recommendations

6.1 Conclusions

The clinical outcome of drug therapy is dependent on the complex interactions of many variables including appropriate dosage; adherence to the prescribed treatment regime; age; the quality of clinical monitoring for both response and potential adverse side effects; and the interaction of other drugs. Pharmacogenetic studies have shown that in at least some cases inherited factors are also involved in variability of response to drug therapy.

Advances in molecular and cell biology in the post-genome era have already detected heterogeneity in what previously appeared to be homogeneous diseases, for example breast and colon cancer, and diabetes. Further research will undoubtedly yield more examples and may lead to a much greater degree of precision in diagnosis and therapy for these conditions. This may lead to an increasing requirement for DNA diagnostics in clinical practice. There are already many examples of variability in drug response due to single gene mutations that follow a Mendelian pattern of inheritance. However, many of them are quite rare and it seems likely that genetic variability in response to most drugs will reflect the interaction of environmental factors with several genes, each with a relatively small phenotypic effect. Although total genome analysis using SNPs or expression systems associated with metabolic and kinetic studies may make it possible to define at least some of the genes involved, it is still too early to anticipate the overall clinical potential of genetic variability in these complex multifactorial systems.

It is unlikely therefore that there will be an immediate change in clinical practice based on pharmacogenetics. Rather, there is likely to be a gradual increase in its clinical applications; its true potential may not become apparent for 15–20 years, during which time a great deal more information may become available about the practicalities of applying information derived from complex multifactorial systems in the clinic. Currently, it seems likely that the most rapid progress will be made in the field of oncology.

To date, the field of pharmacogenetics has yet to reach mainstream clinical practice. To enable pharmacogenetics to enter the clinic it will be necessary to demonstrate clinical use on a case-by-case basis through well constructed and statistically significant clinical trials. Further information needs to be obtained on the economics of using pharmacogenetics in clinical practice; these clinical trials therefore need the input of health economists to address issues of clinical cost effectiveness and the best use of public money.

Pharmacogenetics will clearly be important in drug discovery and development over the next decade, in particular for early identification of variations in drug efficacy and toxicity that could reduce the value of clinical trials or use of the drug. The increasing availability of high quality collections of DNA samples with associated phenotypic data will continue to support the trend of industry using population-based genetic association studies, rather than susceptibility-gene hunting approaches, to help validate the disease association of novel drug targets in the early discovery process.

The growth of DNA diagnostics has brought reliable and rapid diagnostic tests to the clinic. The future impact of pharmacogenetics will be linked to the development of tests that can rapidly deliver useful diagnostic data to healthcare professionals on much larger numbers of tests. As this field develops it will be necessary for regulation to follow scientific developments, particularly if regulators wish to use pharmacogenetic data in the evaluation, approval and labelling of medicines in the future. Regulatory authorities will also have to establish standards of use and validity of genetic tests if pharmacogenetic data are to be incorporated into their licensing procedures.

Pharmacogenetics undoubtedly has a role to play in tackling the common diseases of developing countries, although translation into clinical practice is likely to be slow. It is important to develop simple diagnostic tests for identifying disease-causing organisms that are resistant to therapy, as well as further development of rapid diagnostic tests, for example for the detection of glucose-6-phosphate-dehydrogenase, to help with public health measures towards the prevention and management of diseases such as malaria.

Regardless of the ultimate role of pharmacogenetics in clinical practice, there is no doubt that genetic testing will play an increasingly important role in healthcare delivery in the future. It will be essential therefore to ensure that GPs and other healthcare professionals, including pharmacists and nurses, are better informed about the principles of genetics and that their different roles in providing genetic information and in determining clinical action based on genetic testing is clearly defined. There has also been a serious decline in the number of departments and posts in clinical pharmacology over recent years; if pharmacogenetics is to play a more central role in clinical medicine, universities and research funders will need to try to reverse this trend.

In considering the delivery of pharmacogenetics, the Department of Health will have to take into consideration the public concerns and expectations of the applications of genetic technology. Our public dialogue exercise highlighted areas where the participants' views differed from those of the working group, for example where future expectations about the delivery of genetic tests by pharmacists conflict with the preferences of the public.

6.2 Recommendations

1 Funding for well-designed studies in pharmacogenetics, probably from multiple sources, will be important to establish the relevance of pharmacogenetics to clinical practice. For new drugs, these trials will be conducted by industry. Medicines already licensed and on the market are unlikely to be researched further by industry for pharmacogenetic influences. However, further investigations into the application of new pharmacogenetic therapies to existing medicines are important for maximising efficacy and safety of the medicines that people take today. Studies should be encouraged by Government funding, for example through the Medical Research Council as well as the Department of Health, in partnership with the medical charities and the pharmaceutical and diagnostic industries. The NHS should facilitate such studies by ensuring mechanisms are in place for researchers to gain access to data on patients' records of treatment as well as samples for genotyping. To facilitate genotyping and further research into pharmacogenetic variability, DNA samples should be taken, with proper consent, from as many clinical drug trials as possible. Institutional Review Boards and ethics committees should recognise the value of such collections and should encourage them as a way of maximising value from patients' voluntary contribution in participating in these clinical trials.

2 Analysis of genetic data from clinical trials may lead to the development of medicines with a relatively small potential market. Treatments that are effective for a very limited market, such as those aimed at very uncommon diseases, are known as 'orphan medicines'. The provision of European tax incentives for such developments is important, regulatory authorities will have to review continuously pharmacogenetic developments that are likely to segment the potential treatment population for conventional drugs.

3 We recommend the establishment of an appropriate regulatory framework at a national and European level by the UK Medicines and Healthcare products Regulatory Agency (MHRA) and the European Medicines Agency (EMEA) for the provision of pharmacogenetic tests to be used in the clinic. This must include mandating some form of regular post-market monitoring beyond phase III clinical trials that links genetic variability to clinical outcomes where this is known to be important.

4 Regulators worldwide need to address the problems associated with the transmission, storage and processing of large amounts of complex pharmacogenetic data. This must be done before complex pharmacogenetic data become commonplace in the drug regulatory process. In the UK this will be the responsibility of the MHRA.

5 Clinical trials across international populations can often be hindered as each country has its own laws and guidelines for conducting genetic research. There is a need for greater international harmonisation in this area. We recommend the Department of Health, in conjunction with the International Conference on Harmonisation (ICH), review current guidelines and regulations for the conduct of genetic research across international borders.

6 We endorse the recommendation of the World Health Organization that the introduction of simple DNA diagnostics for common genetic and infectious diseases in developing countries is vital (WHO 2002). This will provide a technological base for studies of the cost effectiveness and clinical value of introducing pharmacogenetic tests, including those to detect the drug resistance of hosts and parasites. The Medical Research Council and medical research charities should commission more research into the use of pharmacogenetics in developing countries, particularly for drugs for malaria, tuberculosis and HIV, and for assessing drug resistance in common parasites.

7 Education in genetics at undergraduate, postgraduate and continuing medical education levels has trailed behind the enormous scientific and technical advances in this field. Training and education programmes for students and healthcare professionals needs to be reviewed urgently by the General Medical Council, the medical Royal Colleges, the Nursing Council and the Royal Pharmaceutical Society of Great Britain to ensure developments in research are translated into clinical practice. These programmes should include:

- Training of medical students to include more emphasis on education in genetics and to provide a greater understanding of human diversity.
- Development of resources for staff in primary and secondary care for greater understanding of issues such as statistics in healthcare, the use of genetics in the clinic, and bioethics.

- Training of clinical and basic science researchers in subjects where there is a shortage, particularly clinical pharmacology, biostatistics and population genetics, in both industry and academia.

8 The newly created NHS Connecting for Health agency is establishing IT systems in the NHS to store a comprehensive record of the patient's history. As part of the programme, the Department of Health should consider carefully the research implications of these data, including pharmacogenetics research. In some cases it will be necessary to re-contact patients who have been identified by such research, for example to request collection of a blood or saliva sample for genotyping. The ethical aspects need to be considered carefully to enable this to be undertaken in the public good, while protecting the rights and confidentiality of the individual.

9 Concerns were raised in the public dialogue about whether the current healthcare arrangements could successfully deliver genetic technology in the future. The Department of Health should consider the support and safeguards for the genetic technology, the institutional culture into which pharmacogenetics is potentially delivered, how the technology shapes this environment, and the costs and feasibility of attempts to provide measures to mitigate these concerns. It should also address differences between the views of the public on issues such as access to information, and what is possible within the healthcare system.

10 The ability to analyse patient data during and after a clinical trial is particularly important. Guidance on the use of data in research needs specific consideration by Government, the NHS, and the newly established Human Tissues Authority. Guidelines should ensure that an ethical framework is in place which gives clarity to industrial and academic researchers for the creation of large databases of patients and the collection and use of tissue samples associated with them.

7 References

Audit Commission (2002). *A spoonful of sugar – medicines management in NHS hospitals*. Audit Commission: London

Brenner S E (2001). *A tour of structural genomics*. Nature Reviews Genetics **2**, 801–809

Burchard E G, Ziv E, Coyle N, Gomez S L, Tang H, Karter A J, Mountain J L, Perez-Stable E J, Sheppard D & Risch N (2003). *The importance of race and ethnic background in biomedical research and clinical practice*. New England Journal of Medicine **348**, 1170–1175

Department of Health (2003). *Our inheritance, our future. Realising the potential of genetics in the NHS*. Government White Paper, The Stationery Office: Norwich

EMEA (2005). *Committee for Medicinal Products for Human Use (CHMP) guidelines on pharmacogenetics*. EMEA: London
Available online at www.emea.eu.int/pdfs/human/pharmacogenetics/2022704en.pdf

Entrez SNP database (2005). National Center for Biotechnology Information: Maryland
Available online at www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=snp

Evans W E & Relling M V (1999). *Pharmacogenomics: translating functional genomics into rational therapeutics*. Science **286**, 487–491

Evans W E & McLeod H L (2003). *Pharmacogenomics—drug disposition, drug targets, and side effects*. New England Journal of Medicine **348**, 538–549

FDA (2005). *Guidance for industry pharmacogenomic data submissions*. FDA: Maryland. Available online at www.fda.gov/cder/guidance/6400fnl.pdf

HapMap database (2005).
Available online at www.hapmap.org

Higashi M K, Veenstra D L, Kondo L M, Wittkowsky A K, Srinouanprachanh S L, Farin F M & Rettie A E (2002). *Association between CYP2C9 genetic variants and anticoagulation-related outcomes during warfarin therapy*. Journal of the American Medical Association **287**, 1690–1698

Hinds D A, Stuve L L, Nilsen G B, Halperin E, Eskin E, Ballinger D G, Frazer K A & Cox D R (2005). *Whole-genome patterns of common DNA variation in three human populations*. Science **307**, 1072–1079

Herxheimer A (2003). *Principles of clinical pharmacology and drug therapy*. In *Oxford Textbook of Medicine 4th Edition* (eds Warrell D A, Cox T M, Firth J W & Benz E J Jnr) 1003-1024. Oxford University Press: Oxford, UK

Human Genetics Commission (2000). *Whose hands on your genes? A discussion document on the storage protection and use of personal genetic information*. Human Genetics Commission: London

International Human Genome Sequencing Consortium (2001). *Initial sequencing and analysis of the human genome*. Nature **409**, 860–892

International Human Genome Sequencing Consortium (2004). *Finishing the euchromatic sequence of the human genome*. Nature **431**, 931–945

Kamatani N, Sekine A, Kitamoto T, Iida A, Saito S, Kogame A, Inoue E, Kawamoto M, Harigai M & Nakamura Y (2004). *Large-scale single-nucleotide polymorphism (SNP) and haplotype analyses, using dense SNP maps, of 199 drug-related genes in 752 subjects: the analysis of the association between uncommon SNPs within haplotype blocks and the haplotypes constructed with haplotype-tagging SNPs*. American Journal of Human Genetics **75**, 190–203

Lander E & Kruglyak L (1995). *Genetic dissection of complex traits: guidelines for interpreting and reporting linkage results*. Nature Genetics **11**, 241–247

Marchini J, Cardon L R, Phillips M S & Donnelly P (2004). *The effects of human population structure on large genetic association studies*. Nature Genetics **36**, 512–517

Meyer U A (2004). *Pharmacogenetics – five decades of therapeutic lessons from genetic diversity*. Nature Reviews Genetics **5**, 669–676

Motulsky A G (1957). *Drug reactions, enzymes and biochemical genetics*. Journal of the American Medical Association **165**, 835–837

Need D C, Motulsky AG & Goldstein D B (2005). *Priorities and standards in pharmacogenetic research*. Nature Genetics **37**, 671-681

Nuffield Council on Bioethics (2003). *Pharmacogenetics: ethical issues*. Nuffield Council on Bioethics: London*

Peltonen L & McKusick V A (2001). *Genomics and medicine. Dissecting human disease in the postgenomic era*. Science **291**, 1224–1229

Petty G W, Brown R D Jr, Whisnant J P, Sicks J D, O'Fallon W M & Wiebers D O (1999). *Frequency of major complications of aspirin, warfarin, and intravenous heparin for secondary stroke prevention. A population-based study*. Annals of Internal Medicine **130**, 14–22

Rieder M J, Reiner A P, Gage B F, Nickerson D A, Eby C S, McLeod H L, Blough D K, Thummel K E, Veenstra D L & Rettie A E (2005). *Effect of VKORC1 haplotypes on transcriptional regulation and warfarin dose*. New England Journal of Medicine **355**, 2285–2293

Phillips K A & Van Bebber S L (2004). *A systematic review of cost-effectiveness analyses of pharmacogenomic interventions*. Pharmacogenomics **5**, 1139–1149

Pirmohamed M, James S, Meakin S, Green C, Scott A K, Walley T J, Farrar K, Park B K & Breckenridge A M (2004). *Adverse drug reactions as cause of admission to hospital: prospective analysis of 18 820 patients*. British Medical Journal **329**, 15–19

Royal Society (2005). *Pharmacogenetics dialogue: findings from public workshops held by the Royal Society's Science and Society programme*. Royal Society: London

Royal Society (2003). *Genetics and health–visions of the future*. Royal Society: London

Royal Society (2002). *Genetically modified plants for food use and human health–an update*. Royal Society: London

Science (2004). *Consortium hopes to map human history in Asia*. Science **306**, 1667

Service R F (2005). *Going from genome to pill*. Science **308**, 1858–1860

Slingerland A S & Hattersley A T (2005). *Mutations in the Kir6.2 subunit of the KATP channel and permanent neonatal diabetes: new insights and new treatment*. Annals of Medicine **37**, 186–195

Society of Pharmaceutical Medicine (2001). *Pharmacogenetics working party report*. International Journal of Pharmaceutical Medicine **15**, 53–100*

Stride A & Hattersley A T (2002). *Different genes, different diabetes: lessons from maturity-onset diabetes of the young*. Annals of Medicine **34**, 207–216

Venter J C et al (2001). *The sequence of the human genome*. Science **291**, 1304–1351

Vineis P, Schulte P & McMichael A J (2001). *Misconceptions about the use of genetic tests in populations*. Lancet **357**, 709–712

Vogel F (1959). *Moderne Probleme der Humangenetik*. Ergebnisse der Inneren Medizin und Kinderheilkunde **12**, 52–125

Wellcome Trust (2003) *Translating pharmacogenetics research into practice: ethical and policy issues*. Wellcome Trust: London*

World Heath Organization (2002). *Genomics and world health*. World Health Organization: Geneva*

Zineh I, Gerhard T, Aquilante C L, Beitelshees A L, Beasley B N & Hartzema A G (2004). *Availability of pharmacogenomics-based prescribing information in drug package inserts for currently approved drugs*. Pharmacogenomics Journal **4**, 354–358

*These papers are considered to be important references and further reading to this report.

Annex 1 Preparation of this report

This report has been prepared by the Royal Society working group on pharmacogenetics. The following members of the working group were invited in their personal capacity rather than as a representative of their organisation:

Chair

Sir David Weatherall FRS
Regius Professor of Medicine Emeritus, Weatherall Institute of Molecular Medicine, University of Oxford, and Chancellor of Keele University

Members

Professor Martin Bobrow CBE FRS
Head of Department of Medical Genetics, Cambridge Institute for Medical Research

Sir Alasdair Breckenridge CBE
Chairman of the Medicines and Healthcare products Regulatory Agency, and Emeritus Professor of Clinical Pharmacology, University of Liverpool

Professor Kay Davies CBE FRS
Head of Department of Human Anatomy and Genetics, University of Oxford

Dr Mike Dexter FRS
Former Director of the Wellcome Trust

Dr Richard Durbin FRS
Head of Informatics and Deputy Director, Wellcome Trust Sanger Institute

Professor Paul Elliott
Head, Department of Epidemiology and Public Health, Imperial College London

Dr Hilary Harris
General practitioner, Manchester

Dr John Stageman
Vice President and Head of Global Sciences and Information, AstraZeneca

Dr Nick Westwood
Royal Society University Research Fellow, Department of Chemistry, University of St Andrews

Secretariat

Dr Simon Edwards, Dr Rebecca Hodges & Dr Rachel Quinn
Science Policy Section, Royal Society
.

Annex 2 Individuals and organisations giving evidence

We sought evidence from a variety of organisations and individuals. We are very grateful to all who responded to our request for information in support of our study.

Evidence submitted at meetings of the working group

Professor John Burn, University of Newcastle upon Tyne
Dr Chris Chaimberlain, Global Head of Medical Genetics, Roche Products Pharma Development
Professor David Goldstein, University College London
Professor Ian Hall, University of Nottingham
Sir Alec Jeffreys FRS, University of Leicester
Professor John Todd, Cambridge Instiute of Medical Research
Mr Paul Weinberger, Director of Business Development, Roche Diagnostics Limited
Professor C Roland Wolf, Cancer Research UK Molecular Pharmacology Unit, Dundee

Meetings with members of the working group

Dr Alison Hill, UK Genetics Team, Department of Health
Ms Dianne Kennard, UK Genetics Team, Department of Health

Responses to the call for evidence

(i) Organisations
Association of the British Pharmaceutical Industry (ABPI)
Alzheimer's Society
AstraZeneca Research & Development
Avon Longitudinal Study of Parents and Children
British Consulate General, San Francisco
British In Vitro Diagnostics Association
Centre for Integrated Genomic Medical Research (CIGMR), University of Manchester
Centre for Technology Assessment, Swiss Science and Technology Council
DxS Limited, UK
Economic and Social Research Council
European Federation of Pharmaceutical Manufactures
GE Healthcare
GeneWatch UK
GlaxoSmithKline
A T Kearney, London
Nuffield Council on Bioethics
Population Health and Use of Medicines Unit, St Vincent's Hospital, Sydney
Public Health Genetics Unit
Roche Products Limited
Roche Diagnostics Limited
Royal College of Physicians
Royal Pharmaceutical Society of Great Britain
Royal Society of Chemistry
The Sanger Institute
The Science Council
Science and Technology Studies Unit, University of York
Solexa Limited, UK
The Wellcome Trust

(ii) Individuals
Professor Russ Altman, Stanford University
Sir Walter Bodmer FRS, University of Oxford
Dr Mike Bonsall, University of Oxford
Dr James Browne
Professor Peter Dunnill, University College London
Dr Adam Hedgecoe, University of Sussex
Dr Werner Kalow, University of Toronto
Professor Munir Pirmohamed, University of Liverpool
Professor Roland Wolf, University of Dundee

Annex 3 Background science

A3.1 Genetic information

Genes can be considered as the instructions, stored within every living cell, that are required to make and maintain a living organism. Genetic information is encoded by the structure of ***deoxyribonucleic acid*** (DNA). A gene is a specific length of DNA that encodes the information to make functional proteins, or parts of them; some proteins are encoded by more than one gene. ***Proteins*** are the macromolecules that perform most cellular functions. The properties and functions of a cell are determined almost entirely by the proteins which it is able to make.

The sum total of the genetic information for any organism is called its ***genome*** and the study of the genome is termed ***genomics***. Genes are carried on structures called ***chromosomes***; humans have 23 pairs of chromosomes, one chromosome inherited from each parent. The specific site of a gene on a chromosome is termed a ***locus***.

Genes may exist in alternative forms, which are called ***alleles***. Specific sets of alleles forming the genome of an individual are called its ***genotype***; the visible appearance or behaviour of an individual is termed the ***phenotype***.

DNA is a double stranded molecule, organised as a double helix. The helix consists of a sugar–phosphate backbone with chemical bases that extend from the backbone like the rungs of a ladder. There are four different bases in DNA: adenine (A), thymine (T), guanine (G) and cytosine (C), termed ***nucleotides***. The bases on one strand can only pair with a specific base on the other strand. A always pairs with T, and G always pairs with C. The order of these bases determines the structure, and therefore the function, of the protein made by the DNA.

The strict base-pairing rules are what allow DNA the remarkable property of self-replication. As cells divide, so do chromosomes, and each of the pair of DNA strands comes apart to serve as a template for the synthesis of two new strands. Therefore, the new pairs of DNA strands are identical to the one from which they were synthesised.

A3.1.1 The human genome

Recently it has been estimated that the human genome contains between 20 000 and 25 000 genes (International Human Genome Sequencing Consortium 2004), although genes comprise only a tiny fraction, perhaps only 1–3%, of the entire human genome. Yet it is thought that virtually all of the functional relevance of an organism is encoded within genes and within the various regulatory regions. In 2001, the draft sequence of the three billion (3×10^9) bases of the DNA that constitute the human genome was determined by the ***Human Genome Project*** (International Human Genome Sequencing Consortium 2001; Venter et al 2001). Humans have many more proteins than genes. Through complex alternative splicing mechanisms, one gene can regulate the synthesis of several proteins.

A3.1.2 Patterns of inheritance

There are two main patterns of inheritance relevant to pharmacogenetics. ***Monogenic inheritance*** implies that a trait, or disease, is due to the action of a single variant gene that is inherited according to Mendel's laws: first, genes are units which segregate, that is members of the same pair of genes, or alleles, are never present in the same gamete (egg or sperm) but always separate and pass to separate gametes; second, genes assort independently. ***Multigenic (or polygenic) inheritance*** implies that a trait or disease requires the action of several variant genes.

A3.1.3 DNA variation

Pharmacogenetics aims to identify genes that may be involved in the mode of action of drugs, and how variations in the structure and function of these genes between individuals is related to differences in the response of patients. Although DNA replication produces identical strands to those from which they were synthesised, sometimes mistakes, or ***mutations***, can occur resulting from a substitution of a different base. This can occur either during cell division, or it may be caused by exposure to DNA-damaging agents in the environment. In most cases, DNA changes are neutral; that is they have no effect on the function of a gene. However, mutations may result in defective gene function and can cause harm, for example lead to disease, susceptibility to disease, or alter the body's response to a therapeutic agent. Very occasionally a mutation can improve an organism's chance of surviving, for example by conferring resistance to disease or other environmental hazards. If mutations occur in cells that make eggs or sperm, they can be inherited and this is the basis for the gradual change in species during millions of years of evolution.

Although human DNA sequences are 99.9% identical to each other, the remaining 0.1% of variation is of great interest. When a variation in DNA between individuals is found sufficiently frequently in normal populations, it is referred to as a ***polymorphism***. Examples of polymorphisms include ***single nucleotide polymorphisms*** (SNPs), ***insertions*** and ***deletions*** of nucleotides, and repetitive sequences (***microsatellites***) (see Section 2.3). SNPs may occur in linked groups called ***haplotypes***, defined as a combination of alleles from closely linked loci found on a particular chromosome.

Sometimes particular linked alleles occur together more than would be expected by chance, a phenomenon called ***linkage disequilibrium***, reflecting selection of the combination.

A3.2 Gene hunting

The identification of a gene that is involved in the actions of a drug can be discovered in two ways: by making an educated guess and examining a gene which has a high probability of being involved (a ***candidate gene***), or by examining the whole genome.

A3.2.1 Candidate gene approach

In pharmacogenetics, appropriate candidate genes are identified whose expression may impact on the action of drugs. This may be based on metabolic pathways, molecular targets or biological response pathways. Generally, the genes are ranked based upon their perceived likelihood of being involved in the drug response and the stronger candidates are then tested first.

A3.2.2 Whole genome analysis

A ***whole genome analysis*** is effectively the opposite of a study based on candidate genes. Rather than focusing on a set of genes that are already expected to be involved in a drug response, scientists attempt to test the entire genome, based on linkage with SNPs or particular haplotypes (see Section 2.3). The benefit of this approach is that unexpected genetic loci may be involved in the response, potentially adding greatly to the understanding of the drug, the disease or general biology. However, this is an expensive approach, given the vast number of genetic loci that have to be tested to cover the entire genome, and it is still prone to error.

Commonly used techniques in pharmacogenetics include: ***DNA cloning***, the copying of any specific part of a DNA (or RNA) sequence to be produced in unlimited amounts; ***polymerase chain reaction*** (PCR), a method used to make multiple copies of DNA; ***DNA sequencing***, the determination of the order of the base pairs in a segment of DNA; and ***fluorescence in situ hybridisation*** (FISH), a technique that uses fluorescent molecules to locate the position of a DNA sequence along the chromosome.

A3.3 Other post-genomic technologies with importance in pharmacogenetics

A3.3.1 Transcriptomics

The complete set of RNA transcripts produced by an organism at any one time is called the ***transcriptome*** and is the link between the genome, the protein complement of cells (known as the ***proteome***) and the cellular phenotype. The transcriptome varies considerably with time because of different patterns of gene expression. Transcriptomics, the study of the transcriptome, is therefore a global way of looking at patterns of gene expression patterns. An extremely powerful technique used in transcriptomics is ***DNA microarrays***. DNA microarrays were developed in the 1990s and have revolutionised the way in which gene expression is now analysed by allowing the RNA products of thousands of genes to be monitored at once.

Microarrays depend on the chemical attraction that any DNA sequence has for its exact complementary sequence. They are miniature devices, about the size of a microscope slide, containing thousands of different known DNA sequences immobilised at different addresses on the surface. The exact sequence and position of every probe on the microarray are known. Thus any nucleotide fragment that bonds to a probe on the array can be identified by an automated scanning laser microscope. Abundant sequences will generate strong signals and rare sequences will generate weak signals. The strength of the signal thus represents the level of gene expression in the original sample. Using microarrays it is possible to compare the relative gene expression for thousands of different genes in any complex mixture of biological samples: for example before and after a patient has been given a therapeutic drug, or before and after certain cells have turned cancerous.

A3.3.2 Proteomics

Proteomics is the large scale analysis of the protein products of genes. The ultimate goal is to try to define the proteome of cells (the proteins expressed) and how proteins interact with one another. Proteomics is complementary to genomics because it focuses its attention on gene products and hence has enormous potential for medical application (Brenner 2001). The structures of proteins can be studied by a variety of different techniques, notably ***X-ray crystallography and nuclear magnetic resonance spectroscopy*** *(NMR)*.

A3.3.3 Transgenics

The mouse has become a critical animal model in studying human disease and gene expression because scientists have access to many inbred strains, each expressing distinctive physiological and behavioural characteristics. Researchers can now insert, knock out, or mutate mouse genes, quickly breed a generation that expresses the change, and then see how it affects a specific phenotype. When disease-linked genes are discovered, they can be inserted and expressed in mice to find out what they do at the molecular, cellular and behavioural levels. Researchers are able to track abnormalities that may lead to symptoms in humans. Although certain animal models may have their limitations, transgenic mice can sometimes be used to test which drugs might modify a genetic ailment, before embarking on a human trial.

Annex 4 Public dialogue methodology

Three public workshops were held in London, Manchester and Oxford during February and March 2005. For each workshop, approximately 24 members of the public were recruited with particular socio-economic characteristics and attitudes towards science and technology (see below). The recruitment was undertaken by a market research agency.

Table 4 Recruitment profile for pharmacogenetics workshops

	Total	Gender		Socio-economic grade		Age		Ethnicity	
London	28	Male	15	ABC1	15	18–34	15	White	0
		Female	13	C2DE	13	35–54	9	Asian	14
						55+	4	Black	14
Manchester	24	Male	12	ABC1	13	18–34	8	White	19
		Female	12	C2DE	11	35–54	10	Asian	4
						55+	6	Black	1
Oxford	24	Male	12	ABC1	13	18–34	0	White	20
		Female	12	C2DE	11	35–54	0	Asian	2
						55+	24	Black	2

The London workshop was stratified by ethnicity (Black and Asian), to explore different cultural issues forged by the technology. The Manchester workshop was stratified by socio-economic status (ABC1/C2DE) as the key variable determining attitudes towards science and technology. The Oxford workshop was stratified by age (participants aged over 55 years), because of potentially different attitudes and behaviours to medicines. Each workshop had a scientist and a social scientist or ethicist in attendance to act as a resource for the group discussion. A member of the Working Group was present at each of the workshops (see below).

Specialist participants in the pharmacogenetics workshops

London
Dr Hilary Harris, General Practitioner, south Manchester*
Professor Peter Lipton, Hans Rausing Professor of History and Philosophy of Science, University of Cambridge
Professor Marcus Pembrey, Professor of Paediatric Genetics at the Institute of Child Health
Dr Ilina Singh, Centre for the Study of Bioscience, Biomedicine, Biotechnology and Society (BIOS) at the London School of Economics and Political Science

Manchester
Dr Mairi Levitt, Deputy Director, Centre for Economic and Social Aspects of Genomics (CESAGen), Lancaster University
Dr Bill Newman, Senior Lecturer Medical Genetics, St Mary's Hospital, Manchester
Dr John Stageman, VP Research and Development, AstraZeneca*
Dr Tuija Takala, Centre for Social Ethics and Policy School of Law, University of Manchester

Oxford
Sir Walter Bodmer FRS, Weatherall Institute of Molecular Medicine, University of Oxford
Professor Kay Davies FRS, Department of Human Anatomy and Genetics, University of Oxford*
Dr Ainsley Newson, Research Associate, Medical Ethics Unit, Imperial College London
Dr Sarah Wordsworth, Health Economics Research Centre, University of Oxford

* Denotes a member of the working group

In each workshop, the public participants were split into two groups of equal size. A facilitator with experience in moderating public discussions on science and technology led each group through a series of questions related to the context and application of pharmacogenetic research. The format for the workshops was as follows:

10 minutes	Welcome, introduction	Background to the project and the Royal Society; aims and format of workshop; how they information will be used
50 minutes	First break out session	Introductions; how gain information on health issues; views on medicine, drug effectiveness, bad reactions to drugs; views on genetics, conditions under which people would like to know about possible future disease; views on genetic predisposition; views on genetic tests in relation to other medical tests
15 minutes	Tea break	
55 minutes	Second break-out session	Review of scenarios on pharmacogenetics on applications for: drug safety; clinical trials; and the molecular understanding of disease. Explore significance for individuals, society.
20 minutes	Plenary	Feedback and next steps