



# Pharmacogenetics

Towards improving  
treatment with medicines



Geneva 2005

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Geneva, 12 January 2005

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## Preface

The notion that genetic factors can be responsible for altered drug response in some patients evolved in the late 1950s. The term ‘pharmacogenetics’ was coined in 1959 to describe a new scientific discipline that dealt with inherited differences in the response to drugs. It has been suggested that selection of drug therapy based on the genetic make-up of a patient may result in not only an improved therapeutic response but also a clinically important reduction in adverse drug reactions.

Increasingly, sponsors of new drugs are integrating pharmacogenetics in their drug development programmes. The outcome of this integration will present challenges to the traditional paradigms for drug development, regulatory evaluation of safety and efficacy and clinical use of drugs. Ethical, legal and pharmacoeconomic issues are also integral to the debate.

Pharmacogenetics is still an evolving discipline and a very active area of research. It promises to revolutionise therapeutics by ‘personalising medicine’. The term ‘personalised medicine’ is potentially misleading and may be interpreted to mean that drugs are *developed* for individual patients. A term that we prefer to use is ‘individually targeted therapy’. In principle, genotype-based individually targeted prescribing ought to be more effective at improving response rates and decreasing the burdens of adverse drug reactions.

The extent to which this promise of pharmacogenetics is fulfilled remains to be seen. The experience to date is mixed with a few successes but many frustrations. Discovering highly predictive genotype-phenotype associations during drug development and demonstrating their clinical validity and utility in well-designed prospective clinical trials will no doubt better define the role of pharmacogenetics in future clinical practice. In the meantime, pharmacogenetic research deserves support from all concerned but without unrealistic expectations.

This Report, an outcome of inspiring discussions among a number of senior scientists from drug regulatory authorities, pharmaceutical companies and academia, addresses many of these issues in detail. It reflects their views and visions today and expectations for the future. The reader will find that there is duplication of information in various chapters. This is deliberate. The CIOMS Working Group on Pharmacogenetics considered that each chapter should be self-standing with its own references.

CIOMS and its Working Group on Pharmacogenetics hope that readers will enjoy this contribution to the ongoing discussions and debate.

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## **Disclaimer**

Although most chapters enjoyed an undivided support, there were others where unanimity was not possible. Therefore, the views expressed in this Report should be considered majority-based consensus views and not necessarily the unanimous views of all the members of the CIOMS Working Group on Pharmacogenetics (*see Annex 1*) or of the affiliations served by these members.

## Chapter 1

# Introduction and Problem Statement

### 1. Introduction

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The latter half of the last century has witnessed the development of most of the drugs that are used today. The introduction of these drugs has led to dramatic changes in the practice of medicine since it has allowed for the first time the effective treatment of many common diseases such as hypertension, angina pectoris, depression, schizophrenia, lymphomas and leukaemias to name only a few.

Right from the beginning of modern drug therapy it was observed that there was substantial variability among patients both in therapeutic efficacy and the occurrence of side effects. Moreover, for all major classes of drugs (angiotensin converting enzyme inhibitors,  $\beta$ -adrenoreceptor antagonists, selective serotonin reuptake inhibitors, tricyclic antidepressants, statins and  $\beta$ -agonists) a significant proportion of patients will not respond, or respond only partially, when standard doses of the particular drug are administered. The realisation that dose was a poor predictor of therapeutic response stimulated efforts in elucidating the mechanisms responsible.

From these studies it became apparent that the rate at which drugs are eliminated from the body showed substantial interindividual differences. In particular, drug metabolising enzymes were identified to play a pivotal role in the elimination process of most drugs. Since individual optimisation of dosage with such drugs in clinical practise is difficult, there follows sub-optimal treatment, prolonged periods of trial and error and non-compliance with a consequential increase in morbidity, mortality and costs. Therefore, considerable efforts have been expended to identify the mechanisms underlying the marked variability of drug response. As possible mechanisms, heterogeneity of the disease and such clinical variables as age, gender, diet, co-administration of drugs, renal and hepatic function were identified. In addition to these factors it was recognised that genetic factors involved in drug disposition (absorption, distribution, metabolism and elimination) or drug action (receptors and signalling pathways) can modify drug response or are risk factors for adverse drug reactions.

## **2. Birth of pharmacogenetics**

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Genetic factors have been suggested, depending on the drug, to account for 20 to 95% of the variability in drug disposition and effects [1, 2]. The concept that genetic factors which alter the pharmacokinetics and pharmacodynamics of drugs can be responsible for altered drug response in some patients evolved in the late 1950s. At that time it was demonstrated that an inherited deficiency of glucose-6-phosphate dehydrogenase was responsible for the severe haemolysis observed in some patients when exposed to the antimalarial primaquine. This discovery also provided an explanation for why primaquine-induced haemolysis mainly affected the African Americans – this deficiency occurred with a much higher frequency in this ethnic group and was rarely observed in Caucasians of Northern, Western and Eastern European descent. [3]

In 1959, Vogel coined the term ‘pharmacogenetics’ to describe a new scientific discipline that dealt with inherited differences in the response to drugs [4]. In recent years, the term pharmacogenomics has been introduced to describe the progressive transition from genetics to genomics realising that the genome is more than the sum of its genes. It introduces an additional element of a genome-wide approach to identify genes that contribute to a specific disease. *Pharmacogenetics* is defined as the study of interindividual variations in DNA sequence related to drug disposition (pharmacokinetics) or drug action (pharmacodynamics) that can influence clinical response. In contrast, *pharmacogenomics* is defined more broadly as the application of genomic technologies to elucidate disease susceptibility, drug discovery, pharmacological function, drug disposition and therapeutic response. This approach will lead to a new classification(s) of diseases at the molecular level. Moreover, identification of new disease genes will provide new drug targets. Of the 30,000 diseases presently known, there is either no drug treatment or improved drug treatment is needed for more than a 100 to 150 major common diseases. The drugs used today are targeted at approximately 500 pharmacologically active biological targets and there is a great hope that there are at least 3,000 to 10,000 ‘drugable’ targets [5].

## **3. Pharmacogenetics and therapeutics**

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Severe adverse drug reactions (ADRs) such as hepatotoxicity or drug-induced arrhythmias continue to be a significant problem both during the development and in the postmarketing phase of new drugs. ADRs increase morbidity and mortality and are associated with considerable cost



to the healthcare system. The timeliness of this problem is emphasised by a recent survey indicating that adverse drug reactions may be responsible for over 100,000 deaths annually in the US and account for about 5% of all hospital admissions [6]. Recent studies indicate that genetic factors play a role in the pathogenesis of both predictable and unpredictable ADRs. It has been suggested that drug therapy based on the individual genetic make-up of a patient may not only result in an improved response but also in a clinically important reduction in ADRs. For example, Philips and co-workers identified in their systematic review 27 drugs frequently cited in ADR studies [7]. Among these drugs, 59% were metabolised by at least one enzyme with a variant allele known to cause poor metabolism. In contrast, only 7% to 20% of randomly selected drugs were metabolised by enzymes that are known to be expressed polymorphically. This analysis suggests that genetic variability in drug metabolising enzymes is a contributor to the incidence of ADRs.

#### **4. Pharmacogenetics and drug development**

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Worldwide, new drug applications are declining although the number of new chemical entities (NCEs) screened has increased with the use of modern high throughput technology. Ninety percent of new candidates selected from the preclinical phase fail during the clinical development. In 80% of those drugs entering the clinical trials, poor response or side effects are the reasons for terminating development. Thus, there is an urgent need to increase the success rate. One way of improving the success rate is to identify potential responders and non-responders to the drug under investigation on the basis of genetic testing before inclusion into a clinical trial. It is hoped that this approach will not only increase the success rate but also lead to a reduction in the number of patients required to demonstrate efficacy of the drug. As a consequence, the time for the clinical phase of development could be shortened and the costs reduced. However, there are safety-related limitations to this approach. At least one to two drugs are withdrawn every year from the market because of severe ADRs. Recent examples include troglitazone, mibefradil, some newer fluoroquinolones and cerivastatin. Since only a very small number of patients experienced these severe ADRs, it is quite likely that genetic factors predispose these patients to toxicity. Withdrawal of a drug is associated with enormous financial costs to the pharmaceutical industry since it costs about 500 to 700 million Euros to develop a drug and take it through its various preclinical and clinical phases. The industry, and indeed the society, cannot afford such withdrawals, as recent data indicate that the fall in the num-

ber of new drugs approved in the US is reaching a crisis point and that new drug applications are down worldwide. Identification of genetic factors associated with severe ADRs could save some of these drugs [8-10].

## **5. Pharmacogenetics and targeted prescribing**

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With the complete sequence of the human genome now available, it is hoped that better targeted medicine will soon become a reality. The expectations are that with the use of genomic information, we will be able to better predict an individual's likely response to a drug and select the appropriate dose of the drug. This would allow achieving the optimal therapeutic response, avoiding therapeutic failure and minimising side effects and toxicity. Although many genes responsible for inherited differences in the metabolism, transport and action of drugs have been identified, this new knowledge has not been translated into clinical practice. With the exception of a few examples of drug metabolising enzymes, the contribution of genetic polymorphisms to individual differences in drug effects and toxicity are not well understood. Moreover, most of these studies have focused on the consequences of a single gene polymorphism for an altered drug response. This approach, however, neglects the fact that drug response phenotype like most disease phenotypes is a complex polygenic trait with non-genetic factors contributing to the manifestation of the phenotype [11].

## **6. Limitations of pharmacogenetics**

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The extent to which genetic factors contribute to drug response/toxicity phenotype will depend on whether the candidate gene is a gene of major, moderate or minor effect. There are also misconceptions with respect to the information provided by a pharmacogenetic test. Even in the case of a gene with maximum effect, the presence or absence of a mutation will not provide a straight forward 'yes' or 'no' answer but rather the likelihood that in a subject with a given mutation, an event will or will not occur. The highest positive predictive value of a genetic test will be observed for genes with major effect. In the case of drug metabolising enzymes, mutations leading to a loss of function will result in higher drug concentrations. If these higher drug concentrations are associated with toxicity, the likelihood that a patient who has this genotype will develop toxicity is increased provided the patient is prescribed the same dose as the remainder of the patients who carry the wild type of the gene. However, the negative predictive value (likelihood that a patient without the mutation will not have toxicity) can be rather poor if non-genetic

factors that lead to high drug concentrations (which are associated with drug toxicity) are neglected. If a patient who carries a wild type gene is concomitantly treated with a drug that inhibits the enzyme, the patient will develop the phenotype of high concentration that is usually associated with the presence of two mutant alleles, a phenomenon known as 'phenocopying'. Neglecting the impact of non-genetic factors on the manifestation of a drug response phenotype has led to claims that genotyping for the deficient alleles of thiopurine S-methyltransferase (TPMT) has a poor predictive value for the development of severe myelosuppression, which is seen with the use of 6-mecaptourine or azathioprine. It is vital therefore that pharmacogenetic information is used to improve prescribing decisions and considered alongside other key information in a holistic manner.

One of the major limitations, which has prevented the use of pharmacogenetic testing in the clinical setting, is the lack of prospective clinical trials demonstrating that pharmacogenetic testing can assist in the selection of the appropriate drug and dose for the individual patient in order to achieve the optimal therapeutic response, avoid therapeutic failure and minimise side effects and toxicity. The current pharmacogenetic research being undertaken by both the private and the public sectors will need to address this deficit.

With the rapid progress being made in molecular genetics, more and more genes that can alter drug response will be identified. Since drug response involves several genes, the positive and negative predictive values of pharmacogenetic testing will be improved by combining information from each of the contributing genes. Thus with the advances made in technology, the cost of genotyping will become affordable and it should be possible to establish pharmacogenetics for optimising drug development and drug therapy.

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## Chapter 2

# Abnormal Drug Response (I): Clinical, Social and Economic Burden

### 1. Introduction

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From the very beginning of monitoring drugs for their safety, attention has been paid to the economic consequences of adverse drug reactions (ADRs) [1-3]. ADRs have long been recognised as a significant cause of morbidity and mortality but the true extent of the problem has remained a matter of discussion and informed speculation. Almost a quarter of a century ago, Mach and Venulet [3] considered methodological issues for estimating the economic aspects of ADRs, and calculated direct and indirect costs using several case scenarios.

Prescribing the most effective drug in individual patients is more often than not a process of trial and error. Therefore, in addition to ADRs, failure of efficacy of a drug also imposes significant burdens. However, data quantifying the healthcare and economic impacts of patients failing to respond to the medicines prescribed first time are sparse.

The most common ADRs are dose- or concentration-related (type A) pharmacological reactions that account for about 75-80% of all ADRs. These include reactions related to prescription of inappropriate drug or inappropriate doses of a drug as well as drug interactions. Usually, clinically relevant drug interactions result in an increase in plasma concentration of one of the interacting drugs to toxic levels. Other common types of ADRs are immunologically-mediated (type B for **b**izarre, idiosyncratic or hypersensitivity reactions). Classification of ADRs has also included those termed type C (following **c**ontinuous or **c**hronic use), type D (that are **d**elayed such as carcinogenic or teratogenic effects) and type E (**e**nd-of-use ADRs that result from withdrawal of a drug; “rebound phenomenon”). Recently, ADRs of type F have been added to this increasingly complex classification and these result from unexpected **f**ailure of therapy.

As early as 1972, it was estimated that 6.9 to 22% of all ADRs are in fact due to drug interactions [4]. Although the majority of drug interactions result in pharmacokinetic changes with no clinical consequences, about 1 in 7 drug interaction studies, submitted to the US Food and Drug Administration (FDA) during the period 1992-1997, led to changes in

labelling, the majority of which involved dose adjustments [5]. One review of the available studies suggests that up to 30% of hospital patients and 70% of ambulatory patients could be receiving potentially interacting drugs [6]. Drug interactions are increasing and are now recognised as a frequent cause of hospital admissions [7-10]. The number of drugs withdrawn recently because of their interaction potential and clinical consequences testifies to this increasing problem, resulting from (generally unintentional) polypharmacy.

There are a large number of international studies that estimate the scale of the clinical burden due to ADRs. Others have attempted to quantify the social and economic consequences of ADRs in terms of healthcare availability, resource implications and gross national productivity. All those involved in the development and use of medicines, whether they be payers, pharmaceutical companies, patients, physicians, or regulators agree that ADRs are associated with suffering and costs.

This chapter reviews a sample of representative studies on the overall impact of ADRs and failure of efficacy.

## **2. ADR-related morbidity and mortality**

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### **2.1 ADRs in community medicine**

In one of the earliest studies assessing the impact of ADRs, Mulroy reported that 1 in 48 consultations in general practice in the UK was due to an ADR [11]. A study by Lumley et al estimated that 0.8% of all general practitioner consultations are directly due to ADRs [12]. Following a survey of 817 patients and using a much broader definition of ADR, Martys reported that 41% of the patients in general practice have had a reaction to the drug prescribed [13].

More recent studies from France have estimated an incidence of about 2 adverse effects per general practitioner per day [14] and 2.6 cases of serious ADRs per general practitioner per year [15]. Despite the enormous progress in therapeutics since the late 1970s, the incidence of ADRs has not changed [16-20].

### **2.2 Drug-related hospital admissions**

Using data compiled prior to 1977, Venulet reported the incidence of ADRs in already hospitalised patients as ranging from 2 to 18% [21]. A

review in 1993, based on 36 English-language studies of ADRs leading to hospital admissions, reported that on average, 5.5% of all hospital admissions are due to ADRs [22]. The incidence varied from 0.2% to 21.7% depending on the population under investigation.

In an Italian hospital, 235 of 5,497 patients who visited the emergency department over a 1-year period (October 1994 to September 1995) did so because of an ADR. Of these, 45 were hospitalised. Dose-related therapeutic failures (55.6%) were the main cause of drug-related admissions whereas ADRs (63.8%) caused the most frequent drug-related visits. Although drug interactions accounted for only 3.8% of the visits, their consequences were more severe, and most of these patients had to be hospitalised [23].

The percentage of hospital admissions due to drug-related causes, including ADRs and therapeutic failures, has been variously estimated to be 11.4% in Denmark (study period was March 1988 to May 1989) [24], 13.8% in Sweden (September 1997–October 1998) [25] and 5.7% in Australia (November 1994–December 1994) [26]. In one study of 452 admissions to a university hospital in the USA, 16.2% of the admissions were considered drug-related which included 8.8% due to drug therapy failure (July 1993–August 1993) [27].

The percentage of hospital admissions specifically due to ADRs has been estimated at 8.4% in Denmark [24], 7.5% in the UK [28], 3.3–7% in Switzerland (from 1996 onwards) [29, 30], 3.2–7.2% in France (March–April 1998 in one of the studies) [31, 32], 2.7% in Australia [26] and 2.4% in Germany (October 1997–March 2000) [33]. The most recent study (November 2001 to April 2002) reported a 6.5% prevalence of ADR-related hospital admissions in two major hospitals in the UK [34].

In the US, the overall incidence of serious ADRs was computed to be 6.7% on the basis of a meta-analysis of 39 prospective studies from hospitals [19]. Of these, 2.1% had occurred in patients while in hospital and 4.7% were present in patients requiring admission as a result of ADRs. Seventy-six per cent of ADRs were Type A dose-dependent. Another meta-analysis of studies confirmed the heterogeneity of the published data. However, these studies do consistently emphasise the considerable proportions of all hospital admissions that are related to ADRs. Larger studies have shown lower percentages although the elderly were reported to be at a 4-fold greater risk. Beijer and de Blaeij reported

that 88% of the ADR-related admissions in the elderly and 24% in the non-elderly were preventable [35].

## **2.3 Drug-related mortality**

The data on drug-related or ADR-related mortality are complicated by the heterogeneous nature of the studies but they do provide an estimate of the problem.

Shapiro et al reported as long ago as 1971 that as many as 160,000 deaths resulted from ADRs each year in US hospitals [36]. The overall evidence from a number of recent studies suggests that 0.3-0.5% of deaths are related to ADRs.

In England and Wales, the number of deaths related to ADRs has risen steadily over the last 10 years. One UK study of 3,277 Coroner's Inquests during 1986 to 1991 identified 10 deaths due to prescribing errors and another 36 deaths caused by ADRs [37]. These 46 deaths accounted for approximately 1 in 2,000 of all the deaths during the study period. A prospective 6-month study from Norway reported 1% drug-related mortality among 3,082 hospitalised patients [38]. Only 2 of these were recognised as drug-related by the attending clinicians. This gross under-recognition of ADR-related mortality is supported by another study from US that compared the number of deaths attributed to ADRs on death certificates with data in the spontaneous post-marketing surveillance system of the FDA (MedWatch) during 1995. During this period, 206 deaths were certified as being due to ADRs, whereas the MedWatch tabulated 6,894 fatalities [39]. It is recognised that the fatal outcomes recorded in MedWatch are not necessarily causally drug-related. However, this 34-fold variation must be a matter of concern.

ADR-related mortality was reported to be 1% in the UK [28] and among 4,331 hospital admissions, 0.18% in Switzerland [29]. ADRs were estimated to be between the fourth and sixth leading cause of death in the USA; the fatality rate as a result of ADRs amongst the hospitalised patients was 0.32 % [19]. Pirmohamed et al reported an overall mortality rate of 0.15% due to ADRs [34].

## **3. Healthcare burden**

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In terms of time spent in the hospital, it is not surprising that a patient with an ADR spends longer time in a hospital and consequently, imposes greater economic burdens on the healthcare systems.



### 3.1 Duration of hospitalisation

Mean duration of hospital stay was 15.1 days for each of the 10 patients with an ADR and 10.7 days for those without an ADR in one study from France (conducted during May 1993–October 1993). In the same study, the mean stay was 19.2 days for the 21 patients in whom the ADR occurred in the hospital [40]. Other studies have estimated the duration of hospital stay at  $13 \pm 10.6$  days in Germany (October 1997–March 2000) [33] and 10.6 days for patients with ADRs and 6.8 days for matched controls in the USA (August 1998–December 1998) [41]. ADR-related excess stay in hospital was computed at 7.6% of all hospital days in France [40] and 5.9% of all emergency beds in Australia [26]. For the 1,225 ADR-related hospital admissions in the UK, the median duration of hospital stay was 8 days [34].

### 3.2 Drug-related hospitalisation costs

Estimates on costs of ADRs leading to hospitalisation are complicated by geographical differences in healthcare costs and a lack of common units of measurement and methodologies.

The cost of ADRs leading to hospitalisation was estimated at Euro 11,357 per hospital bed per year in France [32] while a study from Switzerland estimated a mean cost per case at Swiss Francs 3,586 or a total of Swiss Francs 821,204 over the 6-months study period [30]. In the US, the cost of hospitalisation was US\$ 22,775 per case for patients with an ADR and US\$ 17,292 per case without an ADR [41]. In Australia, the annual cost for all drug-related admissions was estimated at just under A\$ 3.5 million (comprised of A\$ 1.63 million for unavoidable, A\$ 1.67 million for avoidable and A\$ 0.2 million for definitely avoidable admissions) [26]. The cumulative direct costs for hospitalisation over the 30-month study period in Germany were estimated to be Euro 4 million in the two urban study areas and the annual direct cost for the whole country was estimated to be Euro 400 million [33]. In the French study above, about 5–9% of hospital costs were related to ADRs [40]. When Pirmohamed et al extrapolated their findings to the entire National Health Service in the UK, the projected annual cost of ADR-related admissions was estimated to be £466 million [34]. Others had previously estimated these costs in the UK to be in the range of £1.5–2.6 billion [42].

Lazarou et al [19] estimated the direct hospital costs due to ADRs in the US to be US\$ 1.6–4 billion. Ernst and Grizzle [43] updated their previous 1995

estimate of US\$ 76.6 billion for the annual cost of drug-related morbidity and mortality resulting from drug-related problems in the ambulatory setting in the United States to reflect treatment patterns and costs in 2000. They estimated that in 2000, the mean cost for a treatment failure was US\$977 per patient. For a new medical problem, the mean cost was US\$1,105, and the cost of a combined treatment failure and resulting new medical problem was US\$ 1,488. Overall, the cost of drug-related morbidity and mortality in the US exceeded US\$ 177.4 billion in 2000. Hospital admissions accounted for nearly 70% (US\$ 121.5 billion) of total costs, followed by long-term care admissions, which accounted for 18% (US\$ 32.8 billion).

## **4. ADRs and pharmacovigilance**

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### **4.1 Costs of pharmacovigilance**

Pharmacovigilance, or activity and programmes to detect and monitor ADRs, and efforts to reduce and prevent ADRs each incurs significant costs. These costs include administration of national and global monitoring systems (e.g. the Yellow Card Scheme in the UK or the MedWatch Scheme in the US), changes in prescribing information, dissemination of this information and in extreme cases, withdrawal of drugs.

An indirect estimate of costs of ADRs may be obtained by examination of the benefits of Bar Code Regulations issued by the FDA in February 2004 [44]. The preliminary estimate of the cost for implementing this bar coding is thought to be between US\$ 0.5 billion and 1.4 billion over a 10-year period. The purpose of bar coding is to ensure accurate identification of medications, and thereby reduce medication prescribing errors, and ultimately, mortality and morbidity. As stated above, one study estimated these at more than US\$ 177 billion including US\$ 121.5 billion in hospital costs and US\$ 32.8 billion in long-term care expenses [43].

### **4.2 ADRs and drug withdrawals**

Drug withdrawals are costly for the companies. Worldwide there were 121 safety-related drug withdrawals between 1960 and 1999. Market life was known for 87 of these. About 31% of these products were withdrawn within the first two years and up to approximately 50% were withdrawn within the first five years [45].

In the UK, a total of 583 new active substances (NAS) were approved between the years 1972 and 1994 and of these, 59 were later withdrawn.

This represents a withdrawal rate of 2.57 NAS per year over this period [46]. Thirty-four drugs have been withdrawn from various markets for safety reasons over the 15-year period from 1990 to 2004 and have included a number of high profile drugs as shown in Table 1.

**Table 1**  
**Drugs withdrawn from various markets (1990 to 2004)**  
**for safety reason**

Drug	Year of withdrawal	Reason(s) for withdrawal from market
Dilevalol	1990	Hepatotoxicity
Triazolam	1991	Neuropsychiatric reactions
Terodiline	1991	QT interval prolongation and TdP (TdP = torsade de pointes)
Encainide	1991	Proarrhythmias
Fipexide	1991	Hepatotoxicity
Temafloxacin	1992	Hypoglycaemia, haemolytic anaemia and renal failure
Benzarone	1992	Hepatotoxicity
Remoxipride	1993	Aplastic anaemia
Alpidem	1993	Hepatotoxicity
Flosequinan	1993	Excess mortality possibly due to proarrhythmias
Bendazac	1993	Hepatotoxicity
Soruvidine	1993	Myelotoxicity following drug interaction
Chlormezanone	1996	Hepatotoxicity and severe skin reactions
Tolrestat	1996	Hepatotoxicity
Minaprine	1996	Convulsions
Pemoline	1997	Hepatotoxicity
Dexfenfluramine	1998	Cardiac valvulopathy and pulmonary hypertension
Fenfluramine	1998	Cardiac valvulopathy and pulmonary hypertension
Terfenadine	1998	Drug interactions, QT interval prolongation and TdP
Bromfenac	1998	Hepatotoxicity following prolonged administration
Ebrotidine	1998	Hepatotoxicity
Sertindole	1998	QT interval prolongation and potential for TdP
Mibefradil	1998	Statin-induced rhabdomyolysis following drug interaction and concerns on other potential drug interactions, including the risk of TdP
Tolcapone	1998	Hepatotoxicity
Astemizole	1999	Drug interactions, QT interval prolongation and TdP
Trovafloxacin	1999	Hepatotoxicity
Grepafloxacin	1999	QT interval prolongation and TdP
Troglitazone	2000	Hepatotoxicity
Alosetron	2000	Ischaemic colitis
Cisapride	2000	Drug interactions, QT interval prolongation and TdP
Droperidol	2001	QT interval prolongation and TdP
Levacetylmethadol	2001	Drug interactions, QT interval prolongation and TdP
Cerivastatin	2001	Rhabdomyolysis following drug interactions
Rofecoxib	2004	Myocardial infarction and strokes

(TdP = torsade de pointes)

The withdrawals of perhexiline (an antianginal drug) and phenformin (an oral hypoglycaemic agent) in late 1980s are almost certainly related to genetically mediated toxicity. Both these drugs are metabolised almost exclusively by CYP2D6 and their clinical uses were associated with serious neuropathy and hepatotoxicity (perhexiline) and lactic acidosis (phenformin). Available evidence strongly incriminates CYP2D6 as a risk factor for both. For a number of other older drugs now removed from the market, there is a body of evidence which, when viewed collectively, also supports the notion that genetic factors may have contributed substantially to their withdrawal from the market. These drugs include encainide (CYP2D6), terodiline and prenylamine (CYP2D6 and potassium channel mutations) and terfenadine, cisapride and levacetylmethadol (potassium channel mutations). Although the costs of developing new drugs are difficult to estimate precisely, overall costs have been estimated at approximately US\$ 400 million in 1998 and US\$ 800 million in 2001 [47, 48]. Although these are overall costs and include the costs of failures during early development, they do indicate the substantial loss of investment due to ADRs.

Drug withdrawals deprive patients who did not suffer from ADRs of the benefits of the medicine. For example, following the withdrawal of terodiline in the UK (one of the three major markets of this drug), the regulatory authority in the UK received representations from a number of patients and physicians to make this drug available, albeit on a named patient basis. Similar demand had followed the withdrawal of perhexiline, an antianginal drug that was highly effective in patients who did not respond to other drugs and were not suitable for coronary artery bypass surgery.

## **5. ADRs and litigation**

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ADRs inflict additional burdens on healthcare resources through litigations. One study by Kelly [49] identified 1,520 significant adverse drug events published in ClinAlert during the period 1976 to 1997. Of these, 56% (n = 846) were life-threatening, 29% (n = 447) resulted in death and 15% (n = 227) resulted in permanent disability. Litigation was reported in 14% of fatal cases of ADRs and the settlement averaged US\$ 1.1 million. Other data from this study [50-52] relevant to this report are summarised in the Table 2.

**Table 2**  
**Analysis of adverse drug events published in ClinAlert**  
**during the period 1976 to 1997 – adapted from Kelly WN [49]**

	<b>All serious</b>	<b>Life-threatening</b>	<b>Fatal</b>	<b>Permanent disability</b>
Adverse drug <b>events</b> cases identified	1,520 (100%)	846 (55.7%)	447 (29.4%)	227 (14.9%)
Adverse drug <b>reactions</b>	52%	50%	58%	43%
Type A reactions	19%	7%	34%	9%
Type B reactions	61%	93%	66%	91%
Setting where drug started:				
- Hospital	67%	89%	56%	57%
- Out-patient	29%	5%	41%	38%
Usual recommended dose in	73%	82%	64%	43%
Common drug classes				
- CNS	24%	26%	24%	16%
- CVS	10%	11%	12%	5%
- Oncology	11%	7%	17%	15%
Litigation				
- Reported in	13%	1%	14%	56%
- Mean settlement	US\$ 3.1 m	US\$ 1.1 m	US\$ 1.1 m	US\$ 4.3 m

Claims and litigation are an additional burden on healthcare. In the UK National Health Service, these amounted to £400 million in paid litigation in 1998/99 with an expected potential liability of £2.4 billion. In countries such as India, the inclusion of the medical profession under Consumer Protection Act has resulted in ever increasing litigation and malpractice suits [53].

Private litigations against pharmaceutical companies have also increased, as seen in class actions related to dexfenfluramine (“fen-phen” leading to primary pulmonary hypertension and cardiac valvulopathy) and cerivastatin (leading to rhabdomyolysis). The potential liability from such class actions usually runs into billions of dollars. In the US, the sponsor of dexfenfluramine had taken charges related to “fen-phen” related litigation of US\$ 13.2 billion, an amount estimated to be sufficient to cover the overall funding requirements [54]. With regard to cerivastatin, the lawyers had stated that the compensation could total around US\$ 800 million, related to just the fatal cases alone. Given that the total number of all potential claimants is thought to be more than 4,000, it has been estimated that settlement could reach US\$ 5 billion [55].

## **6. ADRs and indirect costs**

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Indirect costs are those sustained by the community as a result of ADRs. They arise from the loss of individual contribution to the gross national product (GNP). This loss in GNP is related to (a) the excess time spent in the hospital, (b) the time taken by the individual to fully recover from an ADR (usually a serious one) to the point when (s)he can return to previous work, (c) the time taken by the individual's family member(s) to care for him or her and (d) social benefits paid to the individual while off work.

These indirect costs may vary enormously and can amount to hundreds of thousands of dollars, particularly in cases in which the ADR results in permanent disability [3]. There is a great need to review and further develop methodology for assessing these indirect costs.

## **7. Conclusions**

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ADRs and other drug-related problems result in considerable clinical morbidity and mortality. They account for a significant proportion of hospital admissions and such patients generally spend longer time in the hospital. Consequently, the direct implications for healthcare and economic resources are considerable. Indirect economic costs and social burdens are difficult to compute but estimates suggest that these may be comparable if not even greater.

A number of valuable drugs have had to be withdrawn from the market as a result of the clinical risks they posed. Withdrawal of these drugs also has consequences for those patients in whom they are effective.

Since the majority of ADRs are dose- or concentration-related, they may be preventable, or at least reduced, by paying careful attention to factors that may increase plasma concentrations. Non-genetic factors such as inappropriate doses or drug interactions may possibly be controlled in the majority of cases. Increasingly, however, many ADRs appear to have a genetic substrate. It seems likely that genetic influences resulting in pharmacodynamic variability may be even more important than those resulting in pharmacokinetic variability [56].

The present agenda for “value for money” in healthcare provides the impetus to better quantify the problem and develop measures that minimise human and healthcare costs. These measures include reduction in the frequency or prevention of ADRs.

Given the advances in pharmacogenetic technology, there is a pressing need to study systematically whether pharmacogenetics can help minimise further the burdens of drug-related problems. This requires at least 'preliminary' evidence indicating that many drug-related problems may in fact have a pharmacogenetic basis.

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## Chapter 3

# Abnormal Drug Response (II): Opportunities for Risk Reduction Through Pharmacogenetics

### 1. Introduction

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An adverse drug reaction (ADR) can result from a variety of risk factors including variability in pharmacokinetics and pharmacodynamics of a drug due to the genetic make-up of an individual. Other important influences are external factors such as co-medications and co-morbidities, which give rise to drug-drug or drug-disease interactions. The net effect of these interactions is that the prescribed dose of a drug is an inappropriate one. Usually, clinically relevant drug interactions result when the plasma concentration of one of the interacting drugs increases to toxic levels.

With careful attention to prescribing information regarding dose, age-related adjustments and populations at risk for drug-drug and drug-disease interactions, the impact of ADRs can be greatly minimised. However, it is unlikely that any single approach will completely eliminate all ADRs. With available data suggesting that some ADRs might have a monogenic or polygenic basis, the application of pharmacogenetics provides an opportunity for further reductions in both the incidence and severity of ADRs.

This chapter reviews some of the data on abnormal drug response related to polymorphisms in drug metabolising enzymes, pharmacological targets and drug transporters. It illustrates how, at least in some areas, pharmacogenetics may offer the prospects of minimising the risks of drug toxicity and therapeutic failures.

### 2. Pharmacogenetics and drug metabolising enzymes

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A number of drug metabolising enzymes displays genetic polymorphisms. Candidate gene association studies, investigating the role of these polymorphic drug metabolising enzymes such as CYP2D6, CYP2C9, CYP2C19, N-acetyltransferase (NAT2), thiopurine S-methyltransferase (TPMT), UDP-glucuronosyltransferases (UGTs) and dihydropyrimidine dehydrogenase (DPD), have already shown that there is a genetic predisposition to a number of ADRs.

It is now generally assumed that because of this genetic predisposition, there may be a great potential for preventing ADRs and improving the

safe and effective use of medicines through the increasing knowledge of genetic factors that determine drug response. Polymorphic genes and products of gene expression have been considered as markers for optimisation of drug therapy, most especially in the field of oncology.

## **2.1 Polymorphic variation in CYP2D6**

Studies over the last two decades have shown that any given population may be divided into two phenotypes – extensive metabolisers (EMs) or poor metabolisers (PMs) – depending on their ability to mediate CYP2D6-dependent hydroxylation of the antihypertensive drug debrisoquine. Among the EM phenotype, there are two subgroups of particular interest at either extreme of the EM population distribution. One subgroup, termed the ultrarapid metabolisers (UMs), is comprised of individuals possessing multiple copies of the gene for normal metabolic capacity and the other group, termed the intermediate metabolisers (IMs), is comprised of a heterozygous genotype (“gene-dose effect”). UMs metabolise drugs so avidly that they attain very low concentrations of the parent drug and high concentrations of rapidly accumulating metabolites while IMs display a modest impairment in drug metabolising capacity.

CYP2D6 is responsible for the metabolism of well over 60 drugs that include antiarrhythmics,  $\beta$ -adrenoreceptor antagonists, antihypertensives, antianginals, neuroleptics, antidepressants, analgesics as well as a number of other miscellaneous drugs. Candidate gene association studies have shown that a number of ADRs to CYP2D6 substrates are related to CYP2D6 genotype (Table 1).

One of the first reports on the clinical significance of CYP2D6 polymorphism and its association with serious toxicity was perhexiline-induced neuropathy in patients with impaired CYP2D6 metabolism. Although the recommended dose of perhexiline was 100mg three times daily, a recent study of 23 patients has shown that to maintain the plasma concentrations of perhexiline within the therapeutic and non-toxic range, PMs required a dose of 10-25 mg/day while EM and ultrarapid EM required 100-250 and 300-500 mg/day respectively [1]. Other clinical consequences for individuals with the PM or ultrarapid phenotypes of CYP2D6 are also shown in Table 1.

Application of pharmacogenetic principles may also improve efficacy. There are several examples where subjects carrying certain alleles suffer from a lack of drug efficacy because of ultrarapid metabolism caused by multiple genes or by induction of gene expression. As with perhexiline,

some patients who are ultrarapid metabolisers fail to respond to conventional doses of nortriptyline and require ‘megadoses’ of this antidepressant. Similarly, poor metabolisers fail to respond to therapeutic effects mediated by metabolites. This is illustrated by the relative loss in PMs of analgesic effects following administration of codeine or tramadol or the loss of antiarrhythmic effects of encainide.

## 2.2 Polymorphic variation in CYP2C9

Retrospective case studies have shown that the presence of mutant CYP2C9 allele (especially CYP2C9\*3 allele) confers a significantly increased risk of bleeding following treatment with warfarin. Available

**Table 1**  
**Clinical consequences for PM and ultrarapid EM phenotypes of CYP2D6**

<b>Clinical Consequences for the Poor Metaboliser</b>	
<i>Increased risk of toxicity</i>	
Debrisoquine	Postural hypotension and physical collapse
Sparteine	Oxytocic effects
Perphenazine	Extrapyramidal symptoms
Flecainide	? Ventricular tachyarrhythmias
Perhexiline	Neuropathy and hepatotoxicity
Phenformin	Lactic acidosis
Propafenone	CNS toxicity and bronchoconstriction
Metoprolol	Loss of cardioselectivity
Nortriptyline	Hypotension and confusion
Terikalant	Excessive prolongation in QT interval
Dexfenfluramine	Nausea, vomiting and headache
L-tryptophan	Eosinophilia-myalgia syndrome
Indoramin	Sedation
Thioridazine	Excessive prolongation in QT interval
<i>Failure to respond</i>	
Codeine	Poor analgesic efficacy
Tramadol	Poor analgesic efficacy
Opiates	Protection from oral opiate dependence
<b>Clinical Consequences for the Ultrarapid Metaboliser</b>	
<i>Increased risk of toxicity</i>	
Encainide	? Proarrhythmias
Codeine	Morphine toxicity
<i>Failure to respond</i>	
Nortriptyline	Poor efficacy at normal doses
Propafenone	Poor efficacy at normal doses
Tropisetron	Poor efficacy at normal doses
Ondansetron	Poor efficacy at normal doses

data, however, indicate that although the CYP2C9\*3/CYP2C9\*3 genotype is associated with dramatic over anticoagulation soon after the introduction of oral anticoagulants, overdose during the maintenance period is mostly related to environmental factors [2, 3]. It is also recognised that interindividual variability in warfarin sensitivity also originates from environmental factors. In one study, age and CYP2C9 genotype accounted for 12% and 10% of the variation in warfarin dose requirements, respectively [4]. Clearly, other pharmacodynamic (such as to an abnormality in the target enzyme vitamin K epoxide reductase) and dietary factors also play an important role. In a retrospective cohort study of patients on long-term warfarin, it was found that the mean maintenance dose varied significantly among the six genotypes of CYP2C9. Compared to patients with the wild type genotype, patients with at least one variant allele required longer time to achieve stable dosing and had a significantly increased risk of a serious or life-threatening bleeding event, although patient numbers were small for some genotypes in this study [5].

Similarly, to achieve a therapeutic serum concentration of phenytoin, patients carrying at least one mutant CYP2C9 allele required a mean phenytoin dose that was about 37% lower than that in patients with wild type genotype (199 mg/day versus 314 mg/day) [6]. Since phenytoin has a narrow therapeutic index and genotyping may be carried out rapidly and at a relatively low cost, dosage adjustment based on CYP2C9 genotype, especially at the induction of therapy, would be of value in order to lower the risk of concentration-dependent phenytoin toxicity in the carriers of mutant alleles.

### **2.3 Polymorphic variation in CYP2C19**

CYP2C19 mediates the major pathway responsible for metabolic elimination of proton pump inhibitors. Since therapeutic activity correlates with exposure to the parent compound, it is not surprising that a number of studies have shown that PMs of CYP2C19 respond better to *H. pylori* eradication therapy. These preliminary findings need to be confirmed in large prospective studies [7]. EMs of CYP2C19 require higher doses of these drugs.

### **2.4 Polymorphic variation in thiopurine S-methyltransferase**

Azathioprine and 6-mercaptopurine are metabolised by thiopurine S-methyltransferase (TPMT). The activity of TPMT is inversely related to the risk of developing acute leucopenia associated with the use of these drugs. A number of studies have shown that the risk of azathioprine-induced acute leucopenia can be greatly reduced by basing the initial azathioprine dose on TPMT genotype or phenotype [8, 9]. Of course, not all

azathioprine-induced toxicities have a genetic basis. In one study of 93 patients, it was noted that azathioprine-related gastrointestinal side effects are independent of TPMT polymorphism [10]. The value of genotyping for TPMT is illustrated by a report from Murphy and Atherton [11] that by initiating therapy at dose levels of 2.5-3.5 mg/kg in atopic eczema patients with a normal TPMT level, they felt confident in reducing the frequency with which tests of bone marrow and liver function had to be undertaken.

## 2.5 Polymorphic variation in UDP-glucuronosyltransferases

Conjugation reactions such as glucuronidation mediated by UDP-glucuronosyltransferases (UGTs) are now also attracting increasing attention, especially in the field of oncology. Glucuronidation is by far the most important conjugation pathway in man. A multigene family encodes the UGTs and a relatively small number of human UGT enzymes catalyse the glucuronidation of a wide range of structurally diverse endogenous (bilirubin, steroid hormones and biliary acids) and exogenous chemicals. Genetic variations and single nucleotide polymorphisms (SNPs) within the UGT genes are remarkably common, and lead to genetic polymorphisms [12, 13]. Some polymorphic UGTs have demonstrated a significant pharmacological impact in addition to being relevant to drug-induced ADRs. Two major isoforms of UDP-glucuronosyltransferase, UGT1A1 and UGT1A9, have been shown to display genetically determined wide interindividual variability in their activities. Studies investigating the role of UGT1A isoforms in the metabolism of drugs such as irinotecan [14, 15], flavopiridol [16, 17], tranilast [18] and atazanavir [19] have been most valuable in explaining the safety issues (myelosuppression, diarrhoea or hyperbilirubinaemia) associated with the use of these drugs.

A meta-analysis by Phillips et al [20] identified 131 specific drugs, 55 drug classes, and 19 therapeutic drug categories as being associated with ADRs. All except three of these drugs were included among the top 200 selling drugs in the United States. The therapeutic categories associated with the most common ADRs were cardiovascular, analgesics, psychoactive drugs and antibiotics. This meta-analysis included 18 of 333 ADR studies and 22 of 61 variant allele review articles. It identified 27 drugs frequently cited in ADR studies. Among these drugs, 59% were metabolised by at least one enzyme with a variant allele known to cause poor metabolism. In contrast, only 7% to 22% of randomly selected drugs were metabolised by enzymes displaying genetic polymorphism ( $p = 0.006 - < 0.001$ ). These data suggest that drug therapy based on the genotype of individual patients may result in a clinically important reduction in adverse outcomes.

### **3. Pharmacogenetics and transporters**

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For the vast majority of drugs, however, the reason for individual susceptibility to ADRs has remained unknown and there are hardly any data on genetic susceptibility. However, recent studies have shown that organ-specific organic anion and cation transporters play an important role in the transport of drugs into the cells. These transporters may account for drug-induced toxicity, hitherto termed “idiosyncratic”.

Molecular studies have found evidence of genetic polymorphisms of these transporters in hepatocytes [21, 22]. Mutations in the genes coding for these transporters may lead to dysfunctional polypeptides, which affect not only the pharmacokinetics of the drugs concerned but also the potential hepatotoxic effects of some of these drugs [23, 24]. Furthermore, the variant alleles show inter-ethnic differences [22, 25] that may possibly explain inter-ethnic differences in the hepatotoxic potential of a drug (such as ibufenac). Studies investigating these transporters in patients with hepatotoxicity offer exciting prospects for exploring the potential role of pharmacogenetics in drug-induced hepatotoxicity (see section 5 below).

These transporters and P-glycoproteins co-localise in organs of importance to drug disposition (intestine, liver and kidney). The expression of P-glycoprotein activity is under the control of the MDR1 gene [26] and is an important factor in the disposition of many drugs. In multi-drug resistance (MDR), the processes involved show considerable inter-individual and inter-ethnic variability. For example, a variant allele recently designated as MDR1\*2 (resulting from three linked SNPs) occurred in 62% of European Americans and only 13% of African Americans [27].

The MDR1 gene and its variants have significant implications in terms of efficacy or development of resistance to anticonvulsants, antineoplastic therapy and anti-HIV drugs [28, 29].

### **4. Pharmacogenetics and pharmacological targets**

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In addition to pharmacogenetic effects on drug metabolism, therapeutically promising examples of genetic variations in pharmacological targets are also beginning to emerge. These targets include receptors, transporters, enzymes, channels and intracellular coupling processes that modulate pharmacodynamic responses. Among the most widely studied are the



pharmacological targets related to cardiac arrhythmias, asthma, depression and the HLA antigen genotype in hypersensitivity reactions.

To date, the focus of pharmacogenetic studies in the context of ADRs has been on drug metabolising enzymes. It is now becoming evident that polymorphisms of pharmacological targets (pharmacodynamic polymorphisms) may in fact be even more important. In one study of 270 cancer patients given antiemetic therapy with 5-HTR<sub>3B</sub> receptor antagonists, approximately 30% suffered from nausea or vomiting despite these drugs. Ultrarapid metabolism of tropisetron (and to a lesser extent for ondansetron) was shown to predispose patients to poor efficacy [30]. In another study by the same group of investigators, patients homozygous for a deletion variant of the promotor region of 5-HTR<sub>3B</sub> gene were shown to experience vomiting more frequently than did all the other patients [31]. In a pharmacogenetic study that compared paroxetine and mirtazapine in 246 elderly patients with major depression, discontinuations due to paroxetine-induced side effects were strongly associated with the 5-HTR<sub>2A</sub> C/C, rather than CYP2D6, genotype. There was a significant linear relationship between the number of C alleles and the probability of discontinuation. The severity of side effects in paroxetine-treated patients with the C/C genotype was also greater [32]. Thus, although paroxetine is metabolised by CYP2D6, polymorphism of 5-HTR<sub>2A</sub> is a more important determinant of paroxetine-induced ADRs.

#### 4.1 Polymorphisms of cardiac potassium channels

Drugs prolonging the QT interval of the surface electrocardiogram (ECG) have attracted considerable attention recently. Excessive prolongation of the QT interval, in the right setting, predisposes to torsade de pointes (TdP), a potentially fatal ventricular tachyarrhythmia [33]. The duration of this interval reflects the duration of ventricular action potential. The major determinant of the action potential duration is the potassium current mediated by the rapid component of the delayed rectifier potassium channels (IKr). Many drugs have been withdrawn as a result of their potential to prolong the QT interval and induce TdP.

Following advances in molecular biology, genetics and pharmacology of ion channels, it has become evident that there is a great diversity of genes that control the expression of these potassium channels. Mutations of the subunits that form these channels, including IKr, are common and give rise to congenital long QT syndromes.

Relatively large numbers of individuals carry variants of long QT syndrome genes that are clinically silent. While these individuals have a normal ECG phenotype, they nevertheless have a diminished repolarisation reserve and are highly susceptible to drug-induced QT interval prolongation and/or TdP following normal therapeutic doses of drugs (such as cisapride, astemizole, terfenadine and halofantrine among others) even in the absence of inhibitors of their metabolism [34]. In an analysis of 341 reports of cisapride-induced ventricular arrhythmias, there were 38 (11%) cases in whom there were no identifiable risk factors or contraindications [35]. These individuals may well represent a population with a concealed genetic defect of their potassium channels.

#### **4.2 Polymorphisms of $\beta$ 2-adrenoceptors and ALOX-5**

Individuals who carry Arg16/Gly16 or Gly16/Gly16 mutations of  $\beta$ 2-adrenoceptors have been shown to respond much less favourably to salbutamol-induced bronchodilatation, in contrast to those with wild type receptor characterised by Arg16/Arg16 genotype – the difference in FEV1 response between Gly16/Gly16 and Arg16/Arg16 genotypes is 6.5-fold [36]. Similarly, asthmatic patients who carry mutations of the core promoter of 5-lipoxygenase (ALOX-5) respond poorly to ALOX-5 inhibitors such as zileuton [37].

Kaye et al [38] have recently shown that in individuals with cardiac failure, patients who were homozygous for the Gln27 allele of the  $\beta$ 2-adrenoceptor displayed a significantly lower proportion of good responders to carvedilol than did patients who were homozygous or heterozygous for the Glu27 polymorphism (26% versus 63%,  $P=0.003$ ).

#### **4.3 Polymorphisms of the serotonin transporter**

Genetic polymorphism in the promoter region of the serotonin transporter (5-HTT) gene is reportedly a determinant of response to fluvoxamine, a selective serotonin re-uptake inhibitor. The insertion variant of this polymorphism (long allele) is associated with higher expression of brain 5-HTT compared to the deletion variant (short allele) [39]. Patients who have one or two copies of the long variant (homozygous l/l or heterozygous l/s) may show a better therapeutic response than patients who are homozygous for the short variant (s/s). The efficacy of fluvoxamine in the treatment of delusional depression has been shown to correlate with 5-HTT genotypes [40].

#### 4.4 Abacavir-induced hypersensitivity reactions and HLA genotype

Hypersensitivity reactions (HSR) to abacavir occur in about 5% of patients who receive the drug for HIV-1 infection. Three independent research groups have identified an association between HLA-B\*5701 and hypersensitivity to abacavir in patients of Caucasian ancestry [41-44]; the sensitivity of HLA-B\*5701 ranged from 46-94%. While two groups suggest that there may be clinical value in prospectively screening Caucasian patients for HLA-B\*5701 prior to the use of abacavir [43, 44], in the largest, and most ethnically diverse study, the association between HLA-B\*5701 and hypersensitivity was much weaker in Hispanic patients and was absent in Black patients [45]. While this is an interesting example of the potential of pharmacogenetics, there is legitimate risk that HLA-B\*5701 screening could unintentionally compromise the highly successful risk management programme established for abacavir hypersensitivity. Specifically, physician vigilance might be reduced in patients who do not carry markers associated with hypersensitivity and marker-negative patients might be at increased risk for experiencing serious and/or life-threatening hypersensitivity reactions because symptoms associated with abacavir hypersensitivity are not promptly recognised and abacavir discontinued. Efforts to analyse thousands of SNPs across the genome for association to HSR are underway to identify additional genetic markers with sufficient predictive value to be clinically useful [46].

### 5. Pharmacogenetics and hepatotoxicity

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Hepatotoxicity is of serious concern not only because of the morbidity and mortality associated with it but also because it is the leading reason for withdrawal of drugs from the market [47]. This is also evident from inspection of Table 1 in Chapter 2. Apart from the role of transporters at the hepatocytes-biliary canalicular interface, there is conclusive evidence for the role of polymorphic drug metabolism in hepatotoxicity associated with some drugs.

For isoniazid, the genetic basis for this toxicity is well known. Individuals who have a low activity of N-acetyltransferase (NAT2 slow acetylators) are at a much greater risk of developing isoniazid-induced hepatotoxicity. Slow acetylators produce a low level of an intermediate metabolite that is also eliminated by acetylation. Failure to eliminate this effectively results in production of an alternative metabolite that is hepatotoxic [48, 49].

Perhexiline-induced hepatotoxicity, a major factor in the drug's withdrawal from the market, is associated with impaired CYP2D6 status [50]. The involvement of genetic factors in drug-induced hepatotoxicity generally is strongly suggested by the susceptibility of the female gender. In addition, there are reports of familial or ethnic susceptibility to hepatotoxicity associated with some drugs such as phenytoin [51] or ibufenac [52] respectively.

## **6. Pharmacogenetics and drug interactions**

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Drug-drug interactions can be dramatically influenced by genotypic differences. A number of studies have shown that CYP2D6 PMs (with alleles expressing no functional enzyme) do not show the drug-drug interactions predicted from *in vitro* studies. This is hardly surprising since there is no functional CYP2D6 activity to inhibit or induce. Likewise, UMs too may fail to exhibit the expected drug-drug interaction unless the dose of the inhibitor is (toxic) high enough. The individuals most likely to display a drug interaction are those who have an intermediate drug metabolising capacity or those who have inherited CYP2D6 alleles with reduced or altered affinity for CYP2D6 substrates. At the level of CYP2D6, the dependence of drug interactions on the metabolic phenotype has already been shown for a number of its substrates, for example codeine [53], propafenone [54, 55], mexiletine [56], encainide [57], metoprolol [58] and desipramine [59]. The organic ion transporters and P-glycoproteins referred to earlier are additional sites of important drug interactions and pharmacogenetic factors are also likely to be important here.

## **7. Predictive genotyping: Improving drug response and minimising ADRs**

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It has been estimated that predictive genotyping (for candidate genes) will lead to benefit in 10-20% of drug treatment by allowing prevention of ADRs [60, 61].

If genetic markers of a greater number of ADRs (candidate genes, SNPs or haplotypes) can be identified and if cheap and rapid genotyping of patients can be done routinely, then the impact of ADRs on morbidity and mortality can be considerably reduced.

Veenstra et al [62] have reviewed cost-effectiveness of genetic tests and have identified five primary characteristics that will enhance the cost-effectiveness of the application of pharmacogenetics. These are:

1. A well-established association between the genotype and drug response
2. The variant gene is relatively common
3. Relatively cheap and rapid genetic test
4. Difficulties in monitoring drug response
5. Severe clinical or economic consequences from not using the pharmacogenetic information

Similar conclusions have been reached by Rioux [63] who has also emphasised the importance of the frequency of the variant allele in determining the cost-effectiveness of the application of pharmacogenetics in therapeutics.

Other workers who have evaluated the potential impact of pharmacogenetics have concluded that its application in therapeutics will be cost-effective “sometimes” and that it would be effective primarily for chronic diseases where unnecessary long-term therapy with an ineffective drug for many years could be avoided in some patients [64].

## **8. Limitations**

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It is not intended to suggest that the application of pharmacogenetics will totally eliminate the problems of ADRs. Recently, Kirchheiner et al have provided a preliminary guidance for a number of drugs metabolised by CYP2D6 and CYP2C19 with a view to introducing genotype/phenotype-specific dose schedules [65]. Recommending inappropriately high dose can easily offset the potential benefits of pharmacogenetics. Co-administration of a metabolic inhibitor converts an extensive metaboliser into a poor metaboliser. It is therefore not surprising that drug interactions feature prominently among the causes that lead to withdrawal of drugs from the market.

One unpublished report analysed 17 studies (with a total of about 1,350 patients) published between 1995-2000 on antipsychotic drug therapy, investigating an association between CYP2D6 genotype and both plasma levels of the drug(s) and response to these drugs [66]. There was a relationship between genotype and plasma concentrations of drugs that were predominantly metabolised by CYP2D6 but a large intra-genotypic variability obscured clinical utility of concentration measurements. However, there was no relationship evident between genotype and drug response (i.e. failure to respond beneficially). There was only a modest positive trend between the genotype, especially the presence of

CYP2D6\*10 allele in the Japanese, and severity of tardive dyskinesia and extrapyramidal syndrome. This may not altogether be surprising since many neuroleptics have active metabolites. When applying pharmacogenetic testing in routine clinical practice, it is important to take note of the pharmacology of the metabolites relative to that of the parent drug, the fraction of the drug cleared by the polymorphic pathway and the therapeutic index of the drug concerned [67].

In humans, diclofenac is metabolised to 4'-hydroxy (OH), 3'-OH and 5-OH metabolites. The polymorphic CYP2C9 is involved in the metabolism of diclofenac to 4'-OH diclofenac and 3'-OH diclofenac. However, the CYP2C9 genotype does not correlate with diclofenac-induced hepatotoxicity or COX-1 and COX-2 inhibition [68, 69]. Similarly, in asthma, patients who are deficient in 5-lipoxygenase due to a genotypic variant in the ALOX-5 gene are non-responsive to 5-lipoxygenase inhibitors. However, most of the 5-lipoxygenase inhibitor non-responders have normal ALOX-5 genes, and the basis of their non-responsiveness lies in other factors, probably related to the nature of their asthma.

However, if a genotype/phenotype relationship can be shown, pharmacogenetics offers another important strategy by which to reduce ADRs. The dose schedules recommended need to be carefully chosen and the clinical awareness of the consequences of co-administration of interacting drugs need to be heightened. Prior genotyping of patients can be used to improve safe and more effective use of specific and carefully chosen medicines by identifying patients most likely to respond beneficially and those most likely to develop an ADR. This strategy would immediately translate into great reductions in healthcare and economic resources that are currently expended in managing the consequences of ADRs.

Even if a correlation between genotype and phenotype can be established, it is worth remembering that drug-related problem(s) may not be completely eliminated. This is because a number of non-genetic external factors interact with genotype or modulate the response to a drug. In addition, there are a number of other factors that complicate what may appear to be a simple relationship. The reader is referred to Chapter 4 on “Exploring Pharmacogenetics in Drug Discovery and Development” and Chapter 12 on “Unresolved Issues and Barriers to Progress”.

## 9. Conclusions

This chapter highlights the potential contribution of pharmacogenetics in reducing the incidence of dose-related and idiosyncratic ADRs. In relation to ADRs, the research aim of pharmacogenetics is to identify a genetic profile that characterises patients who are more likely to suffer an ADR compared with those in whom the risk is unlikely. Using this knowledge in the clinic, the choice of medicine and dose can be targeted for an individual and the overall result may be an improvement in the safety profile of the drug. Moreover, as a result of improved safety following application of pharmacogenetic principles, improved efficacy may also accrue. Many dosing schedules are limited by appearance of side effects. By eliminating the use of high doses in those genotypes most at risk, it may become possible to evaluate the additional benefits of higher doses in the remaining genotypes.

Advances in biotechnology promise the prospects of characterising genetic variations in individual patients rapidly and cheaply with a view to individualisation of therapy. Exploration of the role of pharmacogenetics should be undertaken during drug development and continued well into the post-marketing period to include the study of rare and delayed adverse reactions. This will make the application of pharmacogenetics in minimising morbidity and mortality from A.DRs a realistic and worthwhile proposition.

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## Chapter 4

# Exploring Pharmacogenetics in Drug Discovery and Development

## 1. Introduction

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Although defining pharmacokinetic variability has increasingly become a part of phase I drug development, a very limited number of doses are usually taken into phase III development and are based on safety windows for the whole population assuming that all patients are a homogeneous group. The end result is the recommendation of a “standard” dose schedule to be applied to all patients. This practice does not take into account the considerable interindividual variability that exists within the population at large in the dose-concentration-response relationship of a new chemical entity (NCE). Therefore, the consequences of administering a “standard” dose to individuals at either extreme of the variability are all too obvious.

Interindividual variability results directly from interindividual differences in the two key elements of the dose-response relationship of the drug – pharmacokinetics and pharmacodynamics. Interindividual variability in either of these key elements of the dose-response relationship originates from two broad sets of factors – genetic and non-genetic – which need to be placed in perspective in relation to each other. Drug development programmes need to characterise variability generally and the specific contributions of these genetic and non-genetic factors in determining this variability.

### 1.1 Non-genetic variability

The role of non-genetic factors in pharmacokinetic or pharmacodynamic variability can be significant and arises from the presence of co-morbidity (e.g. hepatic or renal dysfunction), co-administration of drugs that may interact with the index drug or change in internal environment such as endocrine or electrolyte imbalance.

Recognising the pivotal role of pharmacokinetics in determining dose schedules, the effects of co-morbidities and co-medications are almost always explored during drug development. These include the effect of hepatic or renal dysfunction or alterations in the pharmacokinetics of the drug following co-administration of inhibitors or inducers of its metabolism. Other variables that are examined include age, particularly children and the elderly, weight or body mass index and gender. The outcome of

these investigations, when clinically significant, is dose recommendations, contraindications or warnings specific to these variables.

## **1.2 Genetic variability**

Both pharmacokinetics and pharmacodynamics of a drug are strongly influenced by genetic factors as well. The presence of variant alleles often exerts influences that far exceed those due to age, gender or the presence of co-morbidity and co-medications. Genetic polymorphisms of drug metabolising enzymes or pharmacological targets have both been documented to have an impact on variability at a population level and response to drugs resulting in adverse drug reaction (ADR) or failure of response at an individual level.

## **2. Pharmacogenetic Variability**

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### **2.1 Polymorphisms of drug metabolising enzymes**

Between 50-60% of drugs undergoing metabolic elimination are metabolised by cytochrome P450 (CYP) drug metabolising enzymes.

It seems probable that all CYP drug metabolising enzymes display polymorphisms, because changes in the DNA sequence are anticipated every  $10^2$ - $10^3$  bases in all genes. A compilation of human CYP polymorphisms can be found at a website especially dedicated to this at [<http://www.imm.ki.se/CYPalleles/>]. Although all CYP drug metabolising enzymes have genetic variations, the functional consequences of the majority of these are unknown.

Most of the polymorphisms detected earlier were based on whole or partial gene deletions, mRNA splicing defects or truncation or frameshift mutations. These changes generally lead to non-functioning proteins. This is illustrated by classical polymorphisms such as those of CYP2D6 and CYP2C19. Polymorphisms resulting in amino acid substitutions within protein coding regions of CYP genes can lead to variable functional consequences, ranging from total absence of activity to a protein with altered activity. Again, several examples can be found among variants of CYP2D6 and CYP2C19, but there are an increasing number of functional variants among other CYP enzymes as well, for example CYP2C9.

The presence of a variant in the DNA sequence of an enzyme does not necessarily lead to a functional consequence in the activity of that enzyme. When a change leads to a functional consequence, the outcome depends on the sequence position where the change has occurred. Polymorphisms

in regulatory regions can affect levels of expression of P450s and those in coding sequences may lead to a protein with an altered or absent activity. In principle, the effect is usually expected to be identical in all individuals, but differential interactions with transcription factors and co-activators and repressors may have variable consequences.

Gene amplification of CYP2D6 is also a well-documented phenomenon and frequently results in an “ultrapid metaboliser” phenotype. A further complication with these polymorphisms is the variable effect on different substrates and reactions. For example, CYP2C9 I359L polymorphism affects warfarin and diclofenac metabolism, but not tolbutamide metabolism, thus highlighting the need to fully evaluate clinical relevance.

A recent trend has been to develop high-throughput methods of scoring single nucleotide polymorphisms (SNPs). However, the problem with this approach is that only a fraction of SNPs have functional consequences. The most direct way to assess the functional significance of a SNP is to express the variant protein in a heterologous system and to study its catalytic properties. Heterologous expression systems also have their limitations as has been shown in the case of thiopurine S-methyltransferase (TPMT) where expression of the mutant variant in a yeast expression system results in normal protein function. In any case the more relevant approach is to determine whether there is an association of the SNP under study and a defined phenotype. Therefore, a more indirect and less certain but complementary approach is to perform large-scale comparisons of SNPs and functions (with probe or other drugs) in clinical trials.

Table 1 provides a broad overview of CYP variant alleles. These polymorphisms can have profound influence on the pharmacokinetics of a drug and the subsequent development programme. The impact of pharmacogenetics in drug discovery, development, regulatory evaluation of an NCE and its post-marketing surveillance is best illustrated by the genetically determined variation in the activity of drug metabolising enzymes such as CYP2D6. Genetic polymorphism in CYP2D6, responsible for oxidation of debrisoquine and a number of cardiovascular and psychoactive drugs, is to date the most widely investigated and best characterised for its clinical implications. Apart from the well-documented studies on perhexiline, anecdotal reports or retrospective candidate gene association studies have shown that individuals with a particular genotype may be at a greater risk of an ADR following administration of some CYP2D6-metabolised drugs (see table 2). This genetically determined probability of an ADR in a small number of indi-

**Table 1**  
**Variability in the *in vitro* drug metabolism and number of variant alleles found thus far of CYP enzymes in human liver [See also 1, 2]**

Enzyme(s)	“Typical” variation <sup>1</sup> (fold)	Maximal’ variation <sup>1</sup> (fold)	Number of variant alleles <sup>2</sup>	Remarks
CYP1A2	8-18	50-100	12 (5 5’-variants)	None well characterised
CYP2A6	23-28	164	15 (3 deletions)	Frequency of deletion variants in Orientals ~15 %
CYP2B6	20	50	6	None well characterised
CYP2C8	>10	large	5 (2 5’-variants)	Changes in paclitaxel metabolism <i>in vitro</i>
CYP2C9	5-15	40-100	5	Two exon SNPs (*2,*3): decreased metabolism of some substrates
CYP2C19	7-10	>155	10	Most variants have no enzyme activity. Frequency of PM phenotype in Orientals ~15 %. Ethnic variations
CYP2D6	5-18	>80	about 75	A prototype polymorphism with increased, unchanged, decreased or absent activities. Ethnic variations.
CYP2E1	6-10	20-50	13 (5 5’-variants)	Most not well characterised
CYP3A4	8-15	30-100	24 (6 5’-variants)	Practically none is well characterised
CYP3A5	?	?	At least 11	4 splicing defect variants without any activity <i>in vivo</i>

<sup>1</sup> Fold-variations are approximate only. “Typical” variation refers to values for individuals with no known “extreme” CYP-affecting factors in the history. “Maximal” variation refers to values for individuals with known non-genetic influences (e.g. cigarette smoking, inducers, severe liver disease etc) (See reference 2).

<sup>2</sup> According to the CYP allele nomenclature in <http://www.imm.ki.se/CYPalleles/> Many variants actually contain several nucleotide changes.

viduals could greatly influence the risk/benefit appraisal of the NCE even at a population level, depending on the clinical consequences of the ADR.

This is hardly surprising given the variability between the genotypes in the pharmacokinetics of a drug that is subject to polymorphic metabolism. Table3 provides a typical estimate of the variability in various pharmaco-



**Table 2**  
**Clinical consequences for PM and ultrarapid EM phenotypes of CYP2D6**

<b>Clinical Consequences for the PM</b>	
<i>Increased risk of toxicity</i>	
Debrisoquine	Postural hypotension and physical collapse [3]
Sparteine	Oxytocic effects [4]
Perphenazine	Extrapyramidal symptoms [5]
Flecainide	Possibly ventricular tachyarrhythmias [6]
Perhexiline	Neuropathy and hepatotoxicity [7, 8]
Phenformin	Lactic acidosis [9]
Propafenone	CNS toxicity and bronchoconstriction [0, 11]
Metoprolol	Loss of cardioselectivity [12]
Nortriptyline	Hypotension and confusion [13]
Terikalant	Excessive prolongation in QT interval [14]
Dexfenfluramine	Nausea, vomiting and headache [15]
L-tryptophan	Eosinophilia-myalgia syndrome [16]
Indoramin	Sedation [17]
Thioridazine	Excessive prolongation in QT interval [18]
<i>Failure to respond</i>	
Codeine	Poor analgesic efficacy [19]
Tramadol	Poor analgesic efficacy [20]
Opiates	Protection from oral opiate dependence [21]
<b>Clinical Consequences for the ultrarapid EM</b>	
<i>Increased risk of toxicity</i>	
Encainide	Possibly proarrhythmias [22]
Codeine	Morphine toxicity [23]
<i>Failure to respond</i>	
Nortriptyline	Poor efficacy at normal doses [24, 25]
Propafenone	Poor efficacy at normal doses [26]
Tropisetron	Poor efficacy at normal doses [27]
Ondansetron	Poor efficacy at normal doses [27]

EM = Extensive metaboliser

PM = Poor metaboliser

kinetic parameters due to genetic polymorphism in CYP2D6. Often, the variability is even more dramatic (may be up to 20-fold). It is evident that the exposure to the parent drug is considerably higher in poor metabolisers (PMs) than in extensive metabolisers (EMs).

It is worth noting that even in the absence of CYP2D6 genotyping, when dose is adjusted by measurement of plasma drug concentrations, there have been no clinical problems reported with the use of perhexiline in Australia. This emphasises the critical role of monitoring plasma concentrations of some drugs.

**Table 3**  
**Pharmacokinetic consequences of CYP2D6 polymorphism [28]**

Pharmacokinetic parameter of parent drug	Consequences for the PM relative to EM *
Bioavailability	2 - 5 fold
Systemic exposure	
C <sub>max</sub>	2 - 6 fold
AUC	2 - 5 fold
Half life	2 - 6 fold
Metabolic clearance	0.1 - 0.5 fold

\* EM = Extensive metaboliser

\* PM = Poor metaboliser

## 2.2 Polymorphisms of pharmacological targets

Pharmacogenetic factors also exert clinically significant influences at the pharmacodynamic level; that is at the level of an enzyme, a channel, a receptor, a transporter (of neurotransmitters such as serotonin) or an intracellular coupling process. Among the pharmacological targets that best illustrate the significance of polymorphism are those related to asthma, depression and arrhythmias.

Individuals who carry Arg16/Gly16 or Gly16/Gly16 mutations of the  $\beta$ 2-adrenoreceptors, for example, display a much less favourable immediate bronchodilatory response to salbutamol, in contrast to those with wild type receptor characterised by Arg16/Arg16 genotype [29]. This polymorphism also influences airway responses to regular inhaled  $\beta$ -agonist treatment. Patients with Arg16/Arg16 genotype who use salbutamol regularly show a small decline in morning peak expiratory flow (AM PEF). By the end of a 16-week study, Arg16/Arg16 subjects who had used salbutamol regularly had an AM PEF  $30.5 \pm 12.1$  L/min lower ( $p = 0.012$ ) than Arg16/Arg16 patients who had used salbutamol only intermittently as needed [30].

Genetic polymorphism in the promoter region of the serotonin transporter (5-HTT) gene is reportedly a determinant of response to fluvoxamine, a selective serotonin re-uptake inhibitor. The insertion variant of this polymorphism (long allele) is associated with higher expression of brain 5-HTT compared to the deletion variant (short allele). Patients who have one or two copies of the long variant (homozygous l/l or heterozygous l/s) show a better therapeutic response than patients who are homozygous for the short variant (s/s) [31, 32]. The efficacy of fluvoxamine in the treatment of delusional depression has been shown to correlate with the 5-

HTT genotypes. Similar data have been reported for other drugs in this class (fluoxetine, sertraline and paroxetine).

Among the arrhythmia-related pharmacological targets studied extensively are the polymorphisms in voltage-gated potassium channels; more specifically those related to congenital long QT syndromes (LQTS). LQTS is a heterogeneous group of disorders, caused by ion channel mutations at 6 different genetic loci at least, resulting in a prolonged cardiac repolarisation, QT interval prolongation on resting electrocardiogram (ECG) and an increased risk of a potentially fatal tachyarrhythmia known as torsade de pointes (TdP). Four of the congenital long QT syndromes, LQT1, LQT2, LQT5 and LQT6, result from mutations of potassium channel subunits, KvLQT1, hERG, minK and miRP1 respectively, while the fourth one, LQT3 results from mutations of the cardiac-specific sodium channel, SCN5A. LQT7 results from mutations of the gene coding for cardiac (and skeletal) inward rectifying potassium channel. LQT4 results from mutation of the gene (ANK2) coding for ankyrin-B, a member of a family of membrane adapters. All these subtypes of LQTS are characterised by diminished repolarisation reserve.

Potassium channels that mediate the outward repolarising current (especially the rapid component of delayed rectifier current) are the targets of class III antiarrhythmic drugs that exert their therapeutic effect by controlled prolongation of the QT interval. Over the last 10 years, many non-antiarrhythmic drugs have attracted considerable clinical and regulatory attention because of their potential to prolong the QT interval. A number of non-antiarrhythmic drugs have been found to have this undesirable activity on cardiac repolarisation and lead to TdP. The primary potassium channel target of a vast majority of these drugs is the hERG subunit. Congenital LQTS is estimated to have a frequency of 1 in 5,000 individuals in the USA (<http://www.sads.org/LQTS.html>). However, in view of the low penetration of many of the mutant alleles of genes that control the expression of potassium channels, the size of the population with channels that have altered properties or reduced function is substantially larger than that diagnosed by ECG recording alone. While such individuals have a normal ECG phenotype, they have diminished repolarization reserve and are highly susceptible to drug-induced QT interval prolongation and/or TdP, even at the normal recommended doses that are otherwise safe. Studies suggest that up to 15% of cases of drug-induced TdP can be explained by polymorphisms in these genes. The role of genetic factors in drug-induced torsade de pointes is reviewed in detail elsewhere [33]. Individuals who develop drug-induced prolongation of QT interval with or without TdP are not

usually genotyped but available evidence suggests that a substantial proportion of the cases of the drug-induced long QT syndrome might represent cases of “*forme fruste*” of the congenital long QT syndrome.

Understanding genetic variation in pharmacological targets during drug discovery allows preclinical evaluation of any alterations in the affinity of an NCE for these targets and the clinical response to the NCE that can then be explored and evaluated clinically. This data might be of interest for appropriate patient selection, safety monitoring, or any other factor affecting the future performance of the NCE. For example, NCEs are now routinely evaluated for their affinity to bind to the hERG channel, as this most likely predicts the clinical potential for QT interval prolongation. It is clear, however, that a full functional characterisation of any newly discovered polymorphism in a pharmacological target is required before its full significance for the future development of an NCE can be assessed. Unless the full functional consequences are known, it may be impossible to correlate a genotype with drug response. However, it would be inappropriate to require that full functional significance of a polymorphism be known for a marker to have a utility in guiding drug development and delivery. It is not possible at present to say that we have full knowledge of the drug targets of biomarkers such as lipid levels although their utility in improving healthcare is accepted.

It appears that polymorphisms of pharmacological targets may prove to be more relevant clinically than the polymorphisms of drug metabolising enzymes. In a pharmacogenetic study that compared paroxetine and mirtazapine in 246 elderly patients with major depression, discontinuations due to paroxetine-induced side effects were strongly associated with the 5-HTR<sub>2A</sub> C/C, rather than CYP2D6, genotype. There was a significant linear relationship between the number of C alleles and the probability of discontinuation. The severity of side effects in paroxetine-treated patients with the C/C genotype was also greater [34]. Thus, although paroxetine is metabolised by CYP2D6, polymorphism of 5-HTR<sub>2A</sub> is a more important determinant of paroxetine-induced ADRs.

### **3. Pharmacogenetics: Drug development, approval and restrictions**

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#### **3.1 Termination of drugs from development**

Until the completion of the Human Genome Project and the availability of technology to scan the entire genome for SNPs that correlate with

genetically determined drug response, there was (and there still appears to be) a general reluctance within the industry to continue the development of drugs subject to significant genetic variability. For example, predominantly CYP2D6-mediated metabolism of a potential NCE has frequently been seen as a liability ('2D6-liability') and a number of such compounds in 1980s and early 1990s were dropped from further progression. Efforts were instead directed at developing structural analogues of lead compounds that were not eliminated predominantly by CYP2D6-mediated metabolism. A similar situation seems to have now arisen with respect to NCEs that block hERG channels, conferring a 'QTc liability' to the NCE.

Terikalant, a class III antiarrhythmic drug, is metabolised by CYP2D6. It has been shown that the increase in QT interval produced by terikalant correlates well with the degree of impairment in its metabolic elimination by CYP2D6 [14]. The perceived difficulties in managing this genetically driven risk resulted in termination of this compound from further development. There is of course no readily available information on how many other compounds have been dropped during development due to their CYP2D6-mediated metabolism. This approach of discarding polymorphically metabolised candidate drugs has proven resource-intensive and counter-productive, leading to greatly diminished pipeline of innovative NCEs. The application of pharmacogenetics may therefore allow development decisions to be made that will facilitate the progression of NCEs. More recently, metabolism by CYP3A4 is also perceived to be a liability since these drugs (e.g. a number of QT-prolonging drugs or HMG-CoA reductase inhibitors) are highly susceptible to drug interactions.

More recently, the trend seems to be one of developing single isomers of previously marketed racemic drugs in cases where one of the isomers is subject to polymorphic metabolism and introduces wide interindividual variability in AUC at a given dose. This variability can be reduced, with a more predictable efficacy, by eliminating one isomer and administering only the isomer, which is efficacious but less subject to polymorphic metabolism. For example, in case of omeprazole, the ratios of AUC for PMs/EMs of CYP2C19 are 7.5 for (+)-(R)-omeprazole and 3.1 for (-)-(S)-omeprazole [35]. (-)-(S)-omeprazole is now approved and marketed as esomeprazole ('Nexium'). Whether or not this reduction in variability has any clinically relevant practical implications remains to be shown and each drug must be judged on a case-by-case basis. The message here is that drug development programmes should address pharmacogenetics in the context of stereoselectivity in the pharmacology of the NCE when appropriate.

### 3.2 Pharmacogenetically driven labelling restrictions

In order to comply with various regulatory recommendations, sponsors of NCEs often conduct formal phase I studies in a genotyped panel of healthy volunteers to characterise pharmacogenetic influences on pharmacokinetics. Unfortunately, however, the findings of such studies are rarely carried forward to improving the designs and inclusion criteria of phase II or phase III studies. It is most unusual to see phase II dose-ranging studies that include information on the genotype of the individuals randomised. This omission has serious implications for selecting the most appropriate dose for a pharmacogenetically heterogeneous population in phase III pivotal studies. Ideally, where drugs are metabolised by known polymorphic enzymes, phase II dose-ranging studies should include a wide range of prospectively pre-screened subjects to ensure the inclusion of all the important genotypic subgroups, thus impacting on the efficiency of drug development. It is encouraging to note that there is now a greater trend towards integrating pharmacogenetics in drug development.

In some cases where serious toxicity might have a pharmacogenetic basis, the management of clinical safety of an NCE requires detailed labelling on influences of pharmacogenetic factors. Five drugs best illustrate the current regulatory practice of incorporating candidate gene-based pharmacogenetic information into labels to promote safe and effective prescribing.

Thioridazine is metabolised by CYP2D6 and poor metabolisers of CYP2D6 have high plasma levels of the parent drug. Thioridazine predisposes individuals to excessive QT interval prolongation and torsade de pointes. Therefore, the US Food and Drug Administration (FDA) have now contraindicated the drug in patients known to have reduced levels of cytochrome CYP2D6.

Sertindole, an atypical neuroleptic agent, is primarily cleared by CYP2D6. The PMs utilise an alternative pathway mediated by CYP3A4 for its elimination. Since it is not a routine practice to genotype patients, PMs might be at risk if CYP3A4-mediated pathway was inhibited. Consequently, coadministration of sertindole is contraindicated with ketoconazole and itraconazole, both powerful inhibitors of CYP3A4.

S-citalopram (a potent selective serotonin re-uptake inhibitor) has been approved as 'escitalopram' for depression. It is metabolised predominantly by CYP2C19. The usual dosage is 10 mg once daily, which may be increased to a maximum of 20 mg daily. However, for patients who are

known to be poor metabolisers with respect to CYP2C19, the recommendation is to initiate treatment with a dose of 5 mg daily during the first two weeks of treatment. Depending on individual patient response, the dose may be increased to 10 mg daily.

Celecoxib is an orally active, COX-2 selective inhibitor indicated for the symptomatic relief in treatment of osteoarthritis or rheumatoid arthritis. Since celecoxib is predominantly metabolised by CYP2C9, caution is advised when treating patients known to be CYP2C9 poor metabolisers. Fluconazole inhibits CYP2C9 and increases celecoxib mean  $C_{max}$  by 60% and AUC by 130%. It is therefore recommended that celecoxib be used at half the normal doses in patients receiving fluconazole. Arising from the observed inter-ethnic differences in the pharmacokinetics of the drug, it is also recommended that in black patients, the lower dose (200 mg per day) should be used initially. The dose may, if needed, later be increased to 400 mg per day.

When additional data are or become available, a number of other sections of the prescribing information (e.g. special warnings and precautions for use, drug interactions, ADRs) may need to address the pharmacogenetic profile of potential patients. A recently approved drug that well illustrates this complexity of prescribing information is atomoxetine. This drug, approved by the US FDA in December 2002, is indicated for attention deficit hyperactivity disorder and is metabolised primarily through CYP2D6.

CYP2D6 polymorphism has not only the safety but also efficacy implications. PMs are at risk of a lack of efficacy when the therapeutic effect of a drug is mediated principally by its CYP2D6-generated metabolite. Examples here include codeine and encainide. In particular, PMs exhibit a relative loss of analgesic effects following administration of codeine or tramadol as well as a loss of antiarrhythmic effects following administration of encainide. The therapeutic effects of these drugs are mediated primarily by their metabolites, namely morphine, (+)-M1 metabolite of tramadol and O-desmethyl-encainide (ODE) respectively. In contrast, UMs are at risk from rapidly accumulating metabolites and of poor efficacy when the parent drug mediates the therapeutic effect, for example following administration of normal doses of nortriptyline or perhexiline.

Following results of the Cardiac Arrhythmias Suppression Trial (CAST), the indications for class I antiarrhythmic drugs have been severely restrict-

ed. It is interesting to speculate in retrospect on whether the increased risk of mortality associated with flecainide, encainide or moricizine in CAST may be explained by polymorphic metabolism of these drugs or by mutations of ion channels. Likewise, one may question the role of potassium channel mutations in the observed increase in mortality associated with d-sotalol in the Survival With Oral d-Sotalol (SWORD) study.

If drug response is shown to correlate with a particular SNP(s) or SNPs pattern (haplotype), prescribing information in the future may have to include information on not only in terms of drug metabolising enzymes or pharmacological targets but also in terms of SNP(s) or haplotypes.

### **3.3 Pharmacogenetics and drug withdrawals**

In some cases of serious toxicity, it may not be possible to manage the clinical risk even after careful labelling changes, and a decision has to be made on whether the drug can be allowed to remain on the market. Circumstances leading to the withdrawal of a drug from the market are complex but a conspiracy of genetic factors with other factors (probably the presence of co-morbidity or co-medications) is evident in many drug withdrawals or in termination of clinical development.

The withdrawals of perhexiline and phenformin in late 1980s are almost certainly related to genetically mediated toxicity. Both these drugs are metabolised almost exclusively by CYP2D6 and their clinical uses were associated with serious neuropathy and hepatotoxicity (perhexiline) or lactic acidosis (phenformin). Available evidence strongly incriminates CYP2D6 as a risk factor for both. A number of other older drugs have now been removed from the market. There is a body of evidence which, when viewed collectively, also supports the notion that genetic factors may have contributed substantially to their withdrawal from the market. These drugs include encainide (CYP2D6), terodiline and prenylamine (CYP2D6 and potassium channel mutations) and terfenadine, cisapride and levacetylmethadol (potassium channel mutations).

## **4. Regulatory framework**

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It is evident from the foregoing that it is vital to address the influence of pharmacogenetic factors at all stages from research & development (R&D) to post-marketing surveillance of the NCE. Through various guidance notes, regulatory authorities have long articulated their recommendations on the need to address genetic factors during drug develop-



ment. Not surprisingly, therefore, evaluation of influences of pharmacogenetic factors is also critical during regulatory evaluation and post-marketing clinical use of the drug. The development of an NCE may need to be terminated pre-approval, its labelling highly restricted during approval, or its clinical use suspended post-approval if variability from pharmacogenetics cannot be managed.

Although the requirements to address these genetic factors are stated by different regulatory bodies in different terms, the net effect of the requirements is that new knowledge concerning pharmacogenetic variations in drug response will lead to increased requirements for pharmacogenetic documentation. At present, a number of guidelines from the European Union's Committee for Proprietary Medicinal Products (CPMP), US Food and Drug Administration (FDA) and/or International Conference on Harmonisation (ICH) make direct or indirect references to the need for addressing genetic factors when developing new chemical entities. The guidelines from the CPMP and ICH are shown in Table 4.

**Table 4**  
**Pharmacogenetics and CPMP and ICH Guidelines**

<i>Genetic Factors in Pharmacokinetics</i>	
1.	Pharmacokinetic Studies in Man [36]
2.	Drug Interactions [37]
3.	ICH - Ethnic factors in the acceptability of foreign clinical data [38]
4.	Bioavailability and Bioequivalence [39]
5.	ICH - Dose-response information [40] “...metabolic polymorphism...”
<i>Genetic Factors in Pharmacodynamics</i>	
6.	ICH - Dose-response information [40] “variability in pharmacodynamic response...”

The CPMP guideline on “Pharmacokinetic Studies in Man” requires that metabolic studies should indicate whether the metabolism of a drug may be substantially modified in a case of genetic enzyme deficiency and whether, within the dose levels normally used, saturation of metabolism may occur, thereby resulting in non-linear kinetics.

The CPMP guideline on “Drug Interactions” emphasises that subjects participating in metabolic *in vivo* interaction studies should be appropriately

genotyped and/or phenotyped if any of the enzymes mediating the metabolism are polymorphically distributed in the population. In some cases, clinically relevant interactions may only occur in a subset of the total population, for instance, in a PM when an alternative route of metabolism is inhibited or in a heterozygous EM with compromised metabolic capacity.

In April 1997, the US FDA issued a guidance entitled “Drug Metabolism/Drug Interaction Studies in the Drug Development Process: Studies In Vitro” [41]. This states *“Identifying metabolic differences in patient groups based on genetic polymorphisms, or on other readily identifiable factors such as age, race, and gender, could help guide the design of dosimetry studies for such populations groups. This kind of information also will provide improved dosing recommendations in product labelling, facilitating the safe and effective use of a drug by allowing prescribers to anticipate necessary dose adjustments. Indeed, in some cases, understanding how to adjust dose to avoid toxicity may allow the marketing of a drug that would have an unacceptable level of toxicity were its toxicity unpredictable and unpreventable.”*

The Japanese Koseisho has also issued guidelines in 2001 that recommend genotyping in all drug development programmes for drugs that are metabolised by cytochrome P450s [42, 43].

The ICH guideline on ‘Dose-Response Information to Support Drug Registration’ recognises that the choice of a starting dose might also be affected by potential interindividual variability in pharmacodynamic response to a given blood concentration level, or by anticipated interindividual pharmacokinetic differences, such as could arise from metabolic polymorphisms or a high potential for pharmacokinetic drug-drug interactions.

It is also recognised by various regulatory guidelines that certain types of ADRs are due to unusual genetically determined pharmacokinetic variations and it is advised that every effort must be made to elucidate the pharmacokinetic mechanisms if there is any reason (e.g. from the knowledge of secondary pharmacology) to suspect that the ADR is caused by the altered pharmacokinetics of the drug.

One important question regarding the demography of a clinical trial population is the extent to which it represents the target population in terms of genetic, pharmacokinetic and pharmacodynamic variability.

Regulatory guidelines acknowledge the importance of inter-ethnic differences in pharmacokinetics and pharmacodynamics of drugs resulting from non-genetic extrinsic factors as well as from global heterogeneity in the frequency of variant alleles of drug metabolising enzymes or pharmacological targets. This global heterogeneity assumes considerable importance now that sponsors often conduct their studies in populations distant from the ultimate target populations. This global development reduces costs, expedites drug development and addresses the issues arising from global prescribing of drugs. The ICH guideline on “Ethnic Factors in the Acceptability of Foreign Clinical Data” recommends that a regulatory submission should include (1) adequate characterisation of pharmacokinetics, pharmacodynamics, dose-response, efficacy and safety in the population of one region and (2) characterisation of pharmacokinetics, pharmacodynamics and dose-response in the new region. The guideline recognises the role of genetic factors and the steepness of the dose-response curve in determining whether a drug is likely to show significant ethnic differences during its clinical use.

The CPMP guidance note on Investigation of Bioavailability and Bioequivalence also recommends that phenotyping and/or genotyping of subjects may be considered for safety or pharmacokinetic reasons.

The utilisation of genetic information in global development programmes, including bridging studies between populations, will be an area of increasing activity and regulatory interest.

## **5. Investigating pharmacogenetic influences during drug development**

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Although the emphasis of the following sections is exploration and characterisation of variability due to genetic factors and genetic influences on drug response, the role of non-genetic factors should not be overlooked during drug development.

### **5.1 Preclinical studies**

During the preclinical phase, a wealth of *in vitro* and *ex vivo* data are generated, which provide direct and indirect indications of possible pharmacogenetic implications for the compound under investigation. The recommendations from the US FDA and the CPMP regarding the design and use of *in vitro* studies for drug-drug interactions make explicit references to pharmacogenetic polymorphisms of drug metabolising enzymes.

With the aid of current *in vitro* approaches, it is possible to tentatively identify very early during the drug discovery and development process the main metabolites and enzymes catalysing the principal metabolic routes of practically any NCE.

*In vitro* studies provide a direct indication of the participation, or lack thereof, of polymorphic enzymes in the metabolism of an NCE (see table 5), although unqualified extrapolation to clinical setting should not be assumed.

Preclinical data using liver microsomes of course have their own limitations since it is now known that many drug metabolising enzymes are also expressed in other tissues such as the gut wall and these play a substantial role in drug elimination.

The “go/no-go” decision can then be made, based on both qualitative and quantitative information on the role of polymorphic enzymes in the *in vitro* study of an NCE. If it is decided to continue the development of the NCE, these *in vitro* metabolic data provide a rational basis for planning appropriate pharmacological (pharmacogenetic) and clinical studies in a genotyped panel of healthy volunteers and/or patients (for example, with respect to CYP2D6 or CYP2C19) to assess their *in vivo* significance on the kinetics and the dynamics of the compound under study. Observations on the influence of pharmacogenetic factors on the pharmacokinetics of a drug have in the past led to termination of development, restricted labelling or withdrawal of the drug from the market. For these early pharmacogenetic data to be of practical value in terms of labelling and clinical use, it is necessary to show their clinical relevance. Depending on their clinical significance, the labelling can be crafted in terms of indications, dosing regimen, contraindications and precautions or simply providing pharmacological information of interest.

Preclinical studies provide some of the earliest opportunities for investigating the potential of an NCE for drug interactions. For example, in an *in vitro* study of the metabolism of one NCE under development, it was demonstrated that the compound had a high affinity towards CYP2D6 and lesser affinity towards CYP2C19 and CYP3A4 in human liver incubations with CYP-specific probe substrates. On this basis, and correlating with *in vivo* concentrations, it was predicted that the compound might cause *in vivo* interaction with CYP2D6-metabolised drugs, whereas interactions with CYP2C19 or CYP3A4 were less probable. This indeed was later shown to be the case in formal *in vivo* studies. Further, it was demon-

**Table 5**  
***In vitro* approaches to study metabolism of drugs and new chemical entities for the prediction of participation of polymorphic drug metabolising enzymes**

<i>In vitro</i> system	Type of <i>in vitro</i> information on an NCE	Usefulness/Problems
Human liver microsomes	<ul style="list-style-type: none"> <li>* Metabolite pattern and routes</li> <li>* Individual enzyme assignment for each metabolic pathway by selective inhibitors or antibodies</li> <li>* Enzyme kinetics</li> <li>* Interaction studies</li> </ul>	<ul style="list-style-type: none"> <li>* Prediction of variability and interactions at an enzyme level</li> <li>* Prediction of role of polymorphisms</li> <li>* Only phase I and UGT enzymes present</li> </ul>
Human hepatocytes Human liver slices	<ul style="list-style-type: none"> <li>* Metabolite pattern and routes as a function of time</li> <li>* Concentration-dependence of metabolism (kinetics)</li> </ul>	<ul style="list-style-type: none"> <li>* Prediction of role of various pathways to kinetic behaviour, especially those catalysed by polymorphic enzymes</li> <li>* The whole liver enzyme complement expressed in living cells</li> </ul>
Recombinant human enzymes Other human organ <i>in vitro</i> systems	<ul style="list-style-type: none"> <li>* Metabolite pattern</li> <li>* Enzyme kinetics</li> <li>* Organ/tissue-specific metabolic and enzyme data</li> </ul>	<ul style="list-style-type: none"> <li>* Assignment of individual enzymes in the metabolism</li> <li>* Prediction of kinetic behaviour in patients with specific organ diseases</li> <li>* Prediction of metabolism in target organs</li> </ul>
Humanised transgenic animals (actually <i>in vivo</i> system)	<ul style="list-style-type: none"> <li>* Transgene-specific metabolism (and its consequences)</li> </ul>	<ul style="list-style-type: none"> <li>* If a transgene is polymorphic, prediction to what might happen in humans</li> <li>* A single enzyme in a whole-animal incubation matrix</li> </ul>
<i>In silico</i> modelling	<ul style="list-style-type: none"> <li>* Metabolite patterns</li> <li>* Enzymes participating</li> </ul>	<ul style="list-style-type: none"> <li>* Only as alerts for other studies</li> <li>* Quantitative data still largely not possible</li> </ul>
Animal hepatic <i>In vitro</i> systems	<ul style="list-style-type: none"> <li>* Metabolite patterns and activities and participating enzymes</li> </ul>	<ul style="list-style-type: none"> <li>* Comparisons between human and animal data (extrapolation problems).</li> </ul>

strated that the compound was principally metabolised by CYP3A4, with lesser contributions from CYP2C19 and CYP2C9. It was therefore predicted that the compound would show considerable interindividual variability and would be susceptible to CYP3A4 inducers and inhibitors. Indeed, these expectations were also confirmed clinically.

## 5.2 Clinical studies

In an attempt to explore the role of pharmacogenetics in determining drug response during drug development, genotyping of all subjects and patients participating in clinical trials is being increasingly considered. The obvious examples are drugs with a very narrow therapeutic index. At present, the development cost of an NCE is estimated to be US\$ 802 million. The additional cost of genotyping the entire population in a clinical trials programme would be only a very small fraction of the total cost. This is almost certainly a highly cost-effective investment in terms of the useful information relevant to safety and efficacy of the drug but there may be considerable ethical and practical obstacles.

One alternative strategy worth considering is pre-specified post-hoc genotyping (for relevant drug metabolising enzymes and pharmacological targets) and intensive pharmacologic investigations of individuals of specific regulatory interest. This strategy is illustrated in Figure 1. Arguably, as a proactive measure, the protocol of every clinical trial in man could include a section “Variability in drug pharmacokinetics and pharmacodynamics”.

### 5.2.1 Phase I

Early phase I clinical studies should aim at characterising the effect of genotype on the pharmacokinetics of the drug in healthy volunteers. The role of non-genetic factors such as the influence of co-morbidity (such as liver disease) and co-medications (inhibitors or inducers of drug metabolism) should also be explored and the variability from these non-genetic factors should be compared to that due to genetic factors. In order to characterise the true consequences of genetic variability in pharmacokinetics, it is important to investigate not only the interindividual but also the extent of intraindividual variability. This is best done by studies of replicate design in a panel of genotyped healthy volunteers.

Preclinical and *in vitro* studies should have identified the main drug metabolising enzymes and the potential pharmacological targets (responsible for therapeutic as well as toxic effects) of the parent drug and its main metabolites. If any of these are known to be polymorphic, subjects participating in at least one single dose and one multiple dose studies should be appropriately genotyped and the data analysed for association with any genetic influences in pharmacokinetics or pharmacodynamics. Similarly, subjects in drug interaction studies should be genotyped to ascertain the association of the presence or absence of an interaction with any particu-

lar genotype. Genetic influences can be modified or genetic effects reproduced by the presence of co-morbidity. For example, inhibition of a drug metabolising enzyme (e.g. CYP2D6 by fluoxetine) produces a poor metaboliser phenocopy despite an extensive metaboliser genotype.

Intensive pharmacology and pharmacogenetic studies are particularly valuable in those subjects who are pharmacokinetic or pharmacodynamic “outliers” in these phase I studies.

### 5.2.2 Phase II

Following the above phase I studies in healthy volunteers, it may become necessary to investigate the dose-response relationship in phase II studies in genetically defined subgroups of patients.

These studies should be large enough to include the whole range of variability in drug metabolising capacity. If there is any evidence from preclinical and *in vitro* studies of polymorphic pharmacological targets, consideration should be given to at least one concentration-controlled trial in order to address the issues of polymorphisms in pharmacological targets.

By prospective genotyping, phase II studies should aim at ensuring the inclusion of important phenotype/genotype subgroups so as to allow dosing recommendations appropriate to each genotype, rather than a standard dose schedule to suit all. Pharmacogenetic studies may be particularly valuable in those subjects who are “outliers” in these phase II studies – those who show an exaggerated or much attenuated response to a given dose.

The outcomes of phase I and II studies may influence the prospective design of and dose selection for the pivotal phase III studies.

### 5.2.3 Phase III

These studies are likely to provide the ultimate evidence on the role of pharmacogenetic factors in determining drug response. Patients with unexpected drug response (in terms of efficacy and safety outliers) should be genotyped appropriately for polymorphic drug metabolising enzymes and pharmacological targets. The responses of interest in this context are failure to achieve any therapeutic benefit or development of concentration-related or other serious ADRs. If an association of either response with a genotype is found, the subjects should be studied intensively for pharma-

colony of the drug in these patients. The increased size of the phase III studies will allow a more definitive understanding of the relationship between genotype and drug response to be established and the benefits of a diagnostic test to be evaluated. Phase III studies also provide further opportunities for investigating the role of non-genetic factors in drug response.

In some instances, however, data generated from phase II studies may suggest inclusion or exclusion of a given subpopulation, for example those with a specific genotype, from the subsequent development programme. However, this enrichment design studies have their own unique problems that must be addressed.

#### 5.2.4 Phase IV

Since not all ADRs are detected during the clinical development of a drug, it is vital that there is effective pharmacovigilance system in place throughout the post-marketing period of the drug. Although logistically complex, it may be valuable to collect blood and/or DNA samples from subjects displaying delayed or rare ADRs in phase IV to allow genotyping and to study any unusual features of the pharmacology of the drug in such individuals.

## **6. Genotyping versus phenotyping**

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Although the emphasis in pharmacogenetics is on genotyping of patients, phenotyping is a potentially valuable and at times more effective tool. Patients may be phenotyped for their drug metabolising capacity using appropriate substrate drugs as metabolic probes (e.g. dextromethorphan for CYP2D6). Classification of an individual as either an EM or a PM is based on estimation of drug in the serum at a predetermined time point or of the parent drug and its metabolite in urine sample collected over a defined period. The major advantages of genotyping are that it is unnecessary to have a validated assay for measuring the drug in question, no need to administer a probe drug and the lack of interference from interacting drugs that need not be discontinued. For example, in presence of a metabolic inhibitor of CYP2D6, genotyping a patient will correctly identify an EM whereas phenotyping may result in misclassification of an EM as a (phenocopy) PM. For most pharmacological targets, genotyping is at present the only available option to explore the role of genetic factors. Recently, an epinephrine challenge test has been described as a means of establishing an electrocardiographic diagnosis in silent LQT1 mutation carriers.



## **7. Maximising the application of pharmacogenetics**

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The value of applying pharmacogenetics in drug development and routine clinical practice is a complex issue.

The presence of a genetic polymorphism(s) in the path between the administration of a drug and response to the drug does not always adversely affect the risk/benefit ratio even in individuals with genetic mutations. These genetic traits may be of less significance for drugs with wide therapeutic index and/or for drugs with metabolites almost as active as the parent drug.

As for genetic influences on drug response, two models exist - high genetic/low environment versus low genetic/high environment. Genes may be categorised into those that have major, moderate and minor effects. References have already been made above to the confounders arising from drug interactions. Furthermore, application of pharmacogenetics will need to carefully consider the nature of toxicities or the consequences of failure of efficacy. This is in addition to the cost-effectiveness of pharmacogenetic testing. The likelihood of preventing a serious reaction makes pharmacogenetic testing an attractive tool provided the frequency of the variant allele has a critical mass frequency within a population.

Above all, one needs to consider how pharmacogenetics will be applied in routine clinical practice. Availability of reliable and rapid genotyping/phenotyping kits together with physician compliance with prescribing information may prove to be the major determinants of the benefits of pharmacogenetics.

## **8. Conclusions**

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It is evident that polymorphisms of drug metabolising enzymes have a profound influence on the pharmacokinetics of the drug of interest. Abnormal pharmacokinetics result in unintentional overdosing of those who cannot metabolise the drug. The converse is true with respect to exposure to metabolites that may be therapeutically active. Polymorphisms of pharmacological targets also result in abnormal or supersensitivity to the pharmacological effects from concentrations that are therapeutic concentrations in the majority of the population.

These polymorphisms may have consequences that adversely alter the risk/benefit ratio of the drug in some individuals, that is those with muta-

tions. It is therefore imperative that the possibility of genetic influences should be considered from the earliest stages of drug development.

If the possibility of a genetic influence arises, its qualitative and quantitative implications should then be explored and characterised at every stage of the drug development. This is especially relevant to phase II dose-finding studies and the selection of dose(s) for pivotal phase III studies.

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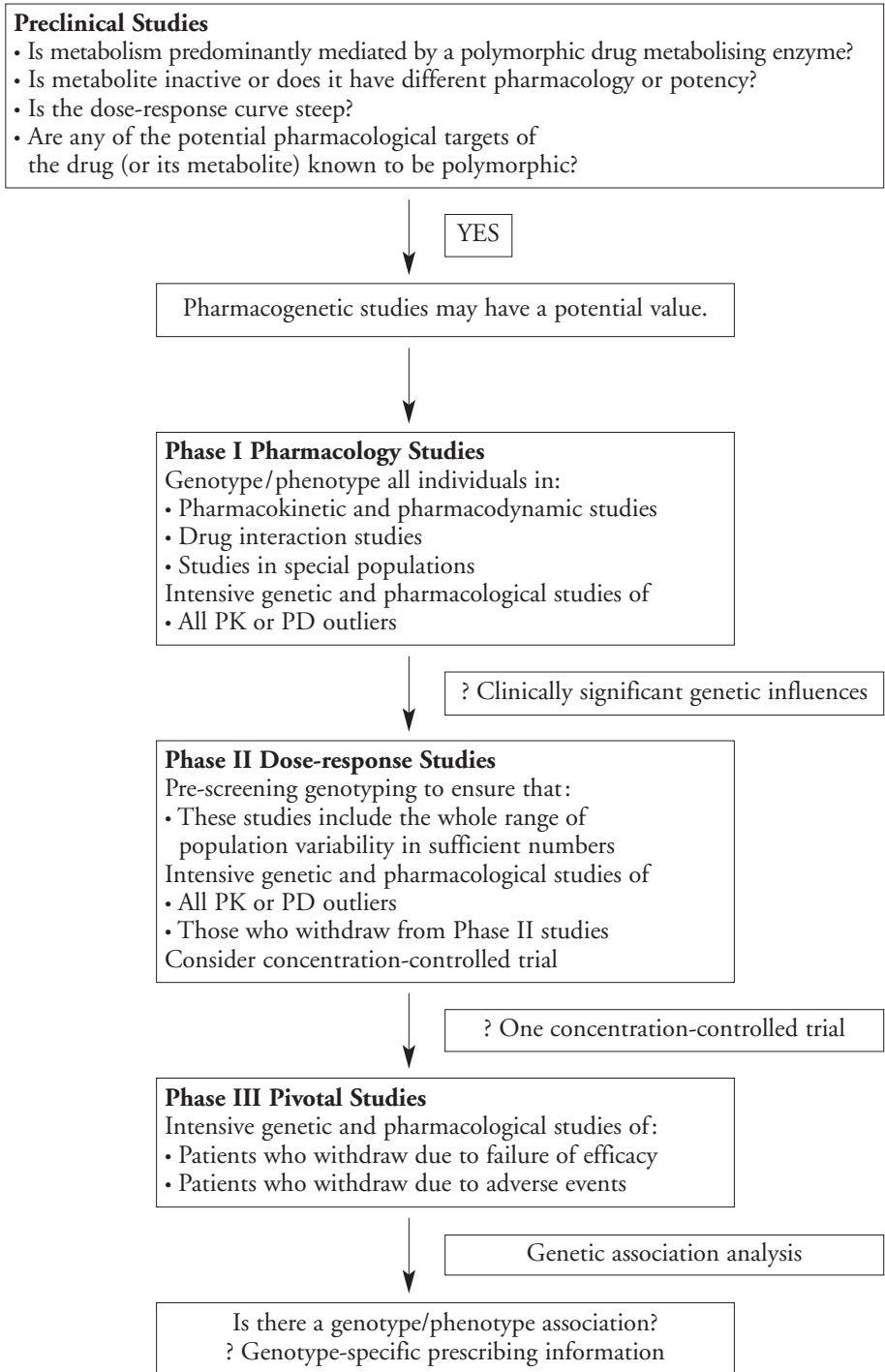
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**Figure 1**  
**Integrating pharmacogenetics in drug discovery and development**



## Chapter 5

# Impact of Pharmacogenetics on Drug Discovery and Development

### 1. Introduction

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In the last 30 years, the pharmaceutical industry has developed and marketed a large number of medicines that have improved the outcome of many diseases whilst generating significant returns on research and development (R&D) investment for pharmaceutical companies. Over the last 10 years, however, a number of key factors have emerged that impact on the delivery of new medicines to the patient such as:

1. Increase in development costs and time due to greater complexity of clinical development
2. Changing regulatory requirements
3. Increased risk of not getting medicines to market as attrition rates in development are increasing
4. Increased risk of medicines not remaining on the market as safety concerns have caused the withdrawal of a number of medicines in recent years
5. The need to model potential impact on clinical, societal and economic aspects of the treatment to the satisfaction of healthcare providers

The progress and the refinement of research tools, combined with the ever increasing societal demand for safer and more effective medicines, continue to fuel the high cost of development of each new medicine.

Consequently the return-on-investment per drug is decreasing, and perhaps more importantly, the flow of new medicines to patients has gradually diminished. Thus pharmaceutical companies need to use all available tools in order to overcome this situation, with pharmacogenetics currently offering a significant potential. Although still at a basic and experimental stage, pharmacogenetic data are already being submitted to regulatory authorities. A recent CMR survey [1] reported nine companies having experience of submitting applications to the authorities that included pharmacogenetic and pharmacogenomic data, with pharmacogenetic data being included in 4 investigational new drug (IND) applications, 4 clinical trial (CT) applications and 1 new drug application (NDA).

In this chapter, we focus on the contribution of genetic variations to understanding variability in drug response. It is recognised that some of

these opportunities and issues are also applicable to other genomic technologies (e.g. gene or protein expression patterns) but will not be specifically covered in this chapter.

The chapter will identify the key development drivers and hurdles relevant to the implementation of pharmacogenetics in drug development programmes, examining the potential role pharmacogenetics may play in the drug development process. The assumption is that pharmacogenetics will improve patient's treatment by allowing prediction of efficacy and/or safety of some medicines, providing additional claims information and improved prescribing rationale. The discussion will be restricted to considering the impact of pharmacogenetics on clinical drug development (phase I to phase IV), looking at possible requirements for additional and complex development steps that pharmacogenetics may entail, particularly in the short-term, as the technology develops.

Each phase of clinical development will be considered in terms of the potential impact of pharmacogenetics on time, risks and overall pipeline costs. Where possible, analysis will be carried out using benchmark data for a new candidate medicine. More technical aspects of the application of pharmacogenetics in drug development are discussed in Chapter 4 on "Exploring Pharmacogenetics in Drug Discovery and Development".

## **2. Summary of the current R&D process**

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For each new drug that is developed, pharmaceutical companies have typically spent an average of \$800 million (i.e. R&D spend divided by number of new medicines) and taken about 15 years from discovery in the laboratory to the marketplace. Of this cost, a significant fraction – estimated as approximately 70% – can be attributed to failures along the way – this is a stark statistic of the effect of attrition on utilisation of R&D resources [2].

Over the last few decades, it has become progressively more expensive to develop a new chemical entity (NCE) with the cost of developing an average NCE having increased from \$138 million in the 1970's through \$318 million in the 1980's to \$802 million in the late 1990's. This rise is evident even when adjusted for inflation, in part due to increased attrition, and in part due to the requirements for larger and, more complex and multiple clinical programmes [3]. As pharmacogenetics is expected to substantially influence the economics of clinical development, we will focus the discussion particularly on this aspect of R&D. It should also be recognised

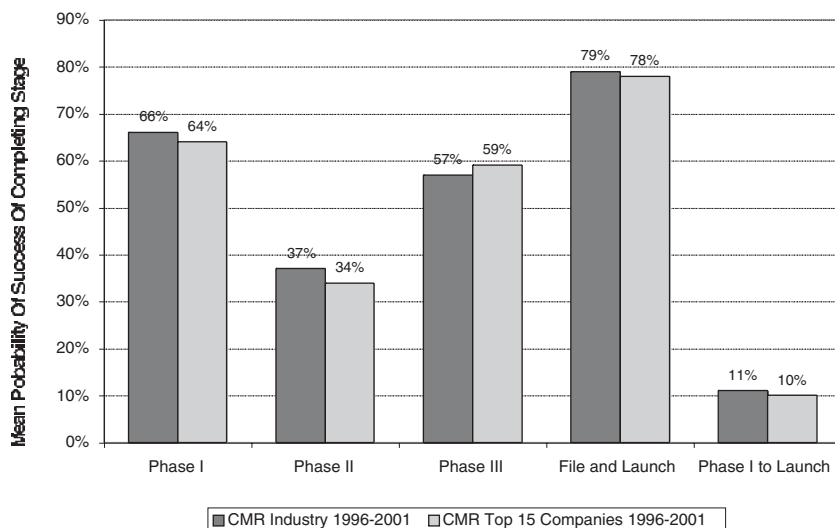


that the absolute cost and timing of each development phase will vary depending on the type of product, the disease/therapeutic area/or whether the candidate medicine is a new entity or an approved medicine being developed for a new indication. Therefore, this chapter will concentrate on development costs associated with a new candidate medicine using benchmark data that take into account the costs of the clinical process.

There are various estimates in the literature of the absolute costs of bringing a particular medicine to the market (i.e. the total costs of all the activities on a given candidate medicine), ranging from \$250 million to \$600 million. Within these figures, the average R&D costs per sector can be broken down into target identification (\$165 million), target validation (\$205 million), candidate selection (\$40 million), lead optimisation (\$120 million), preclinical (\$90 million) and clinical (\$260 million) [4]. These costs are based on all drugs reaching that phase and so include failures. As there are fewer compounds in phase III than in the earlier phases, the contribution of phase III costs to an individual programme is seen to be much higher.

Compounds are lost from drug development at every stage, with less than 10% of compounds entering clinical studies successfully achieving registration and launch. The reasons for attrition can be many and

**Figure 1**  
**CMR data based on cohort approach looking at the fate of NCEs entering phase 1996-1998, with progression decision made by 2001 [6]**



different in nature and pharmacogenetics cannot be expected to address all areas; but with 10% of drugs failing due to adverse drug reactions (ADRs) in humans, 30% failing due to lack of efficacy and 39% failing due to unfavourable pharmacokinetic and metabolic properties, pharmacogenetics has the potential to influence a significant number [5]. Benchmark data (Figure 1) suggests that project failure is highest in phase II of clinical development with a probability of success (PoS) of approximately 35%, but is also significant in phase III with PoS of about 60%. When one bears in mind the significant cost of the average phase II and phase III development programmes, \$40 million and \$160 million respectively, the importance of reducing late stage attrition in order to increase the success of developing new medicine becomes clear.

### **3. Impact of pharmacogenetics on clinical development**

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Pharmacogenetics seeks to associate genetic variations with differences in response to medicines and the knowledge gained by studying the genetics of pharmacological response can be used to help understand the basis for efficacy and/or safety issues and ultimately to improve the therapeutic outcome for patients [7]. Pharmacogenetics can therefore provide scientific insights into variable response that are difficult – if not impossible – to obtain from the more traditional approaches.

For pharmacogenetics to have a defined application in drug development and a clinical value in prescribing, a marker (or combination of markers) must be found that can predict a difference in response, so that the overall improvement in the benefit/risk ratio of the medicine in a given indication is robust enough to guide the prescribing decision. The criteria for what determines a ‘robust’ pharmacogenetic marker will depend on the particular therapeutic area and the disease being treated.

Pharmacogenetics is a tool that provides additional information to guide the drug development process, which may provide insights into response related to efficacy and safety, and can be applied in a number of ways to:

- Identify appropriate patient groups
- Stratify patients in clinical studies
- Guide prescribing in clinical practice (which may involve the use of a pharmacogenetic test)
- Provide a feedback into research to identify unmet need (non-responder group)

- Facilitate R&D decision making by supporting more informed discussions
- Guide decision making for compounds that do not meet benefit/risk product profile in a traditionally defined broad ('all comers') population, resulting in focused development in a defined subgroup.

There is a lot of excitement about pharmacogenetics, and the technology has enormous potential to transform both clinical development and the utilisation of medicines. However, it has to be acknowledged that pharmacogenetics is still a fledgling science, and while the expectations are high, the number of real examples – especially the ones that have influenced clinical practice or development decisions – are few and far between. While the extensive literature on cytochrome P450s has established a clear role for pharmacogenetics in understanding pharmacokinetic variability, it remains to be seen how valuable pharmacogenetics will be in providing insights into more complex phenotypes of efficacy and adverse events. The preliminary data are very encouraging. For example, the strong association of SNPs with adverse events to both abacavir [8] and tranilast [9] suggests that genetic variation can be a strong predictor of such phenotypes. However, more examples will be needed to establish that pharmacogenetic analysis is a cost-effective addition to the more established and traditional clinical development pathways.

Thus, the application of pharmacogenetics must be clearly validated within clinical trials in terms of clinical validity, and its relevance demonstrated to the regulators in order to guide labelling. In the final analysis, the utility of pharmacogenetics with respect to the treatment strategies and clinical outcomes will ultimately be confirmed when the drug is on the market and being prescribed.

#### **4. Pharmacogenetics and clinical development process**

For pharmacogenetics to influence the development and/or prescription of new medicines, it must be embedded into appropriate phases of clinical development. This does not mean that all drugs will be launched with a pharmacogenetic component – or indeed supported by pharmacogenetic data – but it does mean that, where needed, genetic markers of response (efficacy and/or safety) can be identified and validated, ready for use if required.

In order for pharmacogenetics to fulfil the current expectations of enhanced product delivery by providing better product claims, reducing the cost of development and allowing medicines to reach the market

place more rapidly, the traditional development paradigm will need to be challenged. Considerations around powering, population definition and study duration should be considered. As there are a large number of possible variations in the ways by which pharmacogenetics can be applied to the clinical development process, it is difficult to make broad generalisations about the cost, benefit and impact. This is especially true for the later phases of development, where the application of pharmacogenetics will depend, for example, on exploratory data generated earlier in development.

#### 4.1 Phase I

The overall aims of phase I studies are to establish basic pharmacokinetic parameters (usually in normal volunteers) and to exclude safety concerns that would preclude further development of the compound. It is unusual to obtain information on efficacy in phase I studies (although some surrogate pharmacodynamic information may be generated).

Compounds entering this phase of development have a 65% PoS and are therefore likely to complete this phase unless major issues are identified. The duration of this phase is typically 14 months and costs about \$60 million depending on the type of drug, its mechanism of action and the therapeutic area.

Although phase I studies are small and tend to be conducted in human volunteers, the inclusion of pharmacogenetics analysis may be used to:

- explore the basis of unexpected variability in pharmacokinetics
- confirm that the drug acts as anticipated on the relevant target
- confirm the expected elimination (metabolic and/or renal excretory) pathways predicted from *in vitro* studies and their potential consequences
- provide information on safety issues associated with known genetic variants

The main contribution of pharmacogenetics to phase I studies is likely to be insights into pharmacokinetics (or dynamics where appropriate) that allow development decisions to be made with greater confidence. For example, is variable pharmacokinetics due to poor absorption (in which case a new formulation may be needed) or to variable metabolism? In these situations, the properties of a compound are outlined and a decision can be made on the possibility or otherwise of developing the compound without investing time and resource on new formulations.

The inclusion of pharmacogenetics in phase I studies is unlikely to result in a significant change to the timing or cost of the development programme, at least in the short-term. If it becomes necessary to generate extensive pharmacogenetic data as part of the phase I programme, this may cause a delay in proceeding to phase II. However, such extensive genotyping would only result from the identification of a significant issue with the compound, which would of course delay the programme in any event.

## 4.2 Phase II

The major objective of phase II development is to generate exploratory data on safe and effective doses. On the basis of the data obtained, a decision can be made to proceed to phase III. Compounds entering this phase of development have a 35% PoS, and so this is the phase of development with the highest risk of attrition. The duration of this phase is typically 20 months and costs about \$40 million depending on the type of drug, its mechanism of action and the therapeutic area.

The pharmacogenetic objectives of this phase are to generate data on which the choice of dose and optimal enrolment criteria for additional (confirmatory) studies can be made. Phase II studies are larger (100-500 subjects), and are thus capable of generating pharmacogenetic hypotheses for both efficacy and any adverse events. If serious adverse events are sufficiently common during phase II studies to make pharmacogenetic studies feasible, it is highly unlikely that the compound will have an acceptable benefit/risk profile. Thus it is during this phase that pharmacogenetics can potentially play a significant role in understanding attrition, particularly for compounds with variable efficacy.

Like traditional studies, phase II pharmacogenetic studies must be designed to produce enough safety and efficacy data to select the correct dose, but they may also have to be designed to select different doses for different populations/genotypes. Independent of the desired outcome, phase II studies incorporating pharmacogenetics may have to be powered to

1. produce enough safety and efficacy data to fulfil traditional requirements and
2. produce enough data to also support development in pharmacogenetically defined subpopulations or
3. produce enough data to consider developing in one particular pharmacogenetically defined subpopulation only.

Once a genetic marker (or a set of markers) associated with a particular response is identified, different design options can then be considered ranging from additional phase II trials, amendments to ongoing programmes and/or amendment to the planned phase III programme. These design considerations need to take into account whether the development plan will continue along a traditional route (i.e. not using pharmacogenetic data to alter the development programme), an enrichment route (using pharmacogenetic data with possible pre-randomisation genotyping to increase the number of appropriately responding patients in the programme) or a focused route (excluding certain patients likely to show unfavourable response due to either poor efficacy or safety concerns). The final decision will depend on many factors including cost and influence on label claims.

If additional larger clinical phase II trials are required to collate sufficient information on a genetic marker in order to substantiate its relevance for inclusion in phase III trials, this will increase the cost (and possibly the time) of phase II studies. However, this increase may be offset by an increase in PoS in phase III, and in some cases a smaller phase III programme.

At the conclusion of phase II, genetic markers of response (efficacy and/or safety) may not have been identified. In this case, unless there is other supporting information, the clinical development project is more likely to follow the traditional development route, with minimal change in traditional costs or timing.

### **4.3 Phase III**

The primary purpose of phase III studies is to provide the pivotal evidence of efficacy and safety for the purpose of drug registration and to establish efficacy and safety parameters in additional populations/drug regimen conditions. Compounds entering this phase of development have a 60% PoS. The duration of this phase is typically 28 months and costs about \$160 million depending on the type of drug, its mechanism of action and the therapeutic area.

The outcomes of including pharmacogenetics into phase III development may range from:

- Confirming the validity and clinical relevance of the genetic marker and focusing development only in a pharmacogenetically defined population (may be most relevant for pharmacogenetic safety markers).

- Confirming the validity and clinical relevance of a genetic marker set whilst still demonstrating utility in a wider population. This would result in a traditional registration package supplemented with additional prescribing information on the role of pharmacogenetics in different subpopulations and potential use of the pharmacogenetic test if available/applicable.
- Showing no differential response (efficacy or safety) and following a traditional development route, resulting in a traditional label. Much has been written about the potential savings the inclusion of pharmacogenetics in phase III may bring. However, in the short-term at least, the incorporation of pharmacogenetics into phase III development may not always fulfil the promise of reduction in sample size and increased speed to market.
- For development programmes using pharmacogenetics for efficacy, a reduction in sample size required will occur when the genetic markers are used to predict efficacy and to select patients recruited into this phase. The magnitude of reduction will be related to the anticipated difference in efficacy between the selected and non-selected groups. This means the larger the efficacy difference between the two groups, the lower the number of subjects required. However, the expected savings in time may be restricted by the 'traditional' study design duration, whilst the cost savings associated with smaller pharmacogenetic trials may be eroded by the need to screen large number of subjects prior to entry, the latter depending on the frequency of the identified pharmacogenetic trait(s) in the general population.
- Another issue relates to the nature of the safety database required: in many phase III programmes, the size of the safety database required will define the scale of the phase III programme, so increased power from an efficacy enriched population cannot be translated into smaller studies. In fact, there is some debate as to whether an adequate safety database may also be required in the patient population not selected, so that an adequate risk/benefit assessment can be made in the non-indicated (or contra-indicated) patient group to safeguard against off-label use that has been predicted to occur with pharmacogenetically supported medicines. This is a critical issue for development of pharmacogenetics and needs to be debated fully [10]. Concerns regarding prescribing of medicines to a 'non-labelled' population should be discussed against the general background of 'off label use' since this is a general issue applicable to most medicines, and not one uniquely related to pharmacogenetics.
- For development programmes using pharmacogenetics with pharmacogenetic markers of efficacy, phase III studies are generally powered to

demonstrate efficacy but they will be required to address safety concerns. If the pharmacogenetic markers are also used to identify subjects at increased risk of a treatment-limiting ADR, then there may be only an insignificant reduction in the number of subjects required, and costs and time may be increased due to the need to screen greater number of subjects than generally warranted in a traditional development.

- For traditional development with a pharmacogenetic subset, response rates in different populations may be seen but may not be large enough, either to be clinically relevant or to warrant different dosing regimens. In such cases, development time may remain the same, but additional patient numbers and costs for genotyping will be incurred when compared to traditional programmes.

At the end of phase III, pharmacogenetic markers of response (safety and/or efficacy) may not have been fully validated. At this point, project leaders will have to decide whether there is enough information for a traditional development package or whether additional work is needed, depending on the rationale chosen when entering phase III.

#### **4.4 Market launch**

If pharmacogenetic studies during clinical development have established markers associated with efficacy and/or safety that are included in the label at launch, then the usual activities associated with the launch of a new medicine will also have to include additional information on the pharmacogenetic data and their use. While these further development activities – and their associated costs – are not always defined as R&D costs, they will undoubtedly necessitate additional expenditure. This will be particularly true in the short-term, when practising physicians, healthcare providers and patients will be unfamiliar with pharmacogenetically based prescribing. The potential to utilise these new technologies to support labelling claims may result in a significant competitive and financial advantage, although this will have to be considered on a case-by-case basis taking into account also the clinical benefits from a public health perspective.

One could argue that the long-term success/utility of pharmacogenetically based development/prescribing will be dependent on how these innovative products are marketed and supported. Unless physicians, healthcare providers and patients know how to use these new medicines, and perhaps as importantly, know what to expect if these medicines are used correctly, the promise that pharmacogenetics offers may not be fulfilled.



For these early pharmacogenetically based medicines, additional expenditure in education and product support is inevitable.

#### **4.5 Phase 4**

In view of the education and product support needs, phase IV studies may be one of the keys to successful pharmacogenetically based drug development. Traditionally phase IV or post-marketing studies are designed to better understand the utility of a new medicine in a broader population and under real conditions of clinical practice than is possible to study during the normal clinical development. Phase IV studies are much more variable than the pre-registration studies, both in size and complexity (and hence in cost and duration).

The impact of pharmacogenetics on phase IV (in terms of cost, time and risk) will be very dependent upon how pharmacogenetics has been incorporated during development and its contribution to the final label. If a new medicine is launched with pharmacogenetic markers associated with efficacy, phase IV studies will hopefully confirm the applicability of these markers in wider populations, with pharmaco-economic studies being designed and conducted to substantiate public health benefit on large numbers and longer follow-up.

Like traditional development programmes at the phase IV juncture, a pharmacogenetically enhanced medicinal product could follow any number of different opportunities from continued validation of previously identified pharmacogenetic marker sets through to identification of different genetic subpopulations not indicated in the label. During phase IV, although the refinement and further development of a product's characteristics using pharmacogenetics is a possibility, a more beneficial application of pharmacogenetics may be to enhance post-marketing surveillance, providing insights into the rare adverse events that can only appear in the post-marketing arena and which currently cause medicines to be withdrawn from the market [10, 11]. While this is not strictly part of clinical development, using pharmacogenetics to provide scientific insights into these adverse events could have a significant impact on overall R&D productivity (and hence cost-efficiency), as well as enhancing any risk management plan.

#### **4.6 Phase IV post-marketing surveillance systems**

Five hundred and forty eight NCEs were approved from 1975 to 1999. Of these, 56 (10.2%) drugs were labelled with a new black box warning

or were withdrawn from the market. Analysis suggests that the estimated probability of a drug being withdrawn from the market over a 25-year period was 20%. More significantly perhaps, forty-five drugs (8.2%) were marked with one or more black box warnings that were not present when the drug was approved. Sixteen drugs (2.9%) approved between 1975 and 2000 were withdrawn from the market during that period: five had a black box warning prior to approval.

It is estimated that over half of drug withdrawals occur within five years of the product launch [12]. In addition there were 81 labelling changes in the *Physicians Desk Reference* for launched products during 1998-2000. Analysis suggests that over 50% of these changes occurred within seven years following product launch [13].

#### **4.7 Identifying drug-related ADRs in the market place**

Usually, only ADRs that occur with a frequency of 0.1-1% or greater will be detected during clinical trials. Since the average cohort at the time of licensing is between 3,000 and 5,000 patients, this will provide little or no data on rare events. One suggestion could be to increase the size of the registration package. However, this will only prolong the development time and cost equation whilst more importantly delaying access for patients to new medicines, since study sizes would need to increase significantly if rare events are to be detected. For example for an event with a frequency of 1 in 10,000, one would need to expose up to 65,000 subjects to the drug before 3 cases with that ADR are observed during the clinical trial [14].

Therefore one needs to consider risk management programmes that can handle these rare events once the drug is in the market. Pharmacogenetics could be used as part of a risk management tool and has the potential to help investigate rare ADRs and if appropriate, allow continued access to the majority of patients who will gain benefit. Pharmacogenetically based surveillance programme could supplement existing post-marketing surveillance and risk management programmes. The ability to associate a particular serious ADR with a pharmacogenetic profile may take a substantial period of time if the event rate is low. This, coupled with the logistics of collecting cases (and controls), will require dialogue between the pharmaceutical companies and the regulators.

## **5. Development of a pharmacogenetic test**

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For pharmacogenetics to deliver its promise in the clinic, it is important that testing tools, where they are necessary, are readily available to the physician when he/she considers prescribing the medicine concerned. This paradigm requires that development of the pharmacogenetic assay/test must proceed alongside the pharmaceutical agent. If a test is needed to accompany a drug registration package, then there will be an increased development cost and possible delay to market. The cost and the time delay will be dependent upon such factors as when the pharmacogenetic markers are identified, and whether the test is already available or has to be developed.

Many companies involved in pharmaceutical R&D are not manufacturers of diagnostic agents. Hence the development of the test may have to be contracted out or conducted in partnership (see Chapter 12 on “Unresolved Issues and Barriers to Progress”). One option is outsourcing the development of the analytical tools and hence co-sponsor its clinical validation. Another route is to co-develop the test in-house. The additional financial burden of co-developing a commercially viable pharmacogenetic test “kit” has to be considered alongside the opportunities offered by this approach to enhance the business return of the company by establishing a department specializing in test kits.

However in general, the cost of developing a test, without specific clinical claims attached to it, is small compared to the overall cost of developing a medicine, provided that the development of the test can be accomplished within the same timeframe as the medicine without delaying the launch of the medicine.

## **6. Investments and distribution of resources and risks in R&D when introducing pharmacogenetics**

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In order to keep a viable pipeline, the pharmaceutical industry has not only to successfully screen/develop new candidates that might compensate for the attrition rate but also to optimise the investments in clinical development. Pharmacogenetics offers new tools, which are predicted to result in benefits not only from a public health perspective (targeted therapy with optimal efficacy response and reduced ADRs) but also from the financial point of view, providing for the analysis of target variance, a reduction in product attrition during development and a potentially streamlined clinical development.

However, while the above becomes a reality, there are a number of legal, regulatory, societal and technical factors that need to be managed carefully within an appropriate policy framework in order to facilitate a smooth transition towards the full deployment of pharmacogenetics in the development of medicines and medical care. This transition has to be managed at all levels, with a system that is flexible, so that the science of pharmacogenetics develops into a public health and prescribing tool, and is not constrained by inappropriate hurdles.

To integrate pharmacogenetics into drug development, specific investments and choices are necessary at various levels in order to adapt the R&D technology and science framework within a company. For example:

- Delivery of high-throughput, accurate and affordable platforms and genotyping assays
- Computational capability such as bioinformatics, statistical modelling and analysis
- Database construction including tracking systems for maintenance of multiple coding regimens.
- Construction of genetic marker/allelic frequency databases to reference pharmacogenetic variability to support global drug development
- Development of expertise – Pharmacogenetic specialists across R&D

Pharmacogenetic approaches currently employed focus predominantly on candidate genes; that is, genes where an *a priori* hypothesis implies a pharmacogenetics role – for example genes involved in drug metabolism or the pharmacological target. Genome-wide scans are however now being explored. At this time, the utility of this technology has yet to be fully clarified. It is, however, expected to increase significantly the ability to identify clinically relevant pharmacogenetic markers related to variable drug responses, although (currently) at significantly greater cost during development.

There is currently a shortage of real life examples demonstrating the overall effect of pharmacogenetics on drug development costs and PoS. Discussion is reliant on models based on incomplete data. Confirmation of such figures will have to await real examples, and even these may not produce the answers initially, since the first pharmacogenetically based drug development programmes may not have been undertaken in the optimal manner (because this has yet to be determined).

## 7. Conclusions and recommendations

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The need for cost – effectiveness in both R&D expenditure and health-care budgets, as well as the increased pressures to improve R&D from within the pharmaceutical industry and from the market, are likely to be a powerful driving force behind the application, and validation, of any new technology, including pharmacogenetics.

Pharmacogenetics is a technology that is available now and has multiple potential applications in R&D to help alleviate some of these pressures. In order to fully exploit the potential advantages of pharmacogenetics, it should be appropriately applied over the continuum from early clinical development through to the marketing phase. Although the science of pharmacogenetics has yet to fully deliver its promise, it is still anticipated that with the appropriate application, pharmacogenetics can help reduce the risk of late stage failure and thus mitigate the overall financial burden to the company and promote the availability of safer and effective medicines for patients' treatment. In fact it should be considered that each medicine that failed in development, or shortly after launch, is potentially a missed opportunity either for treatment or for better treatment.

It appears however that at present, the changes in development strategy required to include pharmacogenetic approaches may, in fact, not reduce at all the financial investment required in the short-term for an individual compound. The application of pharmacogenetics to select patients for clinical trials and the impact on trial design parameters – e.g. sample size, time to recruitment of patients needed to demonstrate the required risk/benefit ratio – will inevitably vary according to the molecule, target, pathway, specificity and the unmet medical needs/disease in question. It seems, however, that optimisation of phase II clinical trials might reduce the overall duration or size of some of the late pre-approval clinical studies.

There are good reasons to anticipate that integration of pharmacogenetics into the R&D process may provide in the medium term global financial benefit in view of

- Focused and complementary pipelines
- Overall reduction in the attrition rate, particularly during an advanced stage of clinical development
- Pharmacogenetics may lead to (relatively) minimal increases in the cost of developing a medicine. These increased costs should ultimately be offset by the potential additional value of the medicine; that is, spend-

ing more money for each compound but for a shorter time and with less risks of failure during development and after launch.

- If managed correctly and planned for, pharmacogenetics should not significantly increase the time to market for medicine.

In the current transitional phase, the focus should not simply be on the cost savings during development of an individual medicine developed in this way but also on the overall additional value and utility such a medicine might bring. In addition, the value of knowledge gained during a pharmacogenetically based development programme should not be overlooked. R&D budget might have to account for significant and time-sustained investment, especially when considering concomitant development and validation of a pharmacogenetic test.

Few would disagree that pharmacogenetics has the potential to be a useful tool for providing access to additional development and commercialisation strategies. In order for the potential to be fulfilled, it is recommended that

- Exploration and validation of pharmacogenetic markers be increasingly included as part of the R&D strategy with the aim of reducing the attrition rate both during development and after launch. This will also allow appropriate expertise to be developed.
- Generation and discussion of data between pharmaceutical industry and regulators should continue, with the *Voluntary Genomic Data Submission* (VGDS) to the FDA and *Briefing Sessions* with the EMEA as the recognised routes (see Chapter 7 on “Regulatory Perspectives in Pharmacogenetics”)

These recommendations, if implemented, will facilitate the development of the technology in an appropriate and cost-effective manner to maximise the opportunity for pharmacogenetics to deliver healthcare benefit, and also ensure more realistic expectations from the application of pharmacogenetics.

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## Chapter 6

# Improvements in Existing Therapies

### 1. Introduction

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Despite the spectacular successes achieved in drug therapy during the last century (especially the last five decades), none of the existing therapies is either 100% effective or 100% safe. In fact, it may be that a significant proportion of the patients treated with existing therapies obtain only minimal benefit from them, if any at all. Depending on the therapy and the endpoint used to judge response rate, efficacy can range from 25% to more than 90%. The latter is probably a rare scenario in contrast to the prevailing common perception that drugs are beneficial to everyone who takes them.

Historically, drugs have been developed using a “one-size-fits-all” model, assuming that all adults are the same. In the 1950s, it was observed for the first time that heritable deficiencies in enzymes could result in unexpected and even harmful effects. The research performed during the Korean War demonstrated that 10% of black servicemen became anaemic after a particular antimalarial drug. This effect was very rare among white servicemen. The cause was found to be a variation in the gene expressing the enzyme, glucose-6-phosphate dehydrogenase (G6PD). This variation is common among people of African descent. In the US, it is therefore a practice to test for G6PD deficiency in African Americans before treatment with antimalarials that are known to induce haemolysis. Since then, this type of knowledge has resulted only in either limited clinical application or practical outcomes. However, the wordings of many indications approved by regulatory authorities show that regulators are focused in their intent to ensure a better understanding of the drug exposure-response relationship in order that the dosing recommendations are appropriately defined, with the ultimate goal of maximising the risk/benefit ratio. A result of this is a clear trend for drug labels to specify those subgroups of patients likely to respond positively, or negatively, to a particular drug treatment.

The term ‘*existing therapies*’ is used in this chapter to mean all medicines, whether under patent or not, that have already been approved by competent authorities (drug regulatory authorities) for the prevention or treatment of a defined disease/indication in humans. This means that it covers both multi-source pharmaceutical products (‘generics’) and products

manufactured by originators which may or may not be covered by patent protection ('innovators'). In certain cases it is also extended to the products that have been withdrawn after approval from one or all markets, or to the products for which the originator has applied for, but not yet received, a marketing authorization.

Medicines are approved for marketing based on the analysis of safety and efficacy data obtained during their development in a defined population, along with a comparison against existing therapies as well as against placebo when appropriate. The justification for continued use of existing therapies is, in many cases, the lack of more effective and safer alternatives. This has led to the acknowledgement that in general, the net outcome of existing therapies in certain populations is positive. However, this does not mean that all individuals treated benefit from the treatment and/or none suffers from adverse drug reactions, some of which may be potentially fatal. Moreover, certain patients may not benefit at all from an existing therapy but may nevertheless suffer serious adverse effects. For example:

1. Depending on the ability to acetylate isoniazid, a population can be divided into two phenotypes – slow and rapid acetylators. Rapid acetylators are at risk of potential failure of efficacy against tuberculosis while slow acetylators are at risk of neuropathy. Recognition about the mechanism of isoniazid-induced neuropathy has resulted in vitamin B6 supplementation in slow acetylators. By doing so, this neuropathy is now virtually eliminated. Moreover, failure of treatment is only seen in rapid acetylators if the drug is given on a twice-weekly basis.
2. The efficacy of low dose acetylsalicylic acid (ASA) (75-325 mg) in secondary prevention of thrombotic cardiovascular or cerebrovascular disease is well known. In many countries, it is also approved for primary prevention of vascular events of coronary heart disease. Today, it is possibly premature to suggest that all patients with the appropriate indications will benefit equally from the use of low dose ASA as the risk of low dose ASA itself may lead to increased risk of potentially fatal gastro-intestinal haemorrhage or haemorrhagic stroke. The possibility remains that ASA is prescribed today to many patients who may not benefit from its use but may well be at risk of serious side effects. It remains to be elucidated if pharmacogenetics can offer feasible solutions for better targeting of patients with this extremely cost-effective treatment.
3. Pharmacogenetics may help to reduce the risks associated with the use of angiotensin converting enzyme (ACE) inhibitors, a class of drugs that are now used increasingly and widely for a variety of indications.

It is estimated that currently 35-40 million people are treated worldwide [1]. These agents have been shown to be highly efficacious in the treatment of a variety of life-threatening diseases including congestive heart failure (CHF) and myocardial infarction. There is no doubt that this group of drugs can potentially save millions of lives worldwide if there was access to them. Some ACE inhibitors are already out of patent in a number of countries; others are following. However, even in developed countries, only 21-36% of the patients with CHF are treated with ACE inhibitors [2-4] and over 40% of them discontinue the drug within 6 months of starting therapy [2]. There is a clear need to identify in advance which individuals can benefit from ACE inhibitors with minimal risk of serious side effects. Angio-oedema is a well-known side effect of ACE inhibitors, with the reported incidence of 0.1-0.2% that is probably an underestimate [5]. Black people using ACE inhibitors are at a 3-fold higher risk of side effects and experience higher rates of fatal events [6, 7]. However, determining the true incidence of angio-oedema may require monitoring all patients, not just those already identified as being at increased risk, for this potentially serious side effect. If pharmacogenetics can offer tests with high predictability, patients at increased risk for angio-oedema could be switched to the alternative class of medicines instead; thus avoiding extra costs arising from monitoring of patients and from the resulting morbidity and mortality. The benefits may well outweigh the costs of predictive tests.

## **2. What can pharmacogenetics offer for existing therapies?**

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Interindividual variation in response to drugs is a substantial clinical problem. The variation in drug response ranges from failure to respond to adverse drug reactions and drug-drug interactions when several drugs are taken concomitantly. The clinical consequences can be catastrophic. A US study estimated that 106,000 patients die and 2.2 million are injured each year by adverse reactions to prescribed drugs [8]. Pharmacogenetics may reduce the guesswork in prescribing existing medicines, increasing the likelihood of prescribing the right drug, at the right dose, to the right patient at the outset of therapeutic intervention. It may reduce considerably the time, efforts and resources wasted in finding by trial-and-error the correct treatment regimen. Avoiding prescribing medicines to potential 'non-responders' and/or those likely to develop an adverse drug reaction can result in better targeted, or even individualised, pharmacotherapy.

Typically, a physician prescribes the recommended medicines in the average recommended dosage to his or her patient. If the medicine does not work, and the drug is approved for a range of doses, the physician may try a different dose or may switch to an alternative treatment. Time and money are wasted from unnecessary visits to the physician and the cost for ineffective medicine(s) either used or remaining unused (usually cannot be resold). It is becoming increasingly evident that much of the interindividual variation in response to drugs is inherited and it is clear that not all patients who appear to have the same indication benefit from the treatment. Whereas there are some estimates of the magnitude of the problem arising from adverse drug reactions, there is hardly any systematic prospective information on the scale of the problem arising from treatment failure. There are no well-controlled studies to demonstrate how ineffective many of the well-established therapies are. How many years and how many patients does one need to treat with “statins” to avoid one death from cardiovascular disease? Estimates available suggest certainly more than 10 patients for at least two years per one death avoided. If it were possible to predict with very high probability in which individuals these lipid-lowering drugs do not work at all (this may or may not be the case), not only would there accrue an enormous savings in resources but also many patients would be spared unrealistic high expectations of benefit. These patients may well benefit from alternative potentially effective treatments that may work for them.

### **3. Polymorphisms and the human genome**

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With recent advances in molecular genetics and genome sequencing, pharmacogenetic research has attracted enormous attention from both the scientific communities and the public. This is due to new technologies that permit rapid screening for specific polymorphisms, as well as recently gained knowledge of the genetic sequences of target genes such as those coding for enzymes, receptors, ion channels, and other types of pharmacological targets involved in drug response. As a result of the completion of the Human Genome Project and other public initiatives such as The SNP Consortium (single nucleotide polymorphisms, see <http://snp.cshl.org>), comprehensive maps of the human genome have been established including information on genetic variations associated with disease susceptibility as well as pharmacokinetics and pharmacodynamics. However, in general, identification of single nucleotide polymorphisms is ahead of the clinically more important task of correlating genotypes with phenotypes.

Research in pharmacogenomics and pharmacogenetics is developing in two main directions: firstly, identifying specific genes and gene products associated with various diseases which may act as targets for new drugs and/or diagnostic tools and, secondly, identifying genes and allelic variants of genes that affect the response to drug therapies.

Increasing numbers of research programmes have evolved from the Human Genome Project, including genome-wide screens to identify differences between individuals that arise from a single base pair alteration in their DNA or single nucleotide polymorphisms (SNPs). SNPs can be used to map and identify specific genes associated with various diseases such as cancer, diabetes, and arthritis. Many of the proteins encoded by these genes are expected to be new targets for drug therapy but may also improve our diagnostic capabilities and help to stratify otherwise heterogeneous diagnostic groups into more precise subgroups that may have different responses to the existing therapies. The fact that these genes were identified by polymorphism analysis indicates that drugs directed at such targets may have different effects in different patients. This leads to the concept of drug stratification or individualised drug treatment, in which the choice of drug, or the dose of a drug, is influenced by a patient's genetic status.

Genomic analysis has generated an enormous amount of information on human polymorphisms. There are over 4 million single nucleotide polymorphisms in public databases and more will probably be identified over the next few years. However, a greater challenge will be to determine the function of each polymorphic gene or, to be more exact, of the gene product and its variant forms. It should be noted however, that it might not always be necessary to know the function of a polymorphism as it relates to clinical utility. This is often seen in many drug development programmes, where compounds progress to demonstrate clinical utility, without its mode of action having been elucidated. In some circumstances, it may be necessary to determine the functional significance of a gene product for its toxicological importance and whether individual allelic variants are of therapeutic importance. Such expression and function profiling studies that enables the testing of genotype-phenotype correlations are expected to be extremely important for further advances in the field of pharmacogenetics.

In terms of current clinical practice, it is more relevant to determine individual genetic variations that will improve both the efficacy and safety of existing therapies. Because a relatively large number of patients receiving

a drug fail to gain the expected benefit, pharmacogenetics may identify the reasons for lack of benefit in certain individuals. However, adverse reactions are a major societal and economic healthcare problem and patients are more concerned about drugs doing harm to them. Therefore, the overall impact of pharmacogenetics in improving safety is equally important, if not more than in improving efficacy. Polymorphism in any one of many genes including those encoding drug receptors, drug transporters, and cell signalling pathways can be important factors in determining clinical response. It appears that among the polymorphisms of clinical relevance and of immediate utility are those involved in drug metabolism and disposition (e.g. CYP2D6, TPMT).

Functional polymorphisms in any one of these genes can lead to either a lack of therapeutic effect, unexpected clinical responses or an adverse reaction (Table 1).

**Table 1**  
**Potential effects of polymorphic drug metabolism on drug treatment**

1. Adverse drug reactions
2. Extended pharmacological effect
3. Lack of prodrug activation
4. Metabolism by alternative, deleterious pathways
5. Ultrarapid metabolism (e.g. duplicated CYP2D6)
6. Modification of drug-drug interactions

The reader is referred to Chapters 2 and 3 on “Abnormal Drug Response” for additional discussions.

Polymorphisms have now been identified in more than 20 human drug metabolising enzymes, several with substantial inter-ethnic differences in their frequencies. The phenotypic consequences of some of these are critical determinants of therapeutic outcome [9-13]. Important examples are polymorphisms in the cytochrome P450 enzymes and in thiopurine S-methyltransferase (TPMT).

### 3.1 Cytochrome P450 drug metabolising enzymes

The cytochrome P450 drug metabolising enzymes (frequently referred to as CYP isoforms) are a multi-gene family of enzymes found predominantly in the liver (but present also in other tissues such as the brain). They are responsible for the metabolic elimination of a vast majority of

the drugs currently used in medicine. Genetically determined variability in the level of expression or function of some of these enzymes has a profound effect on drug response. In ‘poor metabolisers’ the genes encoding specific cytochrome P450s often contain inactivating mutations, which result in a complete lack of active enzyme and a severely compromised ability to metabolise drugs.

Thus, mutations in the gene encoding cytochrome CYP2D6 (known previously as debrisoquine hydroxylase) give rise to distinct phenotypes in a population – extensive and poor metabolisers. Case reports suggest that this polymorphism has clinical consequences for some individuals (see Chapter 3 on “Abnormal Drug Response”). Polymorphism not only affects drug disposition but can also be important in the conversion of prodrugs to their active form. Codeine is an old and widely used pro-analgesic that is metabolised to the analgesic morphine by CYP2D6, and the desired analgesic effect is not achieved in CYP2D6 poor metabolisers. CYP2D6 is highly polymorphic and is inactive or dysfunctional in about 6-9% of Caucasians of white origin [14]. Thus, millions of people worldwide may be potentially at risk of compromised metabolism or adverse drug reactions when prescribed drugs that are CYP2D6 substrates. Many CYP2D6 substrate drugs are used for treating chronic illnesses such as psychiatric, neurological, and cardiovascular diseases (Table 2). They have a narrow therapeutic window, commonly have side effects and are intended for long-term administration. Clinical problems can also arise from the co-administration of drugs that inhibit CYP2D6 or compete with its other substrate(s). A drug may interact with and inhibit CYP2D6 to the extent that the enzyme is no longer functionally active, resulting in a patient responding like a poor metaboliser even though he or she has an ‘extensive metaboliser’ genotype. Thus, quinidine, a powerful CYP2D6 inhibitor, may exaggerate the effects of other CYP2D6-metabolised drugs that are prescribed concomitantly or may prevent the metabolic activation of drugs such as codeine by CYP2D6.

Another variant results from amplification of the entire CYP2D6 gene, with some individuals inheriting up to 13 copies of the gene, arranged in tandem [15]. This amplification polymorphism results in affected people metabolising drugs that are CYP2D6 substrates so quickly that a therapeutic effect cannot be obtained at conventional doses. For example, it has been estimated that, while a daily dose of 10-20 mg nortriptyline would be sufficient for a patient who is a CYP2D6 poor metaboliser, an ‘ultra-rapid metaboliser’ inheriting multiple copies of the gene could require as much as 500 mg a day [16]. These individuals develop rapidly accumu-

**Table 2**  
**Examples of drugs that are substrates of cytochrome**  
**P450 CYP2D6**

Cardiovascular drugs	Neuro-psychiatric drugs	Analgesics	Miscellaneous
Alprenolol	Amitriptyline	Codeine	Atomoxetine
Bufuralol	Clomipramine	Hydrocodon	Chlorpheniramine
Carvedilol	Desipramine	Oxycodon	Dexfenfluramine
Encainide	Doxepin	Tramadol	Dextromethorphan
Flecainide	Duloxetine		Methadone
Indoramin	Fluoxetine		MDMA (“ecstasy”)
Metoprolol	Haloperidol		Phenformin
Mexiletine	Imipramine		Sparteine
Nebivolol	Levomepromazine		Tolterodine
Oxprenolol	Maprotiline		Traxoprodil
Perhexiline	Mianserin		Tropisetron
Propafenone	Nortriptyline		
Propranolol	Paroxetine		
Timolol	Perphenazine		
	Risperidone		
	Sertindole		
	Thioridazine		
	Trimipramine		
	Venlafaxine		
	Zuclopenthixol		

lating metabolites that may prove toxic. For example, ultrarapid metaboliser may experience morphine toxicity following administration of codeine [17].

CYP2C9 is another member of the cytochrome P450 superfamily, which metabolises warfarin and phenytoin. Its activity influences patients’ response to these well established drugs with narrow therapeutic index and their dose requirements [18-20].

### 3.2 Thiopurine S-methyltransferase

Another clinically important polymorphism occurs in the enzyme thiopurine S-methyltransferase (TPMT) [21, 22] that is responsible for the metabolism of the antitumour agents, azathioprine, 6-mercaptopurine and 6-thioguanine. Genetic mutations at the locus expressing this enzyme are associated with difficulty in avoiding toxicity whilst trying to achieve an effective concentration of these drugs in children with childhood acute lym-



phoblastic leukaemia [23]. Children with inherited TPMT deficiency exhibit severe haemopoietic toxicity when exposed to normal doses of drugs such as 6-mercaptopurine, whereas those with a high activity form of the enzyme require high doses of the drug to achieve any clinical benefit. TPMT polymorphism is relatively rare, with only about 1% of the white population being homozygous for it, but, since these individuals show exaggerated toxic responses to normal doses of these drugs, TPMT phenotype may be an important factor in the successful treatment of childhood leukaemia. Some centres already provide a diagnostic genotyping or phenotyping service to guide the clinical use of 6-mercaptopurine and azathioprine.

Other major polymorphic drug metabolising enzymes, including members of the cytochrome P450 family and phase II conjugating enzymes, have been recently reviewed [10].

### 3.3 Genetic polymorphisms and their potential for improving existing therapies

The following is a brief list of receptor and enzyme polymorphisms that are likely to affect response to existing therapies (selected examples of clinically important polymorphisms)

1.  $\beta$ 1- and  $\beta$ 2-adrenoreceptors
2. Angiotensin-converting enzyme (ACE)
3. Serotonin transporter (5-HTT)
4. 5-lipoxygenase (ALOX-5)
5. Cytochrome P450 enzymes (e.g. CYP2D6, CYP2C9, CYP2C19)
6. N-acetyltransferase 2 (NAT2)
7. Dihydropyrimidine dehydrogenase (DPD)
8. Cholesteryl ester transfer protein (CETP)
9. Multi-drug resistance protein (MDR-1) (P-glycoprotein)
10. Thiopurine S-methyltransferase (TPMT)
11. Leukotriene synthesising enzymes and receptor polymorphisms.

## 4. The current situation

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Pharmacogenetic testing is currently used in a relatively limited number of teaching hospitals and specialist academic centres. The widely practised application of pharmacogenetic testing is the use of CYP2D6 genotyping to aid individual dose selection for drugs used to treat psychiatric illness.

Several independent testing laboratories have started to provide the pharmaceutical industry and medical practice with a high throughput, DNA-

based, testing service for a range of pharmacogenetic polymorphisms. It is, however, difficult to predict to what extent the pharmaceutical industry will routinely incorporate pharmacogenetic testing into prescribing schedules for drugs that are subject to polymorphic metabolism. This will depend to some extent on the attitude of the drug regulatory authorities. The reader is referred to Chapter 7 on “Regulatory Perspectives in Pharmacogenetics”.

The clinical applicability and cost-effectiveness of pharmacogenetic testing depends on the relative importance of each polymorphism in determining therapeutic outcome. Physicians need to be aware of whether a drug they are prescribing is subject to pharmacogenetic variability and know how to use this knowledge. In addition, a reliable, DNA based, testing service needs to be made available. Pre-treatment genotyping may allow a more appropriate choice and doses of specific drugs, particularly those for treating psychiatric disorders. At present, adverse drug reactions occur in a substantial proportion of patients: a recent US study showed that, in patients prescribed psychiatric drugs that are CYP2D6 substrates, adverse drug reactions were observed in every patient with inherited mutations inactivating the CYP2D6 gene [24]. Others have questioned whether genotyping for CYP2D6 alone has much to offer in safe and effective use of neuroleptic drugs [25]. Nevertheless, Kirchheiner et al have provided a preliminary guidance for a number of drugs metabolised by CYP2D6 and CYP2C19 with a view to introducing genotype/phenotype-specific dose schedules [26].

## **5. The future**

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Pharmacogenetics is still an evolving discipline where for certain pharmacogenetic tests, there is ample mechanistic and epidemiological evidence demonstrating their value in improving risk/benefit. For other pharmacogenetic tests, the evidence is only suggestive, but not definitive, of clinical value. We are still a long way from having a pharmacogenetic DNA chip that general practitioners can use to identify all the drugs (or doses of a drug) to which any particular patient is responsive, non-responsive or intolerant.

However, there is increasing evidence that pharmacogenetics may become a valuable tool in health service. One day it may be considered unethical not to carry out such tests routinely to avoid exposing individuals to doses of drugs that could be ineffective or even harmful to them. The ability to identify sensitive individuals, either before drug treatment or after an adverse

drug response, would also be of economic importance as it would avoid the empiricism associated with matching the most appropriate drug at its optimal dose for each patient. It might also substantially reduce the need for hospitalisation, and its associated costs, because of adverse drug reactions.

Increase in knowledge of the mechanisms of drug action, identification of new drug targets and understanding of genetic factors that determine the response to drugs may allow us to design drugs that are specifically targeted towards particular responder populations, avoiding genetic variability in therapeutic response. The extent of genetic polymorphisms in the human population indicates that pharmacogenetic variability will probably be an issue for most new drugs.

The development of pharmacogenetics provides at least one mechanism for taking drug prescription away from its current empiricism and progressing towards a more patient-tailored 'individualised' drug treatment. Already, in the UK, the Department of Health has initiated an innovative GB£4 million start-up funding scheme for supporting research aimed at exploring the role of pharmacogenetics in improving existing therapies that patients are commonly taking now or are likely to be taking soon [27]. Proposals could involve the development of new services or new roles in existing therapies and applications for funding closed on 25 February 2004 [see <http://www.doh.gov.uk/genetics/servicedev.htm>] and six research projects investigating the value of pharmacogenetics in improving existing therapies have been funded.

## 5.1 Predicted developments

1. Changes in product information. Prescribing advice will start to relate dose to genotype and will highlight the possibility of drug interactions when multiple drugs are prescribed concomitantly.
2. Step-wise creation and implementation of prescribing guidelines, based on clinical studies, for drugs that are subject to substantial polymorphic metabolism.
3. Establishing and recording of individual patient genotypes and phenotypes i.e. 'personal pharmacogenetic expression profiles' as part of medical records.
4. Implementing pharmacogenetic testing may substantially reduce the need for hospitalisation following the use of existing therapies, and its associated costs, because of reduction in adverse drug reactions.
5. More public funds channelled to research concerning existing therapies as outcomes may save considerable public spending on existing drugs,

unlock finances for the development of new therapies and achieve better health outcomes for the populations.

*Anticipated benefits of pharmacogenetics and pharmacogenomics for existing treatments:*

1. Improving rational drug use and possible wider access to medicine – identify people most likely to respond to certain drugs and avoid using these drugs in those who may be at risk of serious adverse drug reactions
2. Reviewing for use in specific subgroup of patients those drugs that have been withdrawn and expanding indications for drugs already on the market
3. Step-wise elimination of “trial-and-error” or “one-size-fits-all” approach to prescribing
4. Saving resources.

## **5.2 Limitations and challenges**

1. Motivation to fund research related to existing therapies may be low and compete with motivation to invest into new therapies
2. Public acceptance of genetic profiling may need time
3. For existing medicines, access to more targeted prescribing approach may be too costly to attract funds
4. Distinguishing environmental factors from genetic factors may be more difficult than expected and cause failure to achieve better treatment outcomes with pharmacogenetic approach
5. For existing medicine, complexities of interactions with drugs and other types of health products may not have been investigated and may complicate pharmacogenetic targeting approach.
6. Pharmacogenetic targeting may raise ethical issues that need to be identified and discussed (see Chapter 9 on “Ethical Issues”).

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## Chapter 7

# Regulatory Perspectives in Pharmacogenetics

### 1. Introduction and background

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Environmental and genetic factors, together with therapeutic interventions are the major determinants of public health. The sequencing of the human genome and the development of genetic and genomic technologies promise to improve public health and the economics of healthcare. The technologies can provide knowledge of how pharmacogenetic and pharmacogenomic information can be used to optimise the risk/benefit of many drugs and reduce the incidence of adverse drug reactions.

There is a diversity of opinion regarding the definitions of *pharmacogenetics* and *pharmacogenomics*. *Pharmacogenetics* is defined as the study of interindividual variations in DNA sequence related to drug disposition (pharmacokinetics) or drug action (pharmacodynamics) that can influence clinical response. For example, polymorphic variations in the genes that encode the functions of drug metabolising enzymes, transporters, ion channels and receptors can result in wide interindividual differences in the dose-plasma concentration-response relationships for many important therapeutic agents. Pharmacogenetic studies include applications of single gene sequences or a set of multiple gene sequences to investigate variations in DNA sequence that may influence drug response. In contrast, *pharmacogenomics* is defined more broadly as the application of genomic technologies to elucidate disease susceptibility, drug discovery, pharmacological function, drug disposition and therapeutic response. In this context, pharmacogenomic studies include a whole spectrum of markers ranging from genome-wide scans, single nucleotide polymorphisms (SNP), candidate genes, haplotype markers and alterations in gene expression or inactivation that show promise to be predictive of drug action. Moreover, integrating pharmacogenetic and pharmacogenomic information following recent progress in human genetics and genomics has given new insights into (a) the basis for heterogeneity in disease states (e.g. subtypes of breast cancer), (b) predictive medicine (e.g. risk of developing or preventing Alzheimer's disease) and (c) dosage regimen selection for subgroups of patients (e.g. poor and extensive metabolisers of a drug metabolised by CYP2D6). Pharmacogenetics and pharmacogenomics promise to improve our understanding of the natural interindividual variability in disease susceptibility and drug response and have the potential to improve drug development and therapeutics in the future.

## **2. Drug development and regulatory assessment**

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Genome-based technologies have become more readily available, cost effective and reliable. As a result, pharmaceutical companies today are collecting pharmacogenetic or pharmacogenomic data in an increasing number of early and late clinical drug trials. However, many of these applications in drug development are exploratory and in most cases it is not yet apparent how to determine *a priori* how individuals would respond to a drug. Thus, there are only a few cases where pharmacogenetic or pharmacogenomic data have been incorporated into registration applications as a confirmatory test. In the future however, as our knowledge of hereditary factors and other determinants of drug response evolve, it is anticipated that the drug development process will lead to regulatory assessment, approval and marketing of drugs that would be genetically driven and individually tailored for optimal response.

The current regulatory framework in terms of guidelines that already recommend the sponsors of new drugs to explore pharmacogenetic influences during drug development and in terms of labeling of some drugs is described in Chapter 4 on “Exploring Pharmacogenetics in Drug Discovery and Development”.

Regulatory agencies have the dual responsibility of protecting public health by assessing the risk/benefit, doses and dosing regimens of drugs and of promoting efficient and optimal drug development. Regulatory authorities worldwide share a common goal with the pharmaceutical industry to make available drugs that are effective, relatively free of serious adverse events, and have acceptable risk/benefit ratios. Thus, regulatory agencies and the pharmaceutical industry should encourage and facilitate exploration and utilization of pharmacogenetics and pharmacogenomics in the drug development process when and where it can make a perceptible difference in the practice of medicine.

There are three broad components of public health and drug therapy that are related to the use of pharmacogenetics and pharmacogenomics and are of interest to regulatory authorities:

### **2.1 Drug efficacy and effectiveness**

Pharmacogenetic and pharmacogenomic data can be used to identify drug targets for specific subsets of a disease, or to identify a responder (or non-responder) to a drug in advance and thereby reduce the risk of therapeutic failure.



## 2.2 Drug safety and adverse events

Pharmacogenetic and pharmacogenomic data can be used to identify *a priori* subsets of the target patient population who are at greater risk of developing a drug-related adverse event, and thereby reduce the frequency of adverse reactions.

## 2.3 Drug dose and dosing regimens

Pharmacogenetic and pharmacogenomic data can be used to identify, prior to prescribing a drug, an appropriate dose for different subsets of patients that would improve the risk/benefit of the drug in these subsets in order to individually optimise therapy.

Thus, in many ways, regulatory agencies believe that pharmacogenetics and pharmacogenomics may provide a more effective tool in risk management.

## 3. The Pharmacogenetic/pharmacogenomic paradigm

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The general approach to applying pharmacogenetics or pharmacogenomics in drug development is likely to be a three-step process.

### 3.1 Selection of a target disease or drug candidate

Usually the target disease is a common one whose pathophysiology is heterogeneous and where drug effects on clinical endpoints are highly variable between patients but where variability in response, for the most part, is unrelated to environmental or life-style factors. The candidate drug is likely to be one of several therapies available for a disease and its site and mechanism of action are well characterised.

### 3.2 Development of a predictive pharmacogenetic or pharmacogenomic test

The pharmacogenetic test usually is based on genetic variation in one or more biomarkers as evidenced by SNP or haplotypes, by basal gene expression levels (e.g. mRNA levels) or by predictive expression patterns in target pathogenic tissue (e.g. tumours), or in host tissue. The test is likely to predict responsive disease subsets of patients, the risk of disease progression or the likelihood of achieving efficacy, having adverse events or improving the selection of the dose of a drug for a given patient.

### **3.3 Determination of the analytical validity, clinical validity and clinical utility of a predictive pharmacogenetic or pharmacogenomic test**

The analytical validity defines the accuracy and precision of the pharmacogenetic or pharmacogenomic test in measuring the genotype of interest. It is often expressed as analytical sensitivity and specificity and the performance of the test is commonly compared to a “gold standard”.

The clinical validity describes how good the test is in predicting clinical outcome. It is frequently characterised as the clinical sensitivity and positive or negative predictive values of the pharmacogenetic or pharmacogenomic test for biomarkers of drug efficacy or safety. In order to establish clinical validity, the biomarkers may be identified early and determined later in clinical trials involving patients with the target disease that may develop an adverse reaction, or fail to respond to therapy. This often involves stratification of patient enrolment in clinical trials.

The clinical utility of a positive or negative pharmacogenetic or pharmacogenomic test determines how good the test and associated interventions are in improving health and/or preventing disease. The most rigorous assessment of clinical utility is through randomised, controlled clinical trials in which patients are randomly assigned to different interventions based on the results of the test.

## **4. Limitations and challenges of pharmacogenetics and pharmacogenomics**

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It is important that industry and regulatory authorities recognise the major limitations and challenges of using pharmacogenetic and pharmacogenomic information in clinical trials. Predictive pharmacogenetic and pharmacogenomic tests are complex in that their utility may be related to either disease biology (defining something about a patient’s current or future disease condition) or drug response (defining the probability or likelihood of a clinical outcome both desirable and undesirable).

The limitations and challenges include the following:

- Patient populations are genetically heterogeneous; the phenotypes of the same common diseases, or many diseases with unmet medical need, are the result of complex interactions between genetic traits, and in some cases, the environment

- Because of population heterogeneity, a pharmacogenetic or pharmacogenomic test may identify only a small proportion of patients in which inherited mutations at one or more gene loci contribute significantly to the disease phenotype. This may lead to orphan drug status for an intervention; however, the threshold for an orphan drug differs between countries.
- Responses to drugs are highly variable between subjects, and are influenced by multiple genetic factors as well as non-genetic covariates such as drug interactions or co-morbidities
- Careful consideration must be given to the clinical and regulatory criteria in defining useful genotype-phenotype associations
- There is a need to develop efficient study designs and to adapt statistical methods and information technology paradigms for the accrual, analyses and reporting of pharmacogenetic/pharmacogenomic data

## 5. Current situation

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At present, there are few examples of pharmacogenetic or pharmacogenomic predictive or diagnostic tests that have been approved by a regulatory agency for the purpose of individualising therapy.

Among the few exceptions are the immunohistochemical and DNA-based tests respectively to detect tumour HER-2 over expression in women with breast cancer who would benefit from trastuzumab (Herceptin® Roche), and the use of viral DNA tests to determine the level of drug resistance in patients that are HIV positive as an aid in the selection of a protease inhibitor. To date, much of the discussion between the pharmaceutical industry and regulatory agencies about pharmacogenetics and pharmacogenomics has focused on issues relating to emerging regulatory policy with respect to the validity, predictability, and usefulness of pharmacogenetic and pharmacogenomic data. In many ways, the development and use of pharmacogenetic or pharmacogenomic tests represent an “enrichment” tool for characterising safety or efficacy in clinical trials. Enrichment of target populations in drug development for efficacy promises to allow studies to be smaller and more efficient by excluding the enrolment of non-responders. However, one of the major unresolved concerns is how sufficient safety data will be acquired on a new drug when genotyping for efficacy is used to select patients for enrolment in a pharmacogenetic/pharmacogenomic clinical trial. Applications of pharmacogenetics/pharmacogenomics in the post-marketing surveillance setting may provide options for addressing this concern.

While inclusion or exclusion of particular genotypes or phenotypes (e.g. particular protein or mRNA expression patterns) is similar to other forms of enrichment that are well known to regulatory agencies and industry, there are several short-term considerations for regulatory agencies and the pharmaceutical industry as delineated below:

- Regulatory agencies worldwide have formed internal working groups to focus on issues of pharmacogenetics and pharmacogenomics with the intent of increasing an understanding of the science and to consider the need and feasibility of regulatory guidances or guidelines for industry. The achievement of a harmonised approach to pharmacogenetic/pharmacogenomic data is highly desirable to facilitate global consistency in the use of such data in drug development and regulatory assessment.
- Regulatory scientists anticipate seeing greater use of cytochrome P450-based genotype tests in drug development. This would lead to more information on the use and value of such tests in product information; for example to characterise clinical trial population into extensive and poor metaboliser genotypes and to include descriptions of any new pharmacogenetic or pharmacogenomic data (obtained from advanced technologies) from exploratory or confirmatory clinical trials in regulatory submissions. An important issue will be when and how to incorporate this information into labelling and package inserts.
- It is important to maintain an open dialogue between regulatory agencies, academic researchers and pharmaceutical company scientists to explore ways that encourage and facilitate the exploratory use of pharmacogenetic/pharmacogenomic technologies and exploit the clinical value of these sciences for improving public health, without penalizing companies that choose to do so.
- One possible cause of adverse drug reactions is genetic variation in how individuals metabolise, and in some cases, transport drugs. For those drugs that are metabolised by an enzyme that is polymorphic (e.g. CYP2D6), differences in systemic exposure from a given dose should be assessed early in drug development. If these differences can be shown to be associated with a higher risk of adverse events, or failure of usually recommended doses to provide efficacy in patient subsets, this information should be included in the product label and an appropriate dose should be recommended for the subset of at-risk patients defined by genotype. Consideration would need to be given not only to the prevalence of genetic variants in the intended target population but also the clinical significance of adverse reactions, the overall risk/benefit of the drug and genotyping a large number of potential recipients of the drug.

- If genetic tests were to be used prospectively for identifying drug responders or for identifying at-risk patients, the following evidence would be necessary for regulatory approval:
  - measures of the analytical quality of the test (analytical validation)
  - data from ‘functional’ studies (i.e. studies that relate DNA changes to alterations in protein function and/or levels) identifying predisposing genetic/genomic factors involved with disease pathogenesis to the extent of what is known about a disease, or genetic polymorphisms that may increase the benefits or lower the risk in patients receiving drugs. These data should be supportive of the genotype-phenotype association on which the test is based and
  - information on the clinical validity and clinical utility of the test for therapeutic applications and decision making. Consideration would need to be given to the design of the pivotal clinical trials to provide sufficient information to estimate the positive and negative predictive value of any genetic test (specificity and sensitivity), and the clinical benefit to drug use with and without the use of such a test;
- There will be a need for independent replication of outcomes in the regulation of pharmacogenetic tests, i.e., to have evidence of replication of the findings of an association between the test and clinical endpoints. It will be important to establish the reliability (sensitivity, specificity etc) of the genetic test in several clinical laboratories and to assure the clinical validity of the test (both positive and negative findings). Consideration will need to be given to whether the test specified in the label of a drug product is mandatory (most likely) or optional before prescribing the drug. These considerations will take into account the rationale and level of evidence supporting the clinical utility of the test. Ideally, the regulatory authorities will approve drug-specific predictive tests recommended in package inserts at the time of approval of the drug product.
- Use of case-control pharmacogenetic and pharmacogenomic studies to explore associations between genomic biomarkers and adverse events or effectiveness with drug therapy would be considered exploratory and hypothesis generating in most cases.

## **6. Summary and conclusions**

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Pharmacogenetics and pharmacogenomics should be considered in all phases of drug development. These sciences have considerable potential to improve our understanding of drug safety and efficacy and to improve our development of optimal drug doses and dosing regimens.

However, with this potential in mind, the application of genetic and genomic technologies should be based on good science and applied where it has the greatest chance to improve decision making not only in drug development, but also in regulatory assessments.

Continued dialogue between academic researchers, industry scientists and regulatory agencies is needed to reduce uncertainties in the rapidly evolving fields of pharmacogenetics and pharmacogenomics. Together, they can guide strategies for exploring these technologies and utilizing data in drug development and regulatory assessment in order to optimise the benefit/risk ratios of future drugs for society.

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## Chapter 8

# Genetic Testing, Genetic Data and Genetic Information

### 1. Introduction

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The discussion about genetic testing (including pharmacogenetic testing), genetic data, and genetic information has been impeded by the lack of a clear definition of the term “genetic” in this context. To construct an acceptable definition, it is necessary to consider the possible parameters or criteria that could influence this definition in the context of testing, data, and information.

Importantly, an appropriate definition of “genetic” should not only reflect the factual, scientific or intellectual viewpoint, but also the reasons that have intensified the associated debate. These reasons include ethical, societal and legal implications, as well as the public perceptions and sentiments, which the term “genetic” evokes.

With regard to the implications of genetic (and pharmacogenetic) testing, the most important characteristic of a test is its information content, rather than its genetic nature *per se*. Therefore, distinctions based on the more technical aspects, including a differentiation between genetic and non-genetic tests are not helpful in providing guidance as to how to safeguard and use the respective information.

### 2. Considerations of approaches towards a definition of genetic tests

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A number of different approaches have been used to get at the essence of what constitutes genetic testing. Among these are (i) choice of the analyte (the biochemical entity the test directly measures), (ii) the heritable nature of the disease or parameter tested, and (iii) the understanding and meaning of the term within the spectrum of current public perceptions.

#### 2.1 Definition based on analyte assayed

Two broad categories of analytes assayed can be discerned:

(a) *DNA (nucleic and mitochondrial) sequence (excluding RNA expression data)*:

– Arguments for:

Encompasses only the information that can be transmitted to subsequent generations of offspring (germ-line) or cells (somatic)

but excludes all information influenced by non-inherited factors (except for somatic mutations)

– Arguments against:

Does not encompass any other, non-DNA-based tests that are commonly used to test for single gene disorders and that are publicly perceived as “genetic” tests e.g. protein truncation test in familial adenomatous polyposis coli.

(b) *Nucleic acid based tests (including RNA expression)*:

– Arguments for:

Will capture certain mutations in regulatory regions based on their impact on gene expression even in the absence of knowledge of the relevant mutation

– Arguments against:

Same as under (a) above, and will encounter great difficulty in discerning inherited variants from a host of not primarily inherited phenomena that affect transcriptional activity and/or message stability.

A definition of genetic testing based on analytes only, i.e. DNA or nucleic acid, is too narrow as it would exclude a number of tests that determine the consequences of underlying DNA sequence without directly measuring the DNA sequence. On the other hand, inclusion of all RNA-expression level data would constitute a definition that is excessively broad as it includes non-DNA-based, non-heritable modulation of gene expression.

## **2.2 Definition based on the heritable nature of the parameter/condition tested**

This definition is the one most often encountered in various documents. It usually extends the definition of genetic test to genes, chromosomes, and can include proteins (or metabolic) products.

This approach is a reasonable one for rare monogenic, high penetrance disorders, where non-DNA-based tests results provide essentially the same specific diagnostic or prognostic information as a DNA-based test. However, given that all common complex diseases also show some degree of heritability, most biochemical markers for such diseases will also reveal some genetic information. Therefore, their analysis would also constitute a genetic test of a sort. This approach would result in a definition that is too broad and too vague, because it can legitimately include almost any

and all tests/analytes, even those with quite poor correlation with underlying DNA variance.

*Examples:*

Extremely high plasma cholesterol levels, as encountered in familial hypercholesterolemia, would certainly qualify as a legitimate genetic test for this condition (they carry information that is basically diagnostic of the disorder). However, any cholesterol value may be considered as information that is (in part) genetic because even lower levels are influenced by a multitude of genetic variants of the protein components of various lipid pathways. However, since environmental factors also influence cholesterol levels, it would be very difficult or impossible to determine the genetic and non-genetic components, respectively, in such a case. Similarly it is impossible to correlate most variants of the gene encoding methyltetrahydrate folate reductase with measurements of plasma homocysteine levels (to which they contribute along with dietary factors), whereas the test is diagnostic in families with homocystinuria.

### **2.3 Definition based on the public perception of genetic testing**

Since the public perception of a categorical difference between genetic and other medical tests is providing a major stimulus to the discussion of the topic, it would appear reasonable to consider what the public understands by the term ‘genetic test’ when developing a definition of genetic test.

The public has so far been confronted primarily with two kinds of genetic tests: tests for rare heritable diseases and DNA testing for identification purposes (e.g. in forensic and paternity testing). The experience with these two categories is likely to have substantially influenced the public perception of what a genetic test is, and what genetic data and information mean.

The public thus tends to consider as genetic tests

- Any test (regardless of whether based on DNA or other analytes) that diagnoses or predicts one of the classic, high-penetrance, monogenic diseases; and
- Any test that is based on the analysis of DNA sequence variation (both germ-line and somatic), including paternity and forensic testing (the latter playing an important role in public sentiment).

Significantly, these two categories are characterised by

- Extremely high information content that is unusual in the spectrum of general medical tests, particularly with regard to predicting a serious illness, and with regard to rendering highly accurate personal identification data, respectively; and
- Information content that is exclusively determined by inherited factors.

Given that

- the vast majority of currently available genetic tests with which the public has had any experience or to which the public is exposed pertain to the two categories mentioned (i.e. they are tests that deliver very high information content) and
  - among all medical tests that have an extremely high information content with regard to future disease prediction, the vast majority are genetic tests predictive of rare single gene diseases,
- the public has come to equate genetic testing and genetic data with highly predictive, and thus sensitive, information.

Given also that tests predictive of a single gene disease and DNA-based identity tests are rather different from the majority of all other medical tests, it is understandable that equating these two categories with genetic tests in general can result in the perception that genetic tests are indeed categorically different and of potential threat to privacy and confidentiality.

It is appropriate to be concerned about data with high information content, as the potential for abuse of any data is proportional to the amount of information it contains. It is unfortunate, but understandable, that the current examples of genetic tests which the public is most familiar with have resulted in the perception that it is the genetic nature of the test, rather than its information content which accounts for the test's sensitive quality.

## **2.4 Synthesis of a definition**

Tests that directly provide DNA-structure-derived information (regardless of its somatic or germinal nature) should be classified as genetic tests. Similarly tests that deliver data or information that are, directly indicative of inheritable properties should qualify as genetic tests. The definition of what defines a genetic test reverts to the definition of genetic data or genetic information, which, in common use of the language (the word

‘genetic’ being synonymous with ‘inherited’), refers to heritable characteristics.

It is, therefore, proposed that the term “genetic testing” should include:

1. Any and all tests that directly determine mitochondrial or nuclear DNA structure (sequence and chemical characteristics, and including cytogenetic data) that is transmitted to subsequent generations (of cells or offspring), regardless of its medical consequences.
2. Any and all tests which procure information pertaining to traits and characteristics regardless of the nature of the analyte (such as RNA, proteins, metabolites etc) that allow unambiguous conclusions regarding the underlying DNA sequence.

It is further helpful to distinguish between:

#### 2.4.1 Medical genetic testing

These describe the application of *Genetic Tests* to derive information relevant to healthcare, as it relates to

- disease diagnosis,
- disease treatment,
- disease risk prediction (i.e. test indicative of a particular condition that is not clinically evident at the time of testing and that is only discernible based on the genetic test), and
- reproductive health (predictive of the likelihood of particular conditions to be transmitted to or present in offspring prenatally).

It may be noted that the latter two categories are commonly the ones that raise the greatest concerns with regard to ethical, legal, and social considerations.

#### 2.4.2 Non-medical genetic testing

These comprise the application of *Genetic Testing* for purposes other than medical decision making. Primarily, this relates to the use for identification purposes, e.g. paternity and forensic testing and identification of the presence of animal and plant materials.

### **3. Consideration of approaches towards a contextual definition of genetic testing**

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The current public perception of genetic testing/data/information relates to the experience the public has had so far with the actual practice of

genetic testing (see section 2.3 above), all of which is characterised by one particular property, namely a *very high information content* of the information generated.

High content of information translates directly into the personal sensitivity of the data, i.e. potential for misuse or abuse, thus increasing the concerns that characterise the public debate about genetic testing. The public debate around genetics and genetic data has been based on highly predictive tests. The public has not been sufficiently exposed to the great majority of genetic data, which have much lower information content.

It is the actual information content of any set of data that renders it more or less sensitive, rather than its genetic or non-genetic nature. Therefore it would appear reasonable to differentiate among genetic data, as defined above, on the basis of information content, to arrive at a balanced and rational assessment of any given set of genetic data. Thus, to the definition given above, a metric for information content needs to be added to assess and interpret the meaning of the information. It should be noted that the information content is contextual i.e. the same set of data may carry different information content depending on the question asked.

This will allow one to differentiate, among all genetic data, between information that may have particular consequences for the individual, based on its high degree of information content, and other data whose information content is smaller. Such an approach will provide a more measured and rational approach towards the use of these tests. *Notably, identical considerations apply to all other medical testing which, depending on the test, carry a spectrum of information content ranging from low and non-specific to high and very specific.*

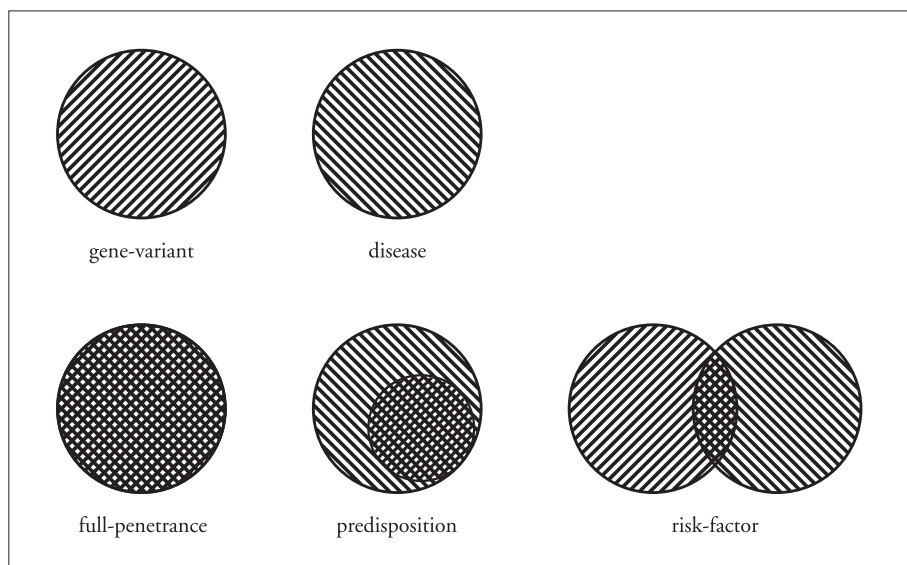
#### **4. Proposal for a differentiated assessment of genetic tests based on information content**

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Given the definition of genetic testing provided above, and in consideration of public perceptions of genetic testing, it is the information content of any given test that ultimately determines its meaning and possible ramifications for the individual. Medical science has a number of well-established parameters to measure and assess the quality of the information provided by a test, such as its positive and negative predictive value (PPV, NPV) for prospective studies, or specificity and sensitivity, for retrospective studies. It is the effective positive/negative predictive power,

or the specificity and sensitivity of a test, along with severity and medical-social impact of the disease or the clinical outcome in question which should determine its medical as well as potential social implications. These parameters are commonly affected by the nature of disease, in particular whether monogenic or complex. Rather than using numerical values of PPV/NPV and sensitivity/specificity to establish a classification for genetic tests, it appears sensible to examine whether the biological mode by which these tests influence health outcomes may offer an opportunity of classifying them. Thus, it is possible to characterise broadly three categories of genetic tests that correlate with differential information content. These definitions have previously been published in a white paper on this topic [1] (see Fig 1).

**Figure 1**



#### 4.1 Full penetrance tests

These apply to classic monogenic conditions that are characterised by a very high correlation between gene variant and disease. Thus, the disease will virtually always occur if the gene variant is present (*full penetrance*), and will virtually never occur, if the gene variant is not present (i.e. there is no “imitation” of the disease based on other causes, so-called *phenocopy*). Testing for the variant gene, if positive, is highly diagnostic/predictive for the occurrence of the specific disease (high positive predictive value, PPV), while in the presence of a negative test, occurrence of the disease is

extremely unlikely (high negative predictive value, NPV). This is particularly true if the test is applied, as is usually the case, to members of families in whom the disease is known to occur (thus raising the *prior probability*, an important parameter of testing fidelity). Such tests are very unlikely to yield either a false negative or a false positive result, and therefore, display high sensitivity and specificity, respectively. Notably, predictive tests of this nature contribute a level of predictive accuracy that is almost deterministic, thus highly unusual in clinical medicine, and indeed encountered almost exclusively in these rare inherited disorders. This high degree of predictability is a consequence of the high penetrance of the genetic variant, and the usually unambiguous results of DNA-sequencing. In such conditions, all diagnostic technologies, regardless of the nature of the analyte used (nucleic acid sequence, protein concentration/structure/function, or other functional tests) may be considered *Genetic Tests* based on the definition introduced in 2.4., as long as these analytes show the same strong correlation with the disease, i.e. as long as their variance is determined by and indicative of the variance present at the level of the DNA template. Examples are Huntington's disease (testing done by DNA-sequence analysis) and phenylketonuria (testing done using a non-DNA-based assay).

## 4.2 Predisposition tests

These apply to familial conditions where penetrance is less than complete, but phenocopies tend not to occur. Thus, while the disease may not occur in all those who test positive (thus, modest PPV or specificity), its occurrence is considered a consequence of the presence of genetic variant when it arises in test-positive individuals. Likewise, if one tests negative, the disease is unlikely to be present or to occur. Therefore, these tests have – within the context of affected families – high sensitivity (no/few false negatives) and high NPV, but limited specificity (false positives occur). Because these constraints tend to be even greater in tests using other analytes (which reflect not only influence of DNA-based variance but are also influenced by many additional factors), only DNA-sequence based tests should be considered *Genetic Tests* in this category, in keeping with the definition provided under section 2.4. Examples are familial (BRCA1/2-related) breast cancer and hereditary hemochromatosis.

## 4.3 Risk factor tests

These apply to common complex diseases where penetrance for any gene variant is low, because several different genetic as well as environmental factors are generally necessary to come together to result in the appearance



of the disease, so one alone is hardly predictive. Since the same clinical presentations may arise based on various combinations of such factors, phenocopies are common. While a positive test for the presence of a particular genetic risk factor thus raises the odds of developing the disease, many of those who test positive will not develop the disease, whereas many of those who test negative may still develop the disease (based on a combination of other risk factors). Therefore, such tests are characterised by limited PPV and NPV (and/or limited sensitivity and specificity). As such, their impact on medical decision making is not different from that of many other, conventional medical tests (e.g. tests for blood pressure or cholesterol level). Therefore, again, only DNA-sequence-based tests should be considered *Genetic Tests* in this category. Examples are the Factor-V-Leiden variant and the ApoE4 alleles.

It is obvious that, as elsewhere in biology, this categorisation reflects a simplification of a spectrum of continuous variables. However, the categorisation outlined above provides a pragmatic approach towards genetic tests of quite different information content, and therefore of different potential medical and social impact on the individual. In practice, as new tests enter the clinical arena, it may be helpful to assign them to one of these categories, depending on the biological behaviour exhibited by the parameter they measure, on a case-by-case basis.

## 5. Pharmacogenetic tests and data

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By definition, the consequences of pharmacogenetic tests will attain their full potential and application in the context of exposure to a pharmacological agent. Two conceptually quite different categories of tests, relating to interindividual differences in drug response, may be distinguished on the basis of the underlying biological variance:

- (a) “Classical pharmacogenetic” tests probe for biological variation that is in itself not disease-causing or -contributory, but becomes clinically relevant *only* in response to exposure to the drug in question. These genetic variants affect either pharmacokinetic (absorption, distribution, metabolism and excretion of drugs) or pharmacodynamic interactions with a given drug.
- (b) “Disease-mechanism-related pharmacogenetic” tests, in contrast, determine biological variation that is directly disease-related and *per se* of pathological importance. In this case, the test diagnoses a subgroup of the overall clinical disease/diagnostic entity. In this scenario, differential responses to a particular drug are related to whether the disease mech-

anism (pathophysiology), which the drug is tailored to target, contributes to the illness in a given patient (i.e. whether the patient belongs to that subgroup of the overall clinical disease entity for which the medicine is intended). Thus, the pharmacogenetic test may be viewed as defining the “molecular differential diagnosis” of the patient.

Although these two categories are conceptually rather different, they result in similar practical consequences with regard to the administration of a drug, namely stratification based on a particular DNA-encoded marker. While this stratification will mostly result in individually different dosing regimens in the former category, and in the determination of eligibility/ineligibility for the drug in the latter, it would still seem legitimate to include both under the umbrella term of “pharmacogenetics”.

The information content for both of these categories of tests tends to be of modest magnitude, i.e. either one or both of the test-performance predicting parameters (PPV/specificity or NPV/sensitivity) will likely be in the range of the “risk factor test” category. It is important to realise that despite the commonly used terminology distinguishing, on the basis of such tests, “slow” and “fast” metabolisers (classical pharmacogenetic tests) or “responders” and “non-responders” (disease-mechanism-related tests), these tests will at best distinguish individuals *likely* to respond or not to respond in a particular fashion, given the limited information content of such tests.

## **6. Implications for medical practice and research**

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For ‘risk factor tests’ and, commonly, for ‘predisposition tests’, any classification into “genetic” and “non-genetic” (including the one proposed here) is an arbitrary one, because the (limited) quality of information that DNA-based tests yield is not materially different from the quality of information provided by any other biomedical test. Likewise (but at the other end of the spectrum), for ‘full penetrance tests’ there is hardly any difference in the (high) information content of the test regardless of whether the test is DNA-based test or non-DNA-based test. Thus, from the standpoint of medical information, all tests (regardless of the analyte examined) should be classified as “medical tests” and the information gleaned should be regarded as “private medical information”.

### **6.1 Confidentiality**

The information content of any medical data, including that derived from *Genetic Tests*, is highly contextual and dependent on the particular cir-

cumstances and the questions applied to them. Thus, a series of genetic markers may hold no predictive information content whatsoever with regard to any health-related issues. However, at the same time, their information content with regard to a forensic or paternity examination may be extremely high. *This mandates that any genetic data, regardless of their apparent information content, be treated with the same high standards of confidentiality as any other personal or medical data.* This mandate applies to both clinical practice and research.

## 6.2 Protection of human subjects

Based on the information content of a test in a particular setting, it may be prudent to examine whether special considerations should be afforded not to the test, but to individuals who are the carriers of highly predictive medical information, regardless of whether or not this information is genetic in nature.

## 6.3 Genetic counselling

The need for genetic counselling as part of a genetic testing procedure is dependent upon the impact of the results on the individual and/or his/her family. It may be appropriate therefore to make a distinction between ‘full penetrance tests’ and ‘predisposition tests’ and ‘risk factor tests’, respectively. The former category has primarily implications on reproductive decisions, and may also affect other family members in important ways. Therefore, genetic counselling is generally viewed as standard of care for carrier detection and prenatal testing for these conditions. The latter two categories should be the domain, principally, of the personal physician who is in charge of the treatment. For example, the magnitude of increased relative risk of carrying the Factor-V-Leiden variant is certainly comparable to being a smoker, and should be managed accordingly.

## 6.4 Quality control and regulatory supervision

As is the case with all medical testing, only stringent quality controls and assurance, and appropriate accreditation of laboratories will ensure reliable results for patients. The history of much of genetic testing – having evolved from research-based tests to clinically applied tests, without necessarily going through the appropriate establishment of standards compliant with the guidelines of Good Clinical Practice – makes it imperative that appropriate standards be set.

## **6.5 Testing for conditions without currently available treatment**

Prenatal and postnatal testing for diagnostic purposes should be freely available, if these are indicated medically. Likewise, when requested by fully informed patients, postnatal predictive testing should be available (and offered) to them since negative test results may be as important as (or even more important than) positive ones. In addition, since most common complex diseases are multifactorial, they are also strongly influenced by environmental and life-style factors. More accurate assessment of the risk of a disease may empower people to make more informed healthcare choices, such as life-style changes that may favourably affect the overall risk. It should be noted, however, that predictive genetic testing for conditions for which no cure/prevention exists and which are likely to occur with delayed onset (e.g. Huntington's disease), there is general consensus that patients not preempt their children's independent decision, once they reach legal age, as to (or not to) having the test performed.

## **7. Social and legal aspects**

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### **7.1 "Controlled testing"**

It is of course acknowledged that many believe that all genetic tests should only be available through the healthcare system. Today, however, DNA-based paternity testing and certain predisposition tests (e.g. for hereditary hemochromatosis) are freely available, often over the Internet. The right to know about one's own body is a fundamental right. Although it is clearly preferable that such testing should occur in the context of a medical consultation, it should not be denied if requested by a well-informed and consenting adult. Regulatory approval of laboratories offering such tests may include the requirement of physician consultation before undertaking such tests.

### **7.2 Data protection**

All patients need assurance that all their medical data will be used only for the purposes authorised by them. However, many believe that patients should be free to relinquish control over the use of their personal samples and personal medical information for defined research purposes, particularly if confidentiality is assured by appropriate processes (such as after full anonymization of samples and data with appropriate systems auditing), and if data will only be used as part of an aggregate analysis.

### 7.3 Subject protection

To serve the intended purpose of delivering better healthcare to an individual, data derived from all medical tests, including genetic tests may need to be shared among a number of healthcare professionals involved in the care of the individual. This potentially opens the door to access of such data by unintended recipients, and misuse or abuse of the data in ways that are neither desirable nor authorised by the subject. Current concerns in this regard pertain mainly to possible discriminatory practices regarding employment and health and life insurance. To avoid such unintended use of genetic test data and, more broadly, of any private medical information, a societal consensus, including legal guidelines, will be necessary that should result in mandatory best practice principles regulating the legitimate use of such private medical data, and prohibiting its use in ways that are harmful to the individual.

## 8. Summary

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The most important characteristic of a medical test is its information content, and distinctions between genetic and non-genetic tests lack scientific rationale and are not helpful in providing guidance as to how to use as well as safeguard the respective information and to protect the carrier from misuse of this information.

It is important, however, to be aware that the potential of discrimination based on genetic information is an issue that is of great public concern. Public apprehension about genetic tests and the potential for stigmatisation and abuse by third parties must be taken seriously and misperceptions addressed so that they do not become ‘rate-limiting’ to healthcare. Most importantly, society must afford its members protection from discrimination based on any medical, including genetic, data. As long as this is not provided, current public contention that all “genetic tests” may give rise to discrimination, regardless of their (mostly limited) information content, may well be justified, setting up a self-perpetuating situation that will defy factual considerations.

Genetic testing, as defined herein, offers potential new advantages for individual healthcare as well as public health. While recognising this potential, it is also important to understand its limitations. Ideally, all tests should be assessed on the basis of their merits with regard to their predictive/diagnostic power rather than to the analyte used in the test.

The public concerns with respect to DNA-based testing in general, however, are recognised and acknowledged.

### *Glossary of Terms:*

<b>Analyte</b>	A biochemical or biological molecule whose qualitative or quantitative properties are analysed in a medical test.
<b>Sensitivity</b>	Likelihood that a person with disease will test positive. The higher the sensitivity, the lower the false negative rate.
<b>Specificity</b>	Likelihood that a person without the disease will test negative. The higher the specificity, the lower will be the false positive rate.
<b>Positive Predictive Value (PPV)</b>	Likelihood that a person with a positive test will have or develop the disease.
<b>Negative Predictive Value (NPV)</b>	Likelihood that a person with a negative test will not have or develop the disease.
<b>Penetrance</b>	Capacity of a gene variant to lead to the associated disease.
<b>Phenocopy</b>	Occurrence of the same disease, but not associated with the presence of a gene variant under consideration.

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## Chapter 9

### Ethical Issues

#### 1. Introduction

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Insight into the genetic variability among individuals and their response to drug treatments promises advances in the discovery, development, and use of drugs, as well as the potential to provide improved efficacy and greater safety. Understanding how patients will respond to a treatment, or if they will experience adverse events, will enable a targeted approach to treating or preventing illness. This information will result in the identification of genetically defined population subgroups that are likely to benefit most or least or even incur harm from a particular therapeutic intervention.

Because pharmacogenetics will influence both clinical research and medical practice, it is necessary to examine the ethical issues that may arise. Many documents and guidelines, both national and international, have addressed the pertinent issues of genetic data confidentiality [1], informed consent [2, 3], genetic profiling, clinical research and clinical practice [4], testing and sampling [5], patient data ownership and property rights [6].

The increase in public and private pharmacogenetic research has increased the visibility of the field and stimulated debate regarding potential ethical implications of pharmacogenetics in clinical research and medical practice. The discussion of some of the ethical issues is timely and relevant, given the public perceptions of genetic tests and genetic information in general.

#### 2. Current ethical guidelines for medical research and practice

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For the ethics of research involving human subjects [7], four basic principles have been defined that are widely accepted and used in biomedicine. These are (i) autonomy, the respect for individuals and their right to self-determination, (ii) beneficence, (iii) non-maleficence, and (iv) justice. In the Belmont Report, these principles have been defined with regard to clinical research on human subjects [8], and in the WHO's 1997 "*Report on Ethical Issues in Medical Genetics and Genetic Services*", the same principles are applied to genetic data in the context of both research and healthcare [9]. These principles may also be applied to pharmacogenetic data and research and their application to clinical practice.

- **Autonomy:**

The principle of respect for individuals and their right to self-determination acknowledges the subjects' beliefs and choices with regard to their participation in medical research or treatments. This principle includes the requirement for providing sufficient and unbiased information to enable them to make a considered decision. Additionally, subjects should understand the range of risk and the voluntary nature of their participation in the research or treatment plan, and the privacy protections regarding their medical data. This opportunity is provided when adequate standards for informed consent are satisfied.

- **Beneficence:**

The principle of beneficence protects the subjects by maximising the possible benefits and minimising the potential harms of participating in clinical research or medical practice. Research sponsors, investigators and ethics committees have the responsibility to gather systematic and comprehensive information about the proposed research in order to assess if the potential benefits justify the risks posed by the research. This assessment will assist the prospective research subject or patient in the decision whether to participate in the research or treatment plan.

- **Non-maleficence:**

The principle of non-maleficence protects research subjects and patients by minimising the potential harms of the proposed intervention. It embodies the spirit of the Hippocrates' Oath "*primum, non nocere*" (first, do no harm) and imposes on health professionals the duty to protect the patient from harm.

- **Justice:**

The principle of justice guides the fairness in distribution of the benefits and burdens of research. The selection of subject populations and the subject as a potential beneficiary of subsequent applications of the research are considered.

While these key ethical principles apply equally to the application of pharmacogenetics in clinical research and medical practice as well as in all other areas of medicine, questions have been raised whether additional ethical considerations and guidelines are needed for pharmacogenetics. This view, implying that genetic testing and the use of genetic information are categorically different from other medical tests and medical information, has been termed "genetic exceptionalism".



### 3. Understanding pharmacogenetic information

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Pharmacogenetic exceptionalism is the view that pharmacogenetic information is more sensitive than other types of medical information and has a higher potential for misuse and therefore requires additional measures to protect patient/subject confidentiality.

#### 3.1 Genetic data categorisation

All genetic data, including pharmacogenetic data, should be considered as part of the overall spectrum of medical data and not classified separately. Information content, not the nature (genetic or otherwise) of test or the data, might be the only criterion that exposes genetic data to potential misuse. Procedures for protecting the confidentiality of genetic data and specimens need to be established and should accommodate variations in predictive information content and impact of the data. The following describe the current predictability choices:

- Predictive Value Unknown – the case for the majority of pharmacogenetic data where the science is evolving and the associations are not consistent or well-established
- Predictive Value Low – one risk factor in a common complex disease, e.g. the clotting Factor-V-Leiden variant in thrombosis
- Predictive Value Intermediate – markers of predisposition in certain familial forms of common diseases, e.g. BRCA1/2 in breast cancer
- Predictive Value High – for rare single-gene diseases, e.g. Huntington's disease

The information content of any medical data, including pharmacogenetic data, is contextual and dependent on the particular circumstances and questions applied to the data. Pharmacogenetic data do not have specific scientific characteristics that distinguish them from other medical data.

#### 3.2 Considerations for public debate

As the vast majority of pharmacogenetic research is still in the exploratory stage, many questions arise as to how such information will ultimately be utilised by healthcare professionals and others. Many of these questions are fuelled by the current debate about the use of genetic information in general, and include:

- How should healthcare professionals and patients handle pharmacogenetic testing and data predictive of a drug response?

- Will the presence of pharmacogenetic information in the medical record compromise individual liberties, and expose individuals to invasion of privacy, or to discrimination?
- May an employer discriminate against current or prospective employees on the basis of their pharmacogenetic data?
- May a health insurer or provider discriminate against an individual on the basis of his or her pharmacogenetic data, or may a life insurance company reject an individual on the basis of his or her pharmacogenetic data?

In order for an informed debate to take place, it is evident that all stakeholders must have sufficient knowledge about the nature and potential application of pharmacogenetic information as applied to healthcare.

### **3.3 Reflecting perceptions and need for education and rational public policy**

The current discussion about genetic information is influenced by the perception that all genetic data are deterministic, convey exceptionally high information content, and are highly relevant with regard to both the genetic marker carrier and his/her relatives. However, the vast majority of our physical and psychological characteristics are not simply a consequence of inherited properties but are also influenced by external factors (environment, life-style, optimisation of drug therapy, etc.).

While tests for certain rare, monogenetic disorders carry such high specificity and sensitivity that the perception of determinism may appear justified (such as in the case of Huntington's disease), there are tests for non-genetic disorders that carry similar information content (e.g. HIV). Pharmacogenetic tests are expected to be much less predictive than those of single gene disorders and to carry more probabilistic information, similar to determination of blood pressure or cholesterol levels. Inappropriate generalisation from the few, highly predictive genetic tests, to the much less predictive pharmacogenetic tests, has led to some perceptions about pharmacogenetic tests as carrying a higher potential for misuse, thus requiring a greater degree of protection. Education regarding the context and value of pharmacogenetic data needs to be developed for both general and medical audiences. This education will help dispel misunderstandings of genetic exceptionalism and counter any unwelcome tendencies toward discrimination based on pharmacogenetic information.

If society continues to embark on genetic exceptionalism or accepts any discrimination based on pharmacogenetic test results, then the recom-

mendations based on information content, rather than on nature or source of data, will become irrelevant. It is extremely important to reinforce rational public policy and dispel public misunderstanding.

## **4. Autonomy issues and pharmacogenetics**

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### **4.1 Clinical research/study: Pre-approval**

Based on the principle of self-determination, participation in pharmacogenetic research should be voluntary. Where possible, this includes not making participation in the actual clinical study contingent on participation in the pharmacogenetic sub-study. Early clinical research or studies conducted for exploratory, hypothesis-generating or hypothesis-testing purposes during pre-approval phase of new therapies should also be subject to this principle of self-determination and autonomy. Thus participation in pharmacogenetic testing, as in any clinical study, should be voluntary and independent of participation in the actual clinical study.

Clinical research or studies involve clinical decisions and well defined inclusion criteria or subject selection based on pharmacogenetic testing (i.e., core selection based on having a particular genotype). In instances, where pharmacogenetic test results provide for an inclusion or exclusion criterion, then the subject's agreement to participate in the clinical study will be linked with the subject's agreement to participate in pharmacogenetic testing; therefore, the subject's participation in the pharmacogenetic portion cannot be independent of the clinical study participation.

#### **4.1.1 Confidentiality**

Confidentiality is a complex concept that is both intrinsic and instrumental, involving several different, but overlapping personal interests [10]. Control over highly personal information is central to the goal of confidentiality within the pharmacogenetic setting. Patients should be informed about who will have access to their pharmacogenetic test results, and must be reassured that no parties, other than the authorised ones they are informed about, will have access to their pharmacogenetic test results. In particular, the sharing of samples among several research groups and across borders must be considered in accordance with international and local laws and practices.

A commitment to adhere to privacy and ethical standards consistent with applicable laws, rules, and regulations is imperative in conducting clinical research.

#### 4.1.2 Informed consent

Informed consent is critical to all clinical research, including pharmacogenetic studies. The substance of the informed consent process emphasises and provides for self-determination, privacy, and confidentiality. While various medical tests and procedures are routinely carried out in the conduct of clinical studies or medical practice, these tests and procedures generally do not require a separate consent to be signed. With regard to pharmacogenetic research studies, involving pharmacogenetic testing, a separate informed consent has become quasi-standard, based primarily on (i) the unwarranted perception that such pharmacogenetic tests will render categorically different information from other medical tests, (ii) the justifiable view that the meaning of most pharmacogenetic tests is largely unclear, but may occasionally carry important information, (iii) the desire for ethics committees to have all information pertaining to pharmacogenetic research on a separate informed consent form so that approval and management of the clinical study could proceed without approval of the pharmacogenetic study. Thus, in clinical pharmacogenetic studies, a separate pharmacogenetic informed consent is the conservative option and the ethics committee reviewing the proposed clinical study protocol must also review and endorse the additional pharmacogenetic informed consent. However, as the field develops, more studies are likely to include genotype as an integral part of determining a drug's profile and/or as an inclusion or exclusion criterion, thus shifting the quasi-standard towards a single consent form.

The following items should be included in the pharmacogenetic informed consent and applicable forms:

- **A statement of clear rationale:**  
Provides justification for conducting the study, usually including an introduction to the concept of pharmacogenetics.
- **Fields of study for sample use:**  
The field may be *narrow*, and restricted to a certain diagnosis, indication, or medicine, as defined by the single protocol or *broad*, and permitting research in several or all-possible indications. Likewise the scope of pharmacogenetic analysis may vary from specified polymorphisms to genome wide scans. Generally, the narrower the scope of the consent, the fewer potential issues it will raise. Some ethicists have questioned the permissibility of obtaining broad consent, arguing that society must pro-

tect individuals from consenting to outcomes that cannot yet be foreseen. Others have maintained that narrow scope results in limitations to the advance of medical knowledge and takes no account of future relevant advances that may occur in this emerging field [11, 12].

- **Length of time the samples will be stored:**

The time range for storage of the samples may be for the duration of the study to many years thereafter, in order to address questions at a later point in the development programme, as long as applicable regional rules and regulations are met.

- **Sample coding:**

The degree of sample coding is strongly associated with the degree of data and privacy protections provided; thus, sample coding has been structured, by consensus, into five categories. These categories have been adopted by the regulatory authorities [13] as well as by industry [14]. The table below provides the industry (Pharmacogenomic Working Group, PWG) and the regulatory (European Medicines Agency, EMEA) terminology. These are the current, established comparisons:

PWG	EMEA
Identified	Identified
Coded	Single-Coded
De-identified	Double-Coded
Anonymized	Anonymized
Anonymous	Anonymous

It must be recognised that the degree of data privacy, except in the case of anonymous samples where only the subject's pharmacogenetic data are collected, is ultimately dependent on the standardised operating procedures applied to the databases and their audit trail. The method of sample encryption has a direct impact on the data handling and thus the application of the data. For example, while anonymized data may be valuable for exploratory research, it may not meet the requirements for regulatory audit or for informing subjects of relevant findings.

- **Options to withdraw the sample:**

The option for a patient to withdraw from a clinical study is a critical element of all clinical research, derived from the Nuremberg Code [15] and this option protects the patient from interventions that affect his/her well being. However, its application to samples, which makes anonymization impossible, is viewed controversially by legal, regulatory, and ethics experts, but must be respected as part of the spectrum

of patient autonomy. Some have argued that, because a patient may change his/her mind later, a waiver of sample withdrawal should not be permissible; others find that as long as this is clearly described in the informed consent, such a sample waiver is acceptable.

- **Expected benefits to the patient or others (if any):**

In most cases, the benefits to patients are currently undergoing hypothesis testing or exploration, and the benefits of the drug and pharmacogenetic differentiation for improving the potential therapeutic outcomes, still need to be established. This point must be clearly stated in the informed consent.

- **Potential risks:**

These might include the direct additional risks of obtaining the pharmacogenetic sample, which are generally minor (the risks of a phlebotomy) and the indirect risks associated with breach of privacy. These risks must be clearly indicated in the informed consent.

- **Treatment of and participant's access to the study results:**

Informed consent forms should clearly state whether or not results of pharmacogenetic tests will be conveyed to participants. Communication of preliminary pharmacogenetic test results to study participants is often not very meaningful, in particular if the clinical relevance of the test has not yet been established. Also, if samples are anonymized, feedback of results to participants is not possible. However, in the case of industrial sponsorship, publication of the aggregate results of studies is usually included in reports issued to research physicians. Still, some advocate that all test results must be made available to participants, and that informed consent forms, which require participants to waive this option, are not acceptable. Even if patients are given access to the results, a provision must be included granting those participants who do not want to learn of their results, the right *not to know*. However, in the case of individual results as opposed to group results, many argue that relaying of non-validated information poses a risk to the participant due to data misinterpretation or misuse; also, such non-validated information or preliminary research data has no meaning to the participant. Given that pharmacogenetics is in its infancy, only occasionally will precise, useful, validated information be obtained as a result of pharmacogenetic research.

- **Handling of intellectual property generated from the use of samples:**

While generally not a topic relevant to clinical trials, the issue of sharing benefit with individuals or the community following the provision of a DNA sample has been raised. This would be inappropriate, as it is not a feature of clinical studies, which have relied on altruism. The notion of sharing is derived from research on minority populations,

not the framework of global research undertaken for pharmacogenetics. This should be made clear in the informed consent process and documents.

- **Ownership or custodianship of sample:**

There are divided opinions about who, if anyone, should own the sample – investigator, study participant, intermediary, etc. One compromise solution suggested is based on *English Common Law* under which ownership of the body and its parts is not possible, thus rendering whoever holds the sample a good-faith custodian. The consent should make clear the details of ownership or custodianship, as appropriate.

- **Ownership or custodianship of data:**

The informed consent should clearly state the ownership of data derived from pharmacogenetic testing along with a clear statement regarding potential intellectual property derived from the data.

- **Access to samples and data:**

Collected samples and data are handled by a variety of processes, including analysis, storage, audit trails, third parties, submission to regulatory authorities, etc. The informed consent document should describe sample storage and access, along with any applicable restrictions and legal requirements.

- **Liability of the investigator:**

As with all other clinical trials, it should be clearly specified the extent to which the investigator and/or sponsor conducting the trial will be held responsible if the participant suffers bodily harm or other damage. No informed consent, whether oral or written, may include any exculpatory language through which the subject or the representative is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution, or its agents from liability or negligence.

#### 4.1.3 Possible exceptions to informed consent

Concerns have been raised that potentially informative repositories of samples, which were collected before the advent of widespread usage of explicit written informed consent for genetic studies, would not be accessible to research. Contacting participants of these studies to make use of these samples is no longer feasible, and is often impossible. For Exceptions to Informed Consent, it is recommended that it be permissible to use such samples if the research protocol has been approved by the appropriate institutional ethics committee(s), including an IRB/IEC's decision for exception, provided this exception is not in conflict with local laws, rules, and regulations.

## 4.2 Medical practice: Post-approval

If the information obtained from a pharmacogenetic test is required to administer a treatment or drug appropriately and safely, either based on the drug's license and label or on standards of medical use/practice, then the pharmacogenetic test is no longer optional and within the domain of the patient's right for self-determination and becomes part of good medical practice. However, the choice of the treatment or drug remains at the physician's discretion followed by the patient's input and acceptance of such treatment; this allows patients who decline pharmacogenetic testing to choose, if available, alternative therapies where such tests are not required; the patient also retains the right to choose not to be treated.

### 4.2.1 Confidentiality

As with results from all medical tests, patients should be informed about who will have access to their pharmacogenetic test results and must be given the reassurance that procedures are in place to prohibit access by non-authorised parties. However, it must also be clear that given the reason for obtaining the test results, the reason will have to be communicated, explicitly or implicitly, to a number of other participants in the patient's extended healthcare team (e.g. pharmacist, healthcare provider, etc). If sharing the reason or test result with others on the healthcare team is not acceptable to the patient, then the test should not be conducted and alternative treatment options be sought.

### 4.2.2 Informed consent

Pharmacogenetic tests carried out in the course of a patient's treatment should be clearly defined for the patient including the clinical value and the significance of these test(s). The definition for the pharmacogenetic test(s) should include information pertaining to:

- **Pharmacogenetic Testing Rationale:**  
Medical treatment and associated pharmacogenetic testing to allow decisions regarding treatment choice.
- **Sample Storage Duration:**  
Samples used for obtaining test results to support a treatment decision are usually destroyed after test results are verified.
- **Sample Coding:**  
Not applicable, as sample(s) cannot be coded in this setting. However, confidentiality of test results needs to be maintained.
- **Post-Approval Surveillance:**  
In some situations, samples may be stored longer term in order to assess medical outcome as part of post-approval epidemiological and drug sur-



veillance initiatives. In such cases, patients should be clearly informed of this activity and where appropriate, sample and data handling to be addressed as outlined for pharmacogenetic research.

## **5. Beneficence and pharmacogenetics**

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The term benefit, as used in research context, refers to something of positive value related to health or welfare. The benefit of pharmacogenetic studies includes both the gathering of comprehensive information for the proposed research and the potential of developing better treatments for the condition investigated. Also, since pharmacogenetic research may affect the individual subjects, the families of the individual subjects, society at large and/or special groups of subjects in society, those making decisions about the justifiability of research must consider the scientific validity of the research.

A number of variables go into such judgments regarding pharmacogenetic research, including the condition of the particular population involved, and the nature and level of the anticipated benefits. This assessment presents both an opportunity and a responsibility to gather systematic and comprehensive information about proposed research, i.e., whether the proposed research is properly designed. The research sponsors and study investigators are therefore responsible for ensuring that the subject understands the benefit of novel clinical research and intervention. This applies whether the clinical studies are hypothesis generating or testing studies or those designed for confirmatory or enriching purposes.

In medical practice, if a drug is marketed with a pharmacogenetic test for a specified population, then questions might arise why the patient is being prescribed the specific drug if either the pharmacogenetic test has not been performed, is inconclusive or shows the patient has minimal chance of gaining therapeutic benefit from that drug. However, in medical practice, the decision about how to prescribe a medicine rests with the physician, whether the use is consistent with the label or is “off-label” use. Therefore, it is ultimately at the physician’s discretion the decision to prescribe a drug with or without ordering an accompanying pharmacogenetic test. In this case, use of the pharmacogenetic test results would be based on the physician’s assessment of risk and benefit for prescribing that drug to the specific patient.

Ethically challenging situations may arise if post-marketing research subsequently shows a pharmacogenetic test to be useful for stratifying popu-

lations into subgroups with greater or lesser likelihood of deriving a benefit from a particular drug even though sufficiently compelling evidence to trigger a re-assessment and a change in the label of the marketed drug may be lacking. In this case, the benefit to the group found to respond less well may still be substantial, yet there may be pressure from third-party payers to no longer reimburse the drug in these patients, potentially denying them the possible (albeit reduced) benefit that they may still derive from the drug. Resolution of these issues will require dialogue among patients, physicians, payers, and public officials; this is similar to other situations where constraints in healthcare funding raise difficult questions about eligibility of patients for treatments with a poor cost/benefit ratio.

As with all other medical tests and treatments, the physician will be the patient's main source for information and advice on pharmacogenetic testing and test results. She/he will advise the patient about the outcome of any existing pharmacogenetic information, and the considerations relevant to a prospective pharmacogenetic test or treatment based on the results of a pharmacogenetic test. Pharmacogenetic tests, which provide the ability to predict a drug response, may either confirm or restrict access to certain therapies and/or treatments. For these reasons the physician plays an important role in helping the patient understand the limitations of various treatment options.

## **6. Non-maleficence aspects of pharmacogenetics**

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Some of the concerns about the possible misuse of pharmacogenetic information often come from how society currently reacts to all genetic information. To realise the benefits of pharmacogenetics, a framework should be developed that prevents misuse of information and a system that minimises collateral information. Careful consideration of the structures and procedures that protect confidentiality while allowing and safeguarding the flow of information for research is essential [16].

Questions, on whether the use of pharmacogenetic testing is likely to create disadvantages for patients, are commonly focused on the issues of possible discrimination regarding health and life insurance and, to a lesser degree, employment. In comparison with genetic testing for rare single-gene disease susceptibility, pharmacogenetic testing is less likely to pose major challenges. Issues arising may be similar to those from testing for risk factors (genetic and non-genetic) for common complex diseases. Both are expected to provide, in most cases, probabilistic assessment or prediction of outcome rather than

deterministic information. However, if a poor understanding of the specific limitations regarding the predictive value of these pharmacogenetic tests results in their use to the disadvantage of individuals, then pharmacogenetic testing might carry the potential for discrimination and may therefore raise complex ethical issues that are neither evidence-based nor justifiable.

## 6.1 Privacy

Access to an individual's genetic data related to disease susceptibility is currently limited; the very nature of pharmacogenetic data calls for a rather more liberal position regarding its intended use for improving the patient's prospect for a successful treatment. In order to benefit from the collected pharmacogenetic data, this data needs to be shared among some participants in the healthcare process. Thus, the prescription for a drug that is limited to a group of patients with a particular genotype will disclose the treated patient's genotype to anyone involved in the patient's healthcare process, both at the medical and administrative levels. The only way to limit this inadvertent and unintentional public disclosure of a patient's genotype (not revealing the actual data, just the information) would require him/her to sacrifice the benefits of the indicated treatment for the sake of data privacy and confidentiality of information. However, it is inappropriate to assume that such pharmacogenetic information requires a higher level of privacy protection than that currently granted for prescribing information. Privacy of a patient's pharmacogenetic data must be handled as any other medical information. The current EU Data Protection Directive, the US HIPAA Act 1996, the UK Data Protection Act 1998, and similar guidance or related legislation apply to personal identifiable data, including all medical data [17, 18, 19].

## 6.2 Discrimination

The potential scenarios for discrimination against individuals based on pharmacogenetic data are being currently debated. These individuals include those identified as (i) having a low likelihood of responding to a specific treatment, (ii) needing unusually high prescription doses (i.e., ultrarapid metabolisers), (iii) more likely to suffer a serious adverse event if alternative treatments are not available, or (iv) having a genotype known to require treatment with a more expensive medicine. The debate is based on the view that such individuals might represent a differential risk to health or life insurance underwriters.

Such potential for discrimination is not only associated with genetics and pharmacogenetics. For example individuals needing expensive or long-

term treatments might also be sometimes discriminated against. Whatever the potential reason, unjustified discrimination regarding access to medicine is not acceptable.

### **6.3 Requirement for protection from discrimination based on pharmacogenetic testing**

Practically speaking, the critical issue is not only the sensitive nature of the medical information, and how it may be disseminated and disclosed, but how and to what end it is used. Therefore, in the interest of both individuals and society, there should be a consensus-derived framework of rules and regulations that governs the legitimate uses of pharmacogenetic and any other medical information to improve healthcare and optimally protect the individual, while finding a reasonable and acceptable compromise solution regarding communal interests. A number of such “anti-discrimination” bills on genetic testing that aim at setting such rules are currently under review in a number of European parliaments as well as in the U.S. legislature. The generation and acquisition of personal medical information and the practical application of such data should always be contingent on the individual’s free choice and consent.

## **7. Justice and pharmacogenetics**

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The principle of justice guides the fairness in distribution of the benefits and burdens of research. Issues to be considered are the selection of subjects for clinical research and the individual subject and the community as a potential beneficiary of subsequent application of findings from the research. This principle applies equally whether the pharmacogenetic research is conducted in special populations, or in emerging economies and developing nations.

### **7.1 Fairness of distribution and potential beneficiary concerns**

Concerns have been raised about the possible effects of pharmacogenetic approaches regarding existing responder subgroups, as well as with regard to creating new, genetically defined, responder subgroups, and what, should any benefits or burdens might arise, if they are different from traditional research efforts.

#### **7.1.1 Ethnicity**

When the results of a pharmacogenetic test are used as an inclusion or exclusion criterion for research or eligibility for treatment, relative genotype prevalence may vary between ethnic group. However, while ethnici-

ty has long been used as a (poor) predictor of clinical response, pharmacogenetic approaches carry the promise of providing more specific information based on actual measurements of likely drug efficacy or toxicity rather than on ethnic or racial stereotypes, thus replacing racial stereotypes with a more predictive response to guide treatment choice for some drugs [20]. If fairness of distribution and potential beneficiary are not addressed by ignoring ethnicity (based solely on an ethnicity factor and not on pharmacogenetic test results) then the justice principle is not implemented.

### 7.1.2 Disease subgroups

Another concern relates to the possibility that in the course of pharmacogenetic research new disease subgroups are identified and defined which are relatively small, such that the development of a subgroup-specific medication is no longer economically feasible under current paradigms. These subgroups may therefore remain untreated in favour of broader indications. While disease subgrouping, in the sense of a newly recognised molecular differential diagnosis, may be novel, the problem is basic to all healthcare systems and related to affordability of potentially expensive treatments for small patient groups. It should be recognised that it is not the application of pharmacogenetics, but the nature of the disease that is at the basis of medical sub-entities. Pharmacogenetic testing does not make patients 'non-responders'; it merely allows them to be better identified. Unrecognised, they would simply not benefit from the standard treatment used for the indication as a whole, yet stand to experience its side effects.

## 7.2 Emerging economies and developing nations

Pharmacogenetics may have the potential for improving drug treatment and quality of life in developing countries. But as with all other advances in healthcare, access will depend on the affordability of such treatments and the availability of the appropriate infrastructure [21].

Public health and international aid efforts should strive to make the benefits of pharmacogenetics available to the developing world, so as not to increase healthcare disparities. Given the reality that basic medical needs are often not met in some of these countries, the use of complex pharmacogenetic treatment algorithms will not feature prominently for first-line treatment at this time.

The justice principle provides that fairness of distribution and concerns of potential beneficiaries be addressed for all research. Thus, pharmaco-

genetic research needs to be considered in the interests of the emerging economies and developing nations as well.

## **8. Recommendations**

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For Education and Rational Public Policy, it is recommended that:

- Pharmacogenetic information should be considered part of the spectrum of all health information.
- Public policy should reject the notion of genetic exceptionalism derived from pharmacogenetics which, even if inadvertently expressed, will impede biomedical research and healthcare delivery.
- All genetic data, regardless of their apparent information content, should be treated with the same high standards of confidentiality as any other personal or medical data.
- Public and professional education must be greatly stimulated to improve understanding of pharmacogenetics and the meaning of pharmacogenetic data.
- Public policy should provide safeguards against the inappropriate use of medical data, including pharmacogenetic data.

For Informed Consent documents, it is recommend that “field of use” needs to be well described but that appropriate broad use may be also permitted.

For Intellectual Property, it is recommended that the issue of handling of intellectual property generated from the use of samples and data be clearly addressed in the Informed Consent documents.

For Exceptions to Informed Consent, it is recommend that it be permissible to use such samples if the research protocol has been approved by the appropriate institutional ethics committee(s) provided this is not in conflict with local laws, rules, and regulations.

For Emerging Economies and Developing Nations, it is recommended that public health and international aid efforts should strive to make the benefits of pharmacogenetics available to the developing world.

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## Chapter 10

# Pharmacoeconomic Considerations in Pharmacogenetics

### 1. Introduction

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Pharmacogenetics is expected to have a significant influence on the practice of medicine with regard to raising the likelihood that medicines will be effective and safe for each individual to whom they are prescribed. The ability of healthcare systems to integrate new therapeutic strategies, with regard to both budgetary and logistic considerations, is a key public health issue. Healthcare systems have undergone significant reforms over the last decade to adjust to the demands of an increasing fraction of the population who are elderly patients, of emerging changes in disease patterns, of important strides in healthcare technology, and of the globalisation of healthcare issues.

Pharmacogenetics may impact healthcare economics by affecting a variety of areas, including the cost of laboratory diagnostics, drug treatment, hospitalisations (including surgical interventions), and healthcare administration, as well as by its impact on performance and profitability of the pharmaceutical, diagnostic, and biotechnology industries. In some of these sectors, net savings may be the result of implementing pharmacogenetics whereas in others, there may be increases in costs.

It is important to note that – quite independently of any particular technological advance which may result in improved cost-effectiveness of a particular intervention – society's expectations of what the standards of healthcare should be, along with its sense of entitlement of access to these increasingly more sophisticated healthcare provision standards, have commonly shown a pattern of outpacing advances in cost-effectiveness of healthcare delivery. This almost inevitably results in increasing overall healthcare expenditures over time; all that novel technologies and approaches are likely to deliver is a curbing of the rate of increase of overall healthcare expenditures.

Historically, the requirements for the investigation and registration of new drugs have gradually increased, beginning with quality in the early 1900's, through safety in the 1930s and efficacy in the 1960s to pharmacovigilance in the 1980s. As a natural follow up to these historical developments, the early 1990's have witnessed the emergence of pharmacoeconomic evaluation. Increasingly, cost-effectiveness parameters are con-

sidered by healthcare payers, including social security systems, private insurance and health maintenance providers, as well as by hospitals, healthcare workers, and patients. Pharmacoeconomic recommendations, good practices and guidelines have already been issued in several countries including National Institute of Clinical Excellence (NICE) in the UK, the Pharmaceutical Benefit Advisory Committee (PBAC) in Australia, Canada, Portugal, The Netherlands, France and Finland amongst others. Not surprisingly, industry has often regarded pharmacoeconomic assessment as a “fourth hurdle” in drug development (after quality, safety and efficacy). Available evidence and trends suggest that pharmacoeconomic evaluations will become an important component in provision of healthcare by all stakeholders in the system. As with new drugs, new technologies such as pharmacogenetics may also require pharmacoeconomic assessments before they are widely introduced.

As evidence-based-medicine (EBM) and evidence-based healthcare (EBHC) become more refined and are used increasingly to guide prescribing, the demand for more efficient use of resources will continue to become stronger [1]. While pharmacogenetic testing may appear a logical tool for improving decisions based on EBM, its costs and influence on health outcomes will require careful analyses on a case-by-case basis to validate, or invalidate, this assumption.

In the following, we shall consider various aspects by which the prescription of drugs based on a pharmacogenetic test may influence pharmacoeconomics, including the assessment of health outcomes, of cost/benefit considerations, of clinical trial design, and of pricing strategies. It is important to understand that our current experience regarding the impact of pharmacogenetics on health economics is extremely limited, as is, therefore, the availability of any validated modelling algorithm. Consequently, most of the discussion in this chapter is quite speculative, based primarily on hypothetical considerations, and awaits further confirmation by real-life experience with actual examples. On the other hand, it is important to keep in mind that pharmacogenetic testing is principally no different than other medical tests currently used to stratify patient populations or for screening, and the respective pharmacoeconomic considerations are likely to be applicable to pharmacogenetic tests as well. It clearly is an important challenge to anticipate how pharmacogenetics will affect medical practice, patient needs, and healthcare payer arbitrations.

## 2. Health outcome assessment

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The objective of pharmacogenetics is to use genetic information in guiding prescribing decisions toward potentially providing better healthcare by delivering more effective medical treatment while reducing the use of inappropriate drugs or inappropriate doses. Based on the use of such information, a patient is expected to show a higher likelihood of responding to a given drug quicker or more completely than had this information not been taken into account. Overall quality of life is expected to improve with reduction in morbidity and mortality from the disease under treatment. Furthermore, since adverse drug reactions (ADRs) are a significant burden on healthcare resources, costs directly related to ADRs (decrease in morbidity, hospital admissions, duration of stay in hospital, etc) are also expected to decrease significantly. Minimising the risk of ADRs may improve patient adherence to the prescribed regimen, which further increases the likelihood of a favourable therapeutic outcome [2]. As a result, the use of pharmacogenetics-guided drug treatment is expected to favourably influence long-term health outcomes in a patient.

However, in solidarity-based healthcare systems (both national health plans as well as individual healthcare provider/payer organizations), health outcomes must always be considered with regard to their impact both at an individual level and collectively across all participants of a given healthcare system. The decision to include any new technology, including a pharmacogenetic test, into a healthcare system requires an adequate level of evidence that it improves health outcome at a societal level. Therefore, the design of a health economic (or pharmacoeconomic) study is important. Assessments of parameters such as cost, effectiveness and quality of life assist in balancing a costly intervention for a few with less costly interventions for many.

Obviously, these considerations will have to factor in the probabilistic nature of the success of pharmacogenetics-guided treatment, as is the case with all medical interventions.

The establishment of validated pharmacogenetic approaches may face certain challenges. The need to select subpopulations may lead to difficulties in the recruitment of sufficient numbers of appropriate study participants, although one may anticipate that smaller sample sizes than those traditionally used will be adequate given the expected improved efficacy of the drug.

It is not inconceivable that new drugs may undergo two pharmacoeconomic evaluations. One evaluation would compare the new drug with existing therapy in the absence of a pharmacogenetic test whereas the other would do so with the integration of the appropriate pharmacogenetic test to see if the cost-effectiveness can be achieved or enhanced. It is clear that the ability to do the former comparison may be restricted to these cases where there is no compelling safety argument to use the test, and in general to drugs whose approval process was not based on pharmacogenetics-based recruitment into pivotal trials.

The factors that need to be considered before conducting formal pharmacoeconomic analysis of pharmacogenetics include, but are not limited to [3, 4]:

- Therapeutic index of the drug
- Frequency of the variant allele in the population concerned (note that there may be ethnic variations)
- Availability of the pharmacogenetic test and time required to obtain results
- Cost of the test
- Strength of genotype-phenotype (i.e. treatment outcome) association of the test
- Magnitude of the test's impact with regard to enhancing efficacy or reducing ADRs
- Severity of the disease to be treated and/or of the ADRs to be reduced

### **3. Factors affecting the economic impact of pharmacogenetics**

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In approaching any cost assessment of a therapy that utilises pharmacogenetic information, the costs that must be considered and evaluated include direct costs, indirect costs, intangible costs, and external (or informal) costs. These should then be juxtaposed to the potential savings (direct and indirect) that may accrue. It is important in these considerations to differentiate between:

- pharmacogenetic testing that defines eligibility (based on likely efficacy and/or lack of ADRs, i.e., stratification), and
- pharmacogenetic testing that aids in finding the correct dose for the individual patient.

In addition, it is important to consider that – particularly as pharmacogenetic approaches are included already in the design and execution

of pivotal registration trials – the use of a pharmacogenetic test may be:

- **Optional:** this would mostly apply to the situation where the pharmacogenetic approach is discovered/developed after market approval of the drug, and will be applicable primarily to tests that improve efficacy and/or dose finding; or
- **Mandatory:** this would apply to situations where patient recruitment into the registration trial was based on the pharmacogenetic test (i.e. there are hardly any data on the drug's performance in test-negative subjects) and the label restricts prescription to test-positive individuals, or where the discovery of a pharmacogenetic marker markedly improves a drug's safety profile (which may eventually result in an amendment to the label, making pre-treatment testing mandatory).

### 3.1 Direct costs

Direct costs are those expenditures directly related to the therapeutic regimen as well as the associated (pharmacogenetic) test.

#### 3.1.1 Drug pricing

The cost of preclinical and clinical research and development of new medicines is substantial, primarily due to the significant uncertainty factor and the high failure rates that drug discovery and development faces. Since only a small minority of all projects progress successfully through the successive phases of preclinical research and clinical development, the profitability of any research-based pharmaceutical company needs to take into consideration the cost of all projects that are terminated somewhere along this path. The pricing of a successful molecule will reflect both the recovery of this investment and the value it represents to the patient. These considerations are true of both conventional drug development as well as the development of pharmacogenetic-based therapies. A number of factors may influence the pricing of innovative drugs that employ pharmacogenetic screening.

Some expect pricing of these drugs to be higher than drugs that do not require such screening, for a number of reasons such as:

- Increased value due to improved efficacy rates and/or reduced adverse event rates
- The introduction of pharmacogenetic tests in clinical trial protocols will increase the complexity and the cost of clinical development (see Chapter 5 on “Impact of Pharmacogenetics on Drug Discovery and Development”) that must be recovered through pricing.

- The introduction of patient-stratifying pharmacogenetics will commonly result in the restriction of eligibility for the drug to a target population that represents a subset of all patients with the indication/disease in question, and thus will result *a priori* in a smaller target market.

Others believe increases in these costs may be offset by factors such as:

- Improved decision making during clinical development resulting in better compound selection, reduced attrition rate, improved patient selection criteria and trial design
- Increased market penetration, driven by enhanced therapeutic outcomes such as greater efficacy and/or fewer ADRs and better satisfaction on the part of stakeholders (payers, physicians and patients). Therefore, depending on the degree of superiority of a pharmacogenetics-based drug, the effective reduction of actual sales (if any) may not correspond to the smaller size of the genotype-specific market segment. Thus, the overall number of patients receiving the drug and/or the total sales volume may be less, equal, or even greater relative to competing drugs with their lower overall efficacy resulting in poorer patient adherence as well as lower market penetration. In limiting the target population by selecting patient subgroups (likely responders or those less likely to develop ADRs), marketers may therefore expect smaller, equal, or larger volumes of drug sales, on a case-by-case basis.

The greater likelihood of treatment success, or the lesser likelihood of ADRs, based on pharmacogenetics-guided prescribing may justify a higher price on a per patient basis as greater value is delivered, and costly unsuccessful treatment or costly ADRs are reduced. Differential dosing, as an outcome of pharmacogenetic testing that predicts the individual patient's pharmacokinetic or pharmacodynamic response, may create additional challenges for appropriate price setting.

### 3.1.2 Pharmacogenetic tests

Costs for diagnostic assays involving DNA sequence variant analysis range from \$75 to well over \$2,000 (for de-novo sequencing of whole genes). This, however, is such an unlikely scenario for a pharmacogenetic test that it does not warrant further consideration. A screening test to assess up to 30-50 alleles of a single gene, such as CYP2D6, may be expected to cost, on average, \$200-\$500.

There is an ongoing vigorous debate on who will pay for these pharmacogenetic tests. In several countries, different authorities are charged with

the reimbursement and/or price setting for medicines and medical tests. In some cases, the patient might be willing to pay for the additional likelihood of a positive clinical outcome associated with his or her particular genotype. When there are clear indications of a medical need and adequate economic incentives, the cost of the pharmacogenetic test will, in all likelihood, be covered by the insurer or healthcare system. However, in many cases, particularly when there are competing drugs and only one of which warrants a pharmacogenetic test before its use, the patient or payer may be less likely to opt for the additional expense unless there is significant gain in healthcare benefit. In such instances, the test might be included at the drug manufacturer's expense with the first prescription. The commercial gain from a therapeutic regimen may also be a major determinant of the price of the test associated with its use. For instance, drugs such as antibiotics that are likely to be used for short-term and have an acceptable therapeutic window are less likely to support the cost of a complex assay. Therefore, it is more likely that the first examples of test plus drug combinations will be for either high cost therapies such as cancer chemotherapy, or for treatment of chronic diseases such as cardiovascular diseases [3-6].

There will be pressure to constrain the cost of pharmacogenetic tests, as no one wishes this to be the factor that limits access to a beneficial therapy. Nevertheless, it is unlikely that the cost of some pharmacogenetic tests, owing to their complexity, will decrease to within the range of routine clinical chemistry tests or immunoassays. As with other diagnostic or predictive medical tests, the use of pharmacogenetic tests raises several specific issues:

- Value-for-money assessment of the test will be requested by payers (and, in some countries, by regulators) and will need to be addressed by specific comparative pharmacoeconomic studies (this applies only to the situation where the test is optional).
- Basic information about the test in terms of sensitivity, specificity, and positive and negative predictive values will be necessary in medical practice and require appropriate assessment of the test. Where reference non-pharmacogenetic diagnostic tests are lacking to assess true and false positives and negatives, only observations from pharmaco-epidemiologic cohorts are currently anticipated to allow the assessment of these basic properties.
- As with any consumer goods, the retail price of the test may be influenced, in addition to the perceived value delivered, by sales volume. Demand for a test at very high sales volumes may allow the price to be

decreased, whereas a more limited volume of sales will generally result in a higher price.

- Experience with medical devices suggests that the generation cycle times of pharmacogenetic tests may be more rapid than the introduction of newer drugs. Thus, a superior test may become available shortly before, or after a pharmacogenetic trial for registration purposes is completed, raising the issue of demonstrating equivalency on the level of analytical accuracy versus clinical utility. Regulators will have to address this issue.

### 3.1.3 Cost for data storage and management of pharmacogenetic information

Apart from potential additional costs associated with differential storage of genetic data based on the notion that all genetic information is categorically different and ethically more problematic ('genetic exceptionalism'), the management and storage of pharmacogenetic data is not expected to generate any costs different from that of the appropriate management and storage of any other medical data. It should be pointed out that whereas the notion of genetic exceptionalism is not uncommon among the public, there is no justifiable reason or need to store pharmacogenetic data in a fashion different from the (high) standard with which all medical data ought to be stored.

## 3.2 Indirect costs

Indirect costs theoretically encompass all resources expended other than those directly incurred in the treatment of a disease [7]. In practical terms, these are the costs arising from the impact of the disease on the patient's (and his caregivers' – see section 3.4) overall, net contribution to the Gross National Product (GNP). Currently there are no international standard guidelines for assessment of indirect costs; as factors that contribute to it are determined by social structure, culture, and status of the economy (developed versus emerging) in different countries. If the importance of taking into account indirect costs is widely accepted, then they should also be integrated into pharmacoeconomic studies, including those related to pharmacogenetic strategies. Various indicators can be used according to their relevance to a specific investigation. These may include the number of days off sick, the number of days off for medical treatment and follow up, or the duration of breaks in personal activities. They may also include indicators related to third party involvement such as the cost of baby-sitting, the cost of family visits, and so forth (see below under "external costs"). With regard to the consideration of such indirect costs, distinc-



tions will likely be in order between patients who are still part of the work force and those who have retired.

### 3.3 Intangible costs

Intangible costs refer to the human and psychological costs associated with the disease. These are important to consider when developing a more complete assessment of the economic environment. Unfortunately, intangible “costs” are difficult to translate into financial units. Most methodologies therefore recommend taking into account intangible costs without using monetary values (for example, through use of quality of life assessments). Some authors recommend avoiding the use of this terminology (i.e. “intangible”) and promote other measurement techniques such as “utility” calculation or “willingness-to-pay”. These approaches are still subject to a number of methodological criticisms and have given rise to controversies in the international scientific literature.

### 3.4 External costs (informal costs)

Costs for caregiver or helper services are frequently described as “external costs” or “informal costs”. These costs relate to chronic diseases where the disease affects not only the patient, but also people around the patient. The concept here is that any positive or negative effect on the patient may have some parallel effect on third parties involved in the patient’s care or assistance. For example, those patients who respond more rapidly will save significant surveillance time on the part of family and caregivers compared to those who do not. External costs may be presented separately from direct and indirect costs, although they are intimately linked to the overall economic impact.

## 4. Factors affecting economic benefits of pharmacogenetics

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Economic benefits from the use of pharmacogenetics-based drugs may occur by lowering the costs and/or accruing savings in any of the categories discussed above.

### 4.1 Direct costs

Higher cost per dose plus the cost of testing for the pharmacogenetics-based drug may be offset by better efficacy or reduced likelihood of developing an ADR in the specific subgroup; a comparison would be based on costs of alternative approaches adjusted by their probability of achieving the desired efficacy and safety.

It is important to recognise that reduction in the occurrence of ADRs and/or increased efficacy is expected to lead to improved compliance. The implications of improved efficacy or reduced ADRs on offsetting costs are likely different, even though both may lead to improved quality of life, reduced hospitalisation, etc. Whether greater cost savings will be achieved through one or the other mechanism will largely depend, on a case-by-case basis, on the degree by which efficacy is improved and on the severity and frequency of ADRs avoided. These outcomes are, of course, also directly linked to the performance of the test (generally, sensitivity or positive predictive value in the case of ADRs; specificity or negative predictive value in the case of efficacy). Currently, there is a dearth of reliable studies addressing these issues. In the absence of a larger pharmacoeconomic database on pharmacogenetics, it is impossible to predict which of the two outcomes will be encountered more commonly. It is clear, however, that no generalised statements across all drugs or diseases are possible or appropriate, and that the impact of reducing ADRs and/or improving efficacy will vary – sometimes one will prevail, sometimes the other.

## **4.2 Indirect costs**

Savings in indirect costs may include:

- faster recovery, resulting in potential reduction of office visits, shortening of hospitalisations, lowering of other medical costs, and decreased need for ancillary support mechanisms.
- the patient's earlier return to the work place and/or to full productivity, thus lesser impact on GNP. This also applies to private caretakers who would then be free to return to their full-time employment.
- advantageous effects on lowering the risk of long-term complications of a given disorder due to superior treatment efficacy and lowering/avoidance of the costs associated with such morbidity.

## **4.3 Intangible costs**

These would be expected to be positively affected by a speedier and more complete recovery.

## **4.4 External costs**

See section 4.2 (“Indirect costs”).

## **5. Pharmacoeconomic assessment**

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Efficiency is the key metric for any new technology to be included in a healthcare system, whether in the public or private sector. If the intro-

duction of a new technology leads to better health outcomes and lower costs, the decision is a simple one – it should be included in the healthcare system. However, the more frequent scenario in the field of healthcare provision is one of higher direct costs to achieve superior health outcomes. These direct costs, however, may be offset by a favourable impact on indirect and external costs. It is in this setting that there is a need for pharmacoeconomic assessment of the new technology.

However, as alluded to earlier, the purely economic issue of cost has to be assessed not at an individual level. A patient that qualifies for a drug as a likely responder based on a positive pharmacogenetic test will always cost more – by the cost of the test – at an individual level, than an equally treated and responsive patient who has not had the test. Rather, the economic issue of pure cost calculations has to be considered together with clinical and quality of life advantages in the wider context of the cohort served by the particular provider/payer.

It is important to note that in addition to this pure cost calculation, there are of course considerations of a humanitarian nature related to societal solidarity that do of course also weigh in. Thus, the key question is whether society (or the subscribers of a particular healthcare plan) is willing to pay extra for the enhanced medical benefit of those individuals that are “less fortunate” (i.e. those who would qualify for a particular treatment provided a pharmacogenetic test is done). This is particularly critical in scenarios where, on strictly economic terms (including all direct and indirect cost-benefit analyses), there is no financial advantage to the stakeholders.

### 5.1 Cost-per-outcome analyses

Based on the profile of a specific disease, the target population, and the potential advantages or disadvantages of competing therapeutic regimens, different kinds of economic analyses can be performed when assessing a new product or technology [3-8]. These include cost-minimisation, cost-benefits, cost-effectiveness, cost-consequences, and cost-utility analyses:

- Cost-minimisation analysis involves comparing the costs of different therapeutic regimens when consequences are otherwise considered equivalent, and then preferring the regimen of minimum cost. It is important to note that in those circumstances where pharmacogenetic evaluations focus on small subpopulations, differences may not achieve statistical significance. Since “no-difference” is not synonymous with “equivalence”, and “non-equivalence” is not synonymous with a

“difference”, cost-minimisation analysis should only be carried out where a true equivalence exists and has been established.

- Cost-benefit analysis involves comparing the costs of a therapeutic regimen with its consequences expressed in financial units. “Absolute cost-benefit analysis” looks at absolute differences between costs and benefits whereas “relative cost-benefit analysis” looks at the ratio between costs and benefits.
- Cost-effectiveness analysis involves comparing the costs of a therapeutic regimen with its consequences expressed in physical units of effectiveness (as generally established in clinical studies). “Mean cost-effectiveness ratio” is the ratio of mean costs to mean effectiveness. “Incremental cost-effectiveness ratio” (ICER) is the ratio between differences in costs and difference in effectiveness. It is expressed as

$$ICER = C2 - C1 / E2 - E1$$

where C is cost and E is effectiveness and 1 and 2 designate old and new interventions, respectively.

Cost-effectiveness analysis ensures that all costs and effects resulting from a healthcare intervention have been properly evaluated. It provides a quantitative assessment of the complex and often conflicting factors involved in the evaluation of healthcare technologies. Its application has increased over the last decade because of increasing healthcare costs and a desire for delivering value for the money. Recently, the United States Panel on Cost-Effectiveness in Health and Medicine provided general recommendations for performing such studies [9]. Similar recommendations have recently been made in other countries [10, 11] and in the U.S. managed care market [12].

- A particular kind of analysis, “cost-utility” analysis, involves comparing the costs of a therapeutic regimen with consequences expressed in qualitative variables. A “utility” measure may be derived from a quality of life assessment and is often referred to as “Quality Adjusted Life Years” (QALYs) which is the product of “the number of life years saved” times the utility measure. There are a number of techniques to calculate “utility”, ranging from specific interviews (such as standard gamble, time-trade-off, etc.) to the use of quality of life measures derived from generic questionnaires (such as EQ5D/EuroQol, HUI, etc.). Results depend on the choice of the technique but are still considered helpful since the approach allows the comparison of different interventions in achieving the same outcome. The QALY assessment provides a guide to rank interventions according to their cost per QALY. This allows healthcare providers to set thresholds for cost/QALY above which an intervention would not be considered cost-effective [8].

Since a large number of assumptions are necessary to mix qualitative and quantitative criteria, this approach is subject to methodological controversies, mostly due to the risk of divergent and inconsistent results that depend on the utility parameters used. Some reimbursement authorities such as the NICE in the UK and PBAC in Australia consider this kind of analysis as part of their decision making process, while other pharmacoeconomic guidelines (such as the French recommendations for economic assessment) emphasise the methodological problems and advise explicitly against cost-utility analysis in reimbursement decision making.

## 5.2 Pharmacoeconomic study design in pharmacogenetics

Incremental cost-effectiveness ratios (ICER) can be presented for a group of patients based on the “number needed to treat” (NNT). However, when assessing pharmacogenetic tests, the “number needed to screen” (NNS) is also relevant (where available) when calculating ICER since it considers how many additional patients are needed to identify one patient who benefits (responder or absence of ADRs).

The overall pharmacoeconomic study design of a therapeutic intervention involving pharmacogenetics will include the cost minus savings of the initial pharmacogenetic test as well as the subsequent interventions, and contrast these to the cost of treating all individuals according to the state of the art for non-pharmacogenetic approaches. In the case of pharmacogenetic tests that stratify for likely responders, or against likely sufferers of ADRs (and assuming that for prescription of the respective drug, the test is mandatory), the factors that have to be considered for a strictly accounting analysis of direct costs include, but are not necessarily limited to, those shown in Table 1.

**Table 1**

Cost of testing all potentially eligible candidates for the drug (based on conventional parameters)		
<i>plus</i>		
Cost of treating the test-positive subgroup with the pharmacogenetics-based drug		
<i>plus</i>	<i>versus</i>	
Cost of treating test-negative patients with conventional therapy		Cost of treating all patients with the conventional therapy

For a pharmacoeconomic comparison of the two approaches shown in Table 1, a cost-effectiveness ratio or a cost-benefit ratio can be calculated for each of the two options (i.e. for either side of the comparison table above), by dividing total costs by effectiveness or by total benefit, respectively. A number of effectiveness parameters may be used, such as success rate, life years saved, etc. It should be noted that all of these parameters would be affected, in the case of the pharmacogenetic approach, by the performance of the test, i.e. by the fidelity with which it predicts a certain outcome in terms of false negative or false positive results.

If using the test is optional (e.g. for pharmacogenetic stratification parameters discovered after a drug's regulatory approval, and therefore not in the label), then somewhat different considerations will apply. Here the choice will be between performing the test and finding the drug most likely to be effective/safe right away, or going through trial-and-error by monitoring the patient's clinical response and switching to alternative medication(s) if the response to any given agent is insufficient or absent. The considerations that apply to this scenario are rather like the ones that apply to pharmacogenetic guidance for dose finding (see below).

Among the critical parameters influencing this balance are:

- prevalence of a positive pharmacogenetic test (i.e. size of the test-positive subgroup relative to all patients with the disease; it should be noted that this may differ significantly among different ethnicities and require ethnicity-specific consideration)
- performance of the test in terms of specificity and sensitivity (false positives will result in unnecessary treatment with the pharmacogenetics-based drug; false negatives will result in withholding the drug with higher likelihood of treatment success and subjecting the patient to the less effective conventional treatment)
- performance of the conventional treatment among all patients and among the test-negative subgroup
- performance of the pharmacogenetics-based treatment in test-positive patients
- difference in price between the conventional and pharmacogenetics-based medication
- price of the test

The case of a pharmacogenetic test that is applied for finding the individually adjusted appropriate dose of a drug, as compared to not using such a test, requires different considerations. Here the relevant factors, in a

strictly accounting analysis of direct cost, include, but are not necessarily limited to those shown in Table 2.

**Table 2**

<p>Cost of running the test on all patients that are treated with the drug in question</p>	<p><i>versus</i></p>	<p>Cost of additional follow-up visits with the physician to adjust the dose (based on clinical efficacy) that could have been avoided</p> <p style="text-align: center;"><i>plus</i></p> <p>Cost of additional morbidity potentially associated with a delayed finding of optimal dosing (e.g. in rapid metabolisers)</p> <p style="text-align: center;"><i>plus</i></p> <p>Cost of ADRs potentially associated with improper dosing (e.g. in slow metabolisers)</p>
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The same considerations apply regarding a pharmacoeconomic comparison of the above two alternatives as previously presented for Table 1. Again, the performance of the pharmacogenetic test is a critical parameter influencing the viability of the pharmacogenetic option regarding cost-benefit or cost-effectiveness ratios.

Among the critical parameters influencing this pharmacoeconomic analysis are

- the prevalence of variant pharmacokinetic or pharmacodynamic phenotypes
- the range of individually adjusted appropriate dosing
- the performance of the test to allow accurate prediction of the appropriate dose
- the urgency, in a given indication, of finding the right dose
- the severity of potential ADRs associated with inappropriate dosing
- the cost of the test
- the cost of additional office-visits for clinical-response assessment.

It should be pointed out that in all scenarios discussed, the time factor plays a critical role. Depending on the time frame considered, the economics of choosing any particular option may differ. Thus, over a short-term, the use of a pharmacogenetics-guided therapy may not render cost advantages; however, such benefits may accrue over longer periods based, for example, on superior prevention of late-stage complications of a dis-

ease. From the standpoint of health economics, these considerations are important since decision making will have to take into account the average retention time of members of the patient group in the payer's health plan. These considerations, of course, apply much less to nationalised healthcare systems than to private third-party payer systems.

Taking into account the factors outlined above (as well as others that may apply in a specific situation), if – for a given patient population – it is cheaper overall to use conventional rather than pharmacogenetics-guided approaches, the economic principles of evidence-based medicine would demand that the test not be performed or offered. If the opposite were true, it would be economically advantageous to perform the test.

## **6. Development of modelling and multi-criteria approaches**

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Patient-stratifying pharmacogenetic approaches will provide new tools for drug development and medical practice. The resulting strategies of enriching recruitment are in almost all respects very similar to well established and commonly used enrichment approaches based on conventional stratification/eligibility requirements applied in most clinical trials. The only difference introduced by pharmacogenetics is that the test is novel, and will often be less well established when it is first implemented and less well understood with regard to its performance than conventional enrichment parameters (such as, e.g. New York Heart Association (NYHA) class or certain tumour staging schemes). Contingent on the robustness of the database for any given pharmacogenetic parameter, therefore, conventional modelling/re-sampling approaches (including the Monte-Carlo method, boot-strapping, jack-knife estimators, and the use of neural network strategies) are likely to be directly applicable. These techniques provide an optimised approach to account for uncertainties regarding cost, increased efficacy, or reduction of ADRs (which, as pointed out before, will be influenced by the performance of the pharmacogenetic test), much as they do in classical randomised controlled trials that share similar uncertainties (i.e. sample representativeness).

## **7. Payer attitude toward pharmacogenetics**

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Whatever the structure of the healthcare system, the payer must arbitrate between the availability of a new technology, such as pharmacogenetic tests, and overall budget management. Introduction of any new



technology may put pressure on allocated budget. However, a new technology may be potentially profitable for the system if it replaces less efficient older techniques, if the effectiveness is significantly higher, if it decreases the risk of morbidity and mortality associated with potentially costly ADRs or complications, if it reduces medical monitoring, or if it reduces the use of concomitant therapies. The objective of pharmacoeconomic arguments for pharmacogenetic strategies will be to establish added value-for-money in order to convince the payer to embrace this new technology without sacrificing good budgetary management rules.

## 7.1 Cost control

Two classical approaches are often used by healthcare systems to control the potential costs that may arise from the use of pharmacogenetics-guided drug prescription:

### 7.1.1 Top-down “directive” approach

Cost controls are rigidly imposed by means of laws, rules, or guidelines. Contract agreements with health professionals could impose guidelines for the use of certain medicines linked to pharmacogenetic tests, thereby limiting their prescriptions. A limited budget could be allocated for pharmacogenetic testing with no prospect for meeting all potential needs. A price-volume agreement could also be set up with firms marketing the pharmacogenetic tests, thereby limiting their prescription.

One of the main advantages of such rigid controls is that they can generally achieve short-term budget control. However, their disadvantages include the frequent inability to achieve long-term effects as well as unintentionally promoting “perverse behaviours” (i.e., stakeholders finding ways for not following the rules).

### 7.1.2 Incentive-based approach

Incentive-based approaches employ techniques that promote an “auto-control” process by rewarding all cost-saving efforts. For example, prescribers may be rewarded when they limit the number of prescriptions. There are varieties of potential incentive-based approaches based on a variety of potential rewards. When implemented, however, the incentive approach is (in general) more successful in achieving long-term cost control and therefore offers certain advantages over the top-down “directive” approach and its short-term cost control.

## 7.2. Pricing

Methods for establishing the price of pharmacogenetic tests and respective drugs will vary with the healthcare system. Prices may be set by payers or fixed and controlled by special agencies such as Canada's Patented Medicines Price Review Board (PMPRB). Each of the major models of healthcare financing and administration has different implications for pricing.

## 7.3. Payment system

There are a number of payment models that might be applicable to pharmacogenetic tests (and the prescription of the corresponding medicines). Among these are "fee for service", case payment, daily charge (based on charge per patient for daily care), flat payment, and prospective payment models. A global budget system might be allocated to cover inpatient services as well as outpatient services. Some health systems employ capitation fees (covering all potential services for one person during a defined period) or fixed salaries to health professionals.

## 8. Conclusions

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Like any innovative technique, the use of pharmacogenetic tests is expected to have some impact on the equilibrium of the economy of healthcare systems at different levels. The factors that will have to be considered are, for the most part, not new and similar to any situation where cost-benefit ratios of a novel medical intervention are assessed.

Whatever the type of healthcare system, it is expected that the introduction of pharmacogenetics would result in greater demands for medical resources (new medical practices, new tests, new monitoring, use of innovative drugs, etc) but would also potentially decrease significantly other costs such as costs arising from morbidity and mortality associated with less effective medicines or of higher incidence of ADRs or their complications. Pharmacoeconomic assessment will allow investigation of how costs associated with the use of pharmacogenetics would be potentially absorbed by the system and how potential savings in costs would balance the additional costs of innovative technology. It is now generally acknowledged that the real market access and success of a new therapeutic strategy are determined by the ability of the payer to reimburse.

Pharmacoeconomic analyses are already being applied with respect to genotype-guided therapy. For example, studies have examined the role of

genotyping for thiopurine S-methyltransferase (TPMT) and treatment with 6-mercaptopurine or azathioprine in oncology [5, 13-16] and angiotensin-converting enzyme deletion-insertion polymorphism (ACE D/I) and statins in cardiovascular diseases [17, 18]. Ethnicity-specific pharmacoeconomic issues arising from CYP2C19 genotyping for the use of proton pump inhibitors have also been studied [19, 20]. The quality of most currently available studies is less than robust and larger, well documented, carefully executed and analysed trials are imperative. A very widely prescribed drug, warfarin, may provide a useful case-scenario for such a study: it is metabolised by the polymorphic enzyme CYP2C9; the prevalence of null genotype is less than 1% in Caucasians and it is not clear whether CYP2C9 genotyping of potential recipients of warfarin would be cost-effective.

With respect to potential savings, there are a number of questions that cannot be answered at present for lack of data, and will probably be difficult to answer at all in general terms. Rather, they will need to be considered on a case-by-case basis. It may be possible in the future to derive some general rules-of-thumb regarding the required performance of a pharmacogenetic test in terms of improving treatment outcomes to achieve likely viability in pharmacoeconomic terms. However, this will require the analysis of a much larger database of accumulated experience than is currently available or is expected to be generated in the short-term.

## 9. Recommendations

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1. Depending on the requirements of a payer in any given healthcare system, the introduction of a new therapeutic strategy utilizing pharmacogenetic information may be supported by pharmacoeconomic assessment that will define the added value provided by the new therapeutic strategy. The need for and the design of formal pharmacoeconomic studies should be determined on a case-by-case basis, recognising that different designs have different utility in value-for-money determinations.
2. Where conducted, pharmacogenetic pharmacoeconomic studies should address multiple parameters (e.g. effectiveness, safety, quality of life and costs) and be developed to make optimal use of multi-criteria methods and modelling techniques.
3. Incentive-based prescribing may offer at least one approach to long-term control of potential costs as pharmacogenetic-based therapies are introduced. Such approaches should be further explored.

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## Chapter 11

# Communication and Education

### 1. Introduction

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Following the publication of the Human Genome, there has been considerable publicity and anticipation that susceptibility to diseases can be predicted well in advance. This has given rise to an understandable apprehension in the public at large. There is a concern that participation in genetically based research may give rise to unwanted anxiety and may also adversely impact on the social and economic aspirations of the participants.

While the media has been quick to exalt the discovery of any disease-susceptibility gene as a “major break-through” with a potential for “cure”, there is little publicity given to the role of pharmacogenetics in drug development and its potential benefits in improving healthcare. Some of the gene discoveries so often exalted have yet to materialise into beneficial clinical applications and understandably, there is a degree of “genetics-fatigue” or scepticism beginning to develop.

There is also unease that during research, genetic information may be gathered without the permission of patients and be disclosed intentionally to, or access gained without authority by, third parties and this information may be used to the disadvantage of a participant. The apparent lack of communication and education at the present time is illustrated by the facts that (a) on one hand, most of the tests in pharmacogenetics are used to avoid drug toxicity and therefore the benefits for the patients should be quite apparent while (b) on the other hand, there are enthusiastic proponents of pharmacogenetic testing who make claims that cannot be supported regarding the predictive value of a genetic test. Furthermore, there are concerns regarding commercial laboratories that carry out the test on a ‘direct-to-consumer’ basis but lack the expertise or the infrastructure necessary for counselling in terms of interpretation of the result and its significance. Communication therefore needs to contain key information such that participants are aware of the benefits that pharmacogenetic research could provide to patients in terms of safer and more effective medicines, and how this will be achieved, whilst minimising any potential risk and anxieties to them as individuals.

Although most surveys show that the public is enthusiastic and optimistic regarding the impact of pharmacogenetics on therapeutics, there are groups

of patients and the public who have many questions, notions and trepidations related to pharmacogenetic testing and DNA-related data. This is to be expected considering the inflated publicity surrounding genetics and current application of medical genetics to diagnosis of serious disease and prenatal screening as well as the publicity on cloning. Clearly, there is an enormous scope for improved communication and education. Participation in pharmacogenetic research, be it clinical or pharmaceutical, by all concerned can be greatly improved and made a satisfying experience if those concerned were well informed through appropriate communication and education.

## **2. Identifying communication and educational needs**

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One of the major impediments to harnessing pharmacogenetics in drug development is the general lack of awareness of what pharmacogenetics is, what it involves and what its implications are. If the potential benefits of pharmacogenetics are to be fully realised, it is important that all the stakeholders are adequately educated concerning its benefits and limitations. There is also an urgent need for a wider appreciation of the economic and societal benefits in terms of healthcare economics. There must be wider dissemination of legislative provisions designed to protect individual confidentiality and of information that distinguishes medical research on disease susceptibility and clinical application of pharmacogenetics to improve clinical outcomes.

Some areas where pharmacogenetic education can be promoted, and ill-informed fears dispelled, immediately come to the fore.

### **2.1 Genetic polymorphism – one major cause of variable drug response**

It is uncertain as to how much public awareness there is regarding the variability in response to a drug administered to a patient population. Without this awareness, it is likely to be a challenge for stakeholders to appreciate the potential of pharmacogenetics. Knowledge about polymorphisms in many of the genes investigated in humans already exists at present, although not all these polymorphisms result in different expression or activity of the gene product, or have a clinical impact. Genes may be categorised into those that have major, moderate and minor effects. Examples of important variations include the monogenic diseases such as cystic fibrosis, adenosine deaminase deficiency in immunodeficiency and haemophilia A.

Other polymorphisms occur in enzymes that are involved in drug metabolism or drug action and modulate an individual's drug response. Among the



polymorphic drug metabolising enzymes, the most extensively investigated are the cytochrome P450s (CYPs), the N-acetyltransferase and the cholinesterases. Variations in the genes for drug metabolising enzymes may lead to an enzyme with lack of or altered activity. This may account for interindividual variations in plasma drug concentrations following a fixed dose. For example, individuals with enhanced activity (subjects are commonly referred to as ultrarapid metabolisers or UMs) of CYP2D6 due to gene amplification fail to attain adequate plasma concentrations of some substrates of CYP2D6 (such as nortriptyline) and often require ‘megadoses’. In contrast, individuals who have markedly reduced enzyme activity, or a complete lack of the enzyme, metabolise drugs poorly and are referred to as poor metabolisers (PMs) and may require smaller doses. The clinical significance of these variations will depend on the contribution of the specific pathway to the overall metabolism of the drug and the therapeutic index of the drug as well as the activity of its metabolites [1]. For a more detailed discussion, the reader is referred to Chapters 2 and 3 on “Abnormal Drug Response”.

## 2.2 What is ‘personalised medicine’?

The term ‘personalised medicine’ is potentially misleading and may be interpreted to mean that drugs are *developed* for individual patients. A preferred term is ‘individually targeted therapy’. The goal of pharmacogenetics is to ultimately improve drug safety and efficacy for each patient by allowing physicians to select treatment that is best tailored to individual patient’s unique genetic makeup [2]. Enhancing the predictability of outcomes in the dosing and timing of treatments offer the patient the chance of quicker and better recovery. This is, amongst others, a relevant contribution to evidence-based medicine. Getting the right medicine at the right dose to the patient first time and reducing ‘trial and error’ prescribing also has the potential to reduce costs by lowering the number of visits to the physician necessary to obtain effective treatment [2]. Pharmacogenetics, of course, only increases the probability of improving therapy by better targeting of drugs and their doses – it should not be seen as a guarantee for a positive health outcome.

## 2.3 Pharmacogenetics: Revolution or evolution?

For all the stakeholders involved, but particularly for the non-experts, it should be emphasised that pharmacogenetics and pharmacogenomics are processes of evolution, not revolution. Pharmacogenetically based difference in interindividual responses to drugs is not a new observation or discipline. The need to study genetically determined biochemical variations that characterise human beings was first considered approximately a cen-

ture ago. In fact, taking appropriate action to protect the patient from failure of efficacy or side effects following clinical use of drugs has been an important growth area of medical practice for decades (e.g. antimalarial drugs and haemolytic anaemia in glucose-6-phosphate-dehydrogenase deficient patients). Pharmacogenetics simply adds yet another set of data to the data that are already being collected routinely. Some of these data are genetic in nature; for example, blood group testing or the collection of family history and yet, these currently cause little, if any, concern to the patient. The novel aspects of pharmacogenetics are its scope and the potential applications to a wide range of medicines and therefore, the relatively large number of patients who will be involved in genetically based testing for the first time. The future healthcare will include the use of pharmacogenetics only gradually as the value of each test is evaluated and validated. Although the benefit achieved will improve patient care, its acceptance may come with reluctance or trepidation and may prove a challenging task.

## **2.4 Better safety and efficacy and economic benefits**

### **2.4.1 Impact on purchaser**

Pharmacogenetics has the potential to make more efficient use of available healthcare resources and thus improve the cost-effectiveness of treatments as well as to maximise benefits to individual patients. Improvements for the patient in terms of reduction in disease burden and in drug-related adverse events should be reflected in economic benefits to the healthcare system and ultimately to the payers and the society. At present, healthcare providers may find it difficult to justify the costs of providing expensive or new medicines that might be prescribed to a number of patients when only a fraction will experience a beneficial effect. As a result, healthcare providers may decide to deny all patients access to expensive medicines because the small minority who are most likely to respond cannot be predetermined. Being able to select patients who are most likely to respond to the treatment seems to offer an efficient and economical solution to this dilemma.

### **2.4.2 Impact on developer**

Emphasis upon genetic variability in drug metabolism and response during the drug development process should result in safer drugs reaching the market and better therapeutic regimens for patients. Further discussions on implications of pharmacogenetics for and its integration into drug development processes can be found in Chapter 4 on “Exploring Pharmacogenetics in Drug Discovery and Development” and Chapter 5 on “Impact of Pharmacogenomics on Drug Discovery and Development”. The potential

for pharmacogenetics seems obvious when it comes to reduction of adverse drug reactions (ADRs) that are most likely to be associated with genetic variations. This may result in further cost savings, given that ADRs are a major cause of hospital admissions, morbidity and death (see Chapter 2 on “Abnormal Drug Response”). For example, observations on polymorphic metabolism of debrisoquine and sparteine by CYP2D6 were first documented 30 years ago. Case reports since the first characterisation of CYP2D6 polymorphism have suggested that the poor metaboliser (PM) phenotype is likely to experience, or may have a higher incidence of, adverse drug reactions (following administration of some of the drugs metabolised by CYP2D6) than the population as a whole or those of the extensive metaboliser (EM) phenotype (see Chapter 3 on “Abnormal Drug Response”). However, before these observations can be applied clinically, there is a pressing need for prospective studies on the clinical utility of pre-treatment CYP2D6 genotyping of patients. In terms of drug development, the legacy of metabolic variability caused by these polymorphisms has been a number of drugs that fail late in clinical development. For polymorphically metabolised drugs under current development, obtaining regulatory approval may prove difficult or such drugs may become vulnerable to drugs from the competitors, which are not subject to such metabolic variability. Thus pharmacogenetics impacts significantly on the drug development process.

## 2.5 Data protection and confidentiality

Numerous statutory and non-statutory guidelines exist (and more continue to be generated) concerning the collection, interpretation and handling of genetic and other medical data, including access by third parties such as insurers and employers. These include the EU Data Protection Directive, the US HIPAA Act 1996, HUGO, etc (see the end of this chapter for website addresses).

However, such guidelines are often written in a manner that does not differentiate between the various forms of information being collected and often assumes that all genetically based information or data have profound and serious implications for the patient. As a result, interpretation and application of these guidelines that are designed to promote data protection and patient confidentiality can sometimes be confusing and contradictory.

## 2.6 Medical research versus clinical application

As a result of advances in the knowledge and technology underpinning pharmacogenetics, many more clinical research studies now include pharmacogenetic exploration. Researchers need to ensure that patients/ sub-

jects understand whether the pharmacogenetic analysis will provide data about an already recognised, clinically valid measurement or will generate new hypotheses about the genetic basis for drug response that may have to be explored further. Researchers will have to explain to subjects that the latter is only exploratory, with no immediate application to healthcare of the individual patient.

### **3. Issues for the Educator**

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#### **3.1 Coping with patient fears and expectations about genetic testing and individually targeted therapy**

Healthcare professionals and researchers will have to provide high quality information, outlining what genetic measurements and the pharmacogenetic analysis actually include; for example, CYP2D6 polymorphism and the implications for dose adjustment of a drug metabolised by that enzyme. Patients will also have to be informed that pharmacogenetic testing cannot predict with absolute certainty which patients will respond or experience an adverse event, but that the knowledge gained may help a physician select an appropriate medicine and its dose and thereby improve the overall risk/benefit of the medicine individually for each patient. Thus the individualisation of therapy does not come with a guarantee. Patients will also have to be informed of the evolutionary nature of pharmacogenetics. Genetic applications such as blood grouping prior to blood transfusions have existed for many years, and not all medicines will suddenly appear with pharmacogenetic information. Only by successfully communicating objective information regarding the advances and limitations of pharmacogenetic testing will the achievements of genetics and genomics over the last few decades reach their full potential in furtherance of human health [3].

#### **3.2 Societal, legal and ethical implications**

Key stakeholders such as healthcare professionals, researchers, policy makers, purchasers and others will have to play an important role in managing the implementation of pharmacogenetics. If pharmacogenetics is to be used as a tool to achieve improved cost-effectiveness, companies involved in research and development of drugs and healthcare purchasers must have in place the systems to evaluate long-term costs and savings.

Pharmacogenetic profiles do not cause adverse events or lack of efficacy. These profiles are merely a scientific tool that allows one to understand better the variability in patient response to a pharmacological agent.

However, the ability to predict a response will potentially restrict access to certain treatments, for example, only to those patients predicted to have a favourable response. Such restriction may be arguably in the best interests of the patient. However, unless the correlation between genotype and drug response is robust, and all other interventions have been explored, a seriously ill patient might feel that his/her last, and perhaps the only, chance of benefit has been taken away. The physician will have to play a key role in managing the expectations of the patient and making appropriate prescribing decisions.

Physician education will have to improve in terms of molecular medicine, pharmacokinetics, pharmacodynamics and factors, including genetic factors that modulate these parameters. Members of non-medical Institutional Review Boards or Independent Ethics Committees (IRB or IEC) may also require education about genetic testing and its advantages and limitations. Currently there exists a considerable variation, both within and between committees, in terms of opinion and requirements.

Regarding the protection of data, the parties involved must understand and discuss how genetic data should be generated, handled, stored, and used as well as restrictions on access to these data by insurers, employers, and others not involved in the research (see Chapter 9 on “Ethical Issues”). Investigators involved directly in research on patients should inform and assure patients that all of their medical data will be used only for the purposes the patients have authorised. Assurances of privacy and confidentiality will be key to increasing the public level of confidence. There must be agreement among all involved parties regarding how genetic data will be generated, handled, stored and used (especially access by insurers and employers to this information) and if appropriate, ultimately destroyed. This will be essential to assure the patients of their personal privacy and protection.

### **3.3 Need for information to all stakeholders**

Education of all stakeholders is essential in order to realise the potential benefits of pharmacogenetics and to assimilate into future healthcare the knowledge acquired through pharmacogenetic investigations. Information about the impact of pharmacogenetics in terms of demand on healthcare across the society is an important area of education and should be encouraged at all levels, from schools to the general population and especially targeted at the interest groups. In particular physicians, pharmacists and other healthcare providers, upon whom many patients rely totally for advice, must have pharmacogenetics built into their core training.

Acceptance for health-related applications of biotechnology should not prevent continuing balanced communication about the benefits and risks.

Key stakeholders include:

- Physicians, pharmacists and laboratory personnel
- Patients and patient groups
- General population
- Healthcare professionals (providers)
- Third party payers (e.g. public health insurance, private insurance)
- Regulatory authorities and policy makers (governments)
- Healthcare industries – pharmaceutical, biotechnology and diagnostic companies
- Academia (researchers and educators)

The ultimate incentive for continued education will be the potential benefits of more effective and safer therapies.

### **3.4 Educational approach**

The promotion of education and provision of information to health professionals about advances in pharmacogenetics and pharmacogenomics are based on the belief that:

- Healthcare globally will be transformed by genetically-driven medicine in the next several decades
- Health professionals will require understanding of the core principles of genetics and the basics of genetics in medicine
- Scientific information about genetics and pharmacogenetics must be current and accurate for education of healthcare professionals

The requirements of each of the stakeholder groups differ. Therefore, programmes of communication and education will have to be well targeted and appropriate to each clinical speciality. Healthcare professionals will not only need to receive appropriate information themselves but also need the skills to manage the concerns and questions from their patients. This is likely to mean a retraining and restructuring of current healthcare services in which education and communications efforts will be pivotal.

### **3.5 Language**

For all stakeholders, the use of clear and relatively simple language is crucial. It should be at a level that is understandable, informative, and appropriate to the target audience. Global consensus definitions of all relevant terminology should be precisely followed when educating stakeholders or conveying instructions to patients. In addition, researchers must

distinguish carefully the different types of genetic testing to ensure that pharmacogenetics (and disease gene testing) is not confused with gene therapy, genetic modification, cloning or genetic engineering. Cultural sensitivities regarding genetic-based information must also be recognised as well as delivering services to patients in a multilingual society.

### 3.6 The message

Educators must convey clearly the following messages:

- Advances in the field of pharmacogenetics offer opportunities and bring benefits – both therapeutic and economic – for patients, healthcare providers and payers and the health industries alike.
- The ability to potentially prescribe at the outset, the right medicine, for the right patient in the right dose and at the right time, should lead to improved effectiveness, improved efficacy through minimising non-response or delayed response, and safety by avoiding serious adverse drug reactions.
- Advances in pharmacogenetics will be gradual, and acceptance will be accompanied by challenges.
- Pharmacogenetics is distinct from testing for disease-related genes, gene therapy, genetic modification, cloning or genetic engineering.

## 4. Role of the regulatory authorities

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The regulatory aspects of pharmacogenetics are discussed in detail in Chapter 7 “Regulatory Perspectives in Pharmacogenetics”. With regard to communication and education of stakeholders including the public, one key area is the development and access to genetic tests and their inclusion in product-related information.

### 4.1 Genetic tests

The growing connection between diagnostics and therapeutics and the increasing availability of direct-to-public genetic tests will require regulatory authorities to address the level of regulation that is appropriate for various individual tests.

The Human Genetics Commission (HGC) in the UK has recently proposed consideration of regulatory controls and safeguards. For example, genetic tests predictive of serious illnesses should be available only after medical consultation, while other tests may be suitable for wider access. The HGC report “Genes Direct” can be accessed at: <http://www.hgc.gov.uk/genesdirect/>

However, the debate on which tests should be subject to greater and more stringent regulatory controls is yet to be resolved and harmonised.

## **4.2 Product information**

Regulatory agencies anticipate seeing greater use of cytochrome P450-based genotyping tests in drug development. In turn, this will necessitate inclusion of more information on the use and value of such tests in package inserts.

Since patient information leaflets now require fairly detailed information on tests to be undertaken before a drug is prescribed and dosing regimen as well as contraindications, there will be increasing expectations of appropriate pre-treatment tests from the patients. These would include not only the traditional laboratory-based tests such as an electrocardiogram or liver or renal function tests but also genotyping tests.

## **5. Role of the media**

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The media is an important source of healthcare information for the general public. Media descriptions of pharmacogenetics are therefore likely to strongly influence the public perception of the benefits and risks of such applications. Information, knowledge and potential outcomes should be communicated without unduly raising the expectations. Therefore, it is imperative that a strong educational and communication foundation is built so that information can be understood and positioned appropriately by journalists and the sensationalist stories of genetic findings do not prove hurdles to healthcare improvement.

## **6. Communication and education strategy**

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### **6.1 Goals**

It is the responsibility of policy makers as well as the industry to provide stakeholders with accurate information on pharmacogenetics.

Reaching and educating these groups with effective communications will require planning and strategic design. It will also require continual effort as new information is applied to everyday life.

These goals should remain at the forefront:

- Create awareness of how the applications of pharmacogenetic research will impact human health, including patient treatment and care



- Communicate research initiatives and findings to educate and update stakeholders especially on their relevance to clinical practice
- Organize and harmonise realistic policy on provision of information (wording and content) by all players (at least within groups such as physicians and companies developing drugs and/or diagnostic kits).

## 6.2 Implementation

There are a number of means by which to communicate and educate. Methods that are highly effective in promoting good communication and achieving educational goals, especially with regard to pharmacogenetics, include:

- Production of core support materials to ensure consistency and appropriate messages, such as videos, websites, etc.
- Communication of successful research as well as its clinical relevance. This would mean proposing and sharing best practices
- Media outreach programmes
- Organized meetings to coordinate educational and communication efforts
- Sharing of knowledge with key audiences through organized activities
- Roundtable discussions to explain benefits and discuss issues
- Drawing on experience of professions where genetic medicine is a significant part of the practice for information and support; use core competencies of medical schools, regulatory authorities and industry
- Partnerships with advocacy groups

## 6.3 Development of key messages

Key messages are most effective when relevant and developed with regard to the stakeholders' interests, current knowledge and level of understanding. The interdependency of stakeholders for the effective management of pharmacogenetics in healthcare should be taken into account. The messages should be the same for both educational and communication activities.

Key message development should:

- Increase awareness of pharmacogenetics and its benefits and impact on healthcare
- Help stakeholders organize and evaluate information about pharmacogenetics and genetics research
- Create a promising, but realistic future with realistic expectations and time frames.
- Differentiate genetic research for preventing or treating disease (related to medicines) from cloning and genetic engineering
- Increase understanding by relating genetic concepts and knowledge to specific applications and benefits

All communications and educational efforts should enhance the stakeholders' understanding of pharmacogenetics, laying the groundwork for its support, acceptance and implementation.

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Pharmacogenetics: Focus on pharmacodynamic.  
*Int J Pharm Med.* 2001; 15: 74-82

## SOME USEFUL WEBSITES

- A. National Institute of Health – USA:  
<http://www.nigms.nih.gov/pharmacogenetics/>
- B. Human Genetics Commission – UK  
<http://www.hgc.gov.uk>
- C. Human Genetics Advisory Commission – UK  
<http://www.doh.gov.uk/genetics/hgac.htm>
- D. Nuffield Council on Bioethics  
<http://www.nuffieldbioethics.org>
- E. Pharma Genomics:  
<http://genomics.phrma.org/>
- F. Pharma Genomics:  
<http://genomics.phrma.org/pharmacogenomics.html>
- G. UK Dept of Health Genetics White Paper  
<http://www.doh.gov.uk/genetics/whitepaper.htm>
- H. Public Health Genetics Unit (PHGU), Cambridge  
<http://www.cgkp.org.uk/index.php>
- I. The Human Genome Organization (HUGO)  
<http://www.gene.ucl.ac.uk/hugo/>
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Working document on the applications of genetics for health purposes  
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## Chapter 12

# Unresolved Issues and Barriers to Progress

### 1. Introduction

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Pharmacogenetics has captured the public's attention as a new means of providing safer and more efficacious medicines. The possibility of selecting, using, and developing drugs based on the patient's individual genotype is highly appealing. Pharmacogenetics has been featured in medical and scientific journals, and also in the popular press, such as *Newsweek* and *Business Week*. Indeed, the possibility of using the right drug at the right dose the first time has a universal appeal – greater therapeutic benefit faster for patients, less guesswork for physicians, and lower costs for payers. Why, then, are there so few instances in which genetics is used in the prescription and development of drugs?

The answer is complex. In part, the time needed to advance from scientific discovery to practical application in any field often takes longer than we would expect. However, in the case of pharmacogenetics there are also specific factors that are impediments to progress.

1. **Biological complexity:** The current limit to our understanding of the intricacies of biological systems, including drug responses, is that of a simple application of genotyping to clinical decision making.
2. **Technical obstacles:** Practical and technical obstacles can slow down the discovery of genes related to drug responses and impede the development of simple tests that can be used for patient management.
3. **Business-related obstacles including drug development, regulatory and commercial issues:** Business concerns about appropriate use of resources can put pharmacogenetic approaches at a disadvantage to more conventional approaches to the development and marketing of drugs.
4. **Obstacles in medical practice:** Physicians and other caregivers must be convinced of the medical value of pharmacogenetics.
5. **Public perception:** Variable perception of risks and benefits on the part of potential users adds further uncertainty for the future of pharmacogenetics.

This chapter will review these factors and project expectations for the future.

## 2. Biological complexity

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Genetics is seldom a simple, predictive biological process. In some cases it is, such as with rare inherited disorders like Huntington's disease, or biochemical characteristics like ABO blood types. But most phenotypes, even in clearly inherited conditions, are seldom unequivocal. Genes may have multiple alleles (thalassemias), variable expressivity (male pattern baldness), or multiple, independent genes (height). As a consequence, there remains considerable interindividual variation in phenotypes among people who have the same genotype for a particular relevant gene.

The same is the case for interindividual differences in responses to drugs. While drug metabolism may be strongly affected by one's genotype for drug metabolising enzymes, this does not always translate into meaningful differences in drug response. For instance, CYP2D6 poor metabolisers (PMs) treated with tricyclic antidepressants will develop elevated drug levels [1-4] but the clinical responses these individuals will exhibit can be highly variable. One individual might have nervousness and agitation while another might suffer from intolerable sleepiness [5]. Indeed one recent study concluded that inability to efficiently metabolise antidepressants that are CYP2D6 substrates does not necessarily lead to increased frequency of antidepressant-related adverse drug reactions [6]. Paradoxically, some PM subjects with high drug levels may fail to respond at all. Much of the variability may be due to the influence of other genes that affect drug transport and deposition or the drug target itself. Such genes may have major, moderate or minor effect, and can contribute to the variability in patient responsiveness even when plasma drug levels are the same.

This is exacerbated by complexity in the diseases themselves, even when the disease has a strong genetic component. In many clinical conditions there may be multiple pathways that can lead to similar outcomes, and not all of these may be under the same genetic influence. In asthma, patients who are deficient in 5-lipoxygenase due to the genotype in the ALOX-5 gene are non-responsive to 5-lipoxygenase inhibitors [7]. However, most of the 5-lipoxygenase inhibitor non-responders have normal ALOX-5 genes, and the basis of their non-responsiveness lies in other factors, probably related to the nature of their asthma. This complexity is further complicated by the effect of additional genes, which can enhance or reduce the primary effect.

Additional complexity is imparted by the differences in allele frequencies among different ethnic and racial groups [8]. Clinically important alleles

may be rare in one ethnic group but common in another, such as alleles that confer PM status of CYP2C19 in Asians and Caucasians. Investigation of only a single ethnic population may lead to results that are poorly representative of the target population as a whole.

Effective use of pharmacogenetics will require either the discovery of gene effects clearly correlated to clinical outcomes, or wider acceptance of laboratory results as the basis for prescription. Laboratory results, such as plasma drug levels, tend to reflect genotypes more closely than do clinical outcomes. The use of a laboratory result is a reasonable and attainable goal. A mere demonstration that an individual is a PM may be adequate to make decisions on drug selection or dosing, irrespective of the direct correlation to a particular adverse event.

### **3. Technological obstacles**

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Applying genetics to the selection and appropriate use of drugs requires both the identification of the genes that influence drug response and the development of genetic tests that are easy to use and highly predictive. Both of these present practical and technical challenges that have yet to be overcome.

Since the publication of the complete human genome sequence, the discovery of genes related to specific functions has been advancing rapidly. Nevertheless, genes related to drug responses will be among the more difficult to identify. This is especially the case with genes that are involved with a specific drug or disease. In order to identify genes that relate to a response to a particular drug, for instance, it is necessary to obtain and analyse DNA samples from several hundred patients who are clear responders and clear non-responders. Access to this number of well-characterised patients usually involves a controlled clinical trial. Such trials are generally supported only for purposes of drug evaluation and regulation, and do not always have a sufficient number of patients to provide the numbers necessary for gene discovery. In the case of genes related to adverse drug reactions, the relative rarity of adverse responses to a drug that has advanced to large clinical trials will make it especially difficult to obtain DNA samples from adequate numbers of cases and controls.

Nevertheless, progress is being made. Genes related to drug metabolising enzymes, for example, have been well investigated. These investigations have taken advantage of the role of genetic polymorphism in each enzyme that metabolises many different drugs and the existence of DNA samples

from a large number of individuals treated with these drugs under controlled conditions. There are, however, only a few examples at present of discovery of genes that relate to specific drugs or idiosyncratic toxicity. The discovery of the involvement of specific genes in hypersensitivity to the HIV protease inhibitor, abacavir sets an excellent example of how such studies can succeed. Roses and his collaborators [9] collected DNA samples from 200 abacavir patients, 85 of whom had well characterised hypersensitivity reaction and 115 did not. DNA sequence polymorphisms were compared at 114 loci in 12 gene families. The results clearly showed disproportionate frequencies of alleles in two loci within HLA-B, from which the authors concluded that, within the Caucasoid population studied, HLA genotyping has the sensitivity to identify hypersensitive patients of 55%. A similar study relating HLA genotypes to this hypersensitivity reaction found even higher sensitivity [10]. This example takes advantage of a clearly defined adverse reaction that can be attributable to the drug treatment in most cases, and access to appropriate number of patients with (cases) and without (controls) the reaction in a post-marketing observational study. Advances in the pharmacogenetics of adverse reactions will require circumstances such as this for success in the foreseeable future.

Although the development of clinical tests to detect DNA polymorphisms is often regarded as a significant hurdle to be overcome, technologies for clinical nucleic acid testing are largely available today [11]. The most serious practical impediment to the implementation of these tests is the need for thorough validation of the assays. Clinical validation will require testing of numerous cases and controls in a clinical setting, which in the case of a test related to a particular drug response, may require the exposure and monitoring of hundreds of patients or more. If a test is intended to match a dose level with a genotype, the validation study will need to be even bigger to accommodate different doses.

#### **4. Business-related obstacles**

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The discovery of genes related to drug responses and the application of genetic knowledge to the use of drugs is highly dependent upon active participation by pharmaceutical companies. Pharmaceutical companies have access to clinical data relating to response of most investigational drugs, and sponsor the clinical trials in which the genetic research can be carried out. In order for pharmaceutical companies to fully embrace pharmacogenetics, it must be demonstrated first that the use of these approaches will enhance the companies' primary business goals of profitability and growth.

## 4.1 Drug development

Pharmaceutical companies more and more are including genetic analysis as part of the design of clinical trials, particularly in studies that assess pharmacokinetics. Genetic data can contribute to better interpretation of results, better design of trials, and in some cases, to the avoidance of unnecessary exposure of patients who might be at risk for toxicity. The number of genetic studies submitted to the US FDA has been increasing at a rate that has doubled annually (Lesko L and Huang S-M, personal communication). A similar increase has been noted at the European Medicines Agency (EMA).

Nevertheless, many drug developers remain sceptical of the value of pharmacogenetics and continue to question the appropriateness of including genetic analysis in clinical trials. Pharmacogenetics may add to the expense and complexity of clinical studies, and could lengthen the time needed to enrol subjects and complete the trial. This concern can be attributed to several factors.

1. Collection of genetic data might slow clinical trials by complicating review of protocols by Independent Ethics Committees or Institutional Review Boards or discouraging some patients from enrolling.
2. Genetic studies may require additional training of clinical trial staff and investigators.
3. Gathering genetic information may increase the informational risk to trial subjects.

These drawbacks are readily apparent before the study is initiated and at the time that funding must be committed, but the benefits of the results will only be known after the trial has been completed. It is difficult to tell which drug candidates will tangibly benefit from knowledge of gene-based patient responses. In many clinical trials, these drawbacks are considered to outweigh the expected benefits of obtaining pharmacogenetic results.

Many believe the greatest benefits from pharmacogenetics will arise from the targeting of drugs for genetically defined sets of patients who will have high likelihood of beneficial response and low risk for side effects. However, this approach to pharmacogenetics is one that often meets the greatest resistance. Testing of a drug within a genetically defined group of patients in a drug registration trial is likely to lead to restrictive labelling such that the product would not be promoted to the entire population [12]. This niche marketing approach is not favoured in the pharma-

ceutical industry, despite the successes of trastuzumab (Herceptin® Roche), imatinib (Gleevec® or Glivec® Novartis), and a few other targeted drugs. A new compound that is directed toward the entire disease population will likely be favoured over one that has a restricted patient base.

Uncertainty is one of the greatest drawbacks to application of pharmacogenetics in the development of drugs. It is impossible today to predict how well a genetic marker will correlate to a particular drug response, whether positive or negative. The research needed to find genes related to a response and then to demonstrate the benefit of pre-selection of patients is expensive and time consuming and at its initiation has no clear measure of the likelihood of success. Uncertainty is a nightmare to business managers. Overcoming the problem will require more information on the genetics of drug responses, on the decision making behaviour of physicians and patients, and on the medical impact of the results. Until there are more publicised examples of drugs that have been made successful through the application of pharmacogenetics, progress in this area will be slow.

## **4.2 Regulatory obstacles**

There is growing recognition by regulatory bodies of the role of genetics in drug use and development, and an apparent eagerness to use genetics as a means of evaluating the potential risks and benefits of drug usage [13-15]. Nevertheless, the role of genetics in the regulatory process is not well established. For instance, the description of genetic contribution to drug effects may appear at any of a number of sites in a drug label. A review of labels of drugs that are primarily metabolised by polymorphic cytochrome P450s (CYPs) found mention of genetic-based effects in several different sections, including dose recommendations, contraindications, adverse reactions, drug interactions, warnings, precautions and pharmacokinetics, or no mention at all. Neither the drug developer nor the prescribers have a clear idea of how such information should be dealt with, nor where the information can be found.

New techniques of genomics have presented regulatory concerns that are new to both scientists and regulators. A single high-density array analysis of gene expression of SNP genotypes can produce tens of thousands of data points. These data are then analysed either by focusing on only a subset of the data, or by statistical methods that perceive patterns among many data points. Such results, if submitted to a regulatory agency, might be subjected to various *post hoc* analyses or interpretations. For instance, a reviewer might concentrate on a different subset of data or might use alternative statistical methods of pattern recognition. These re-analyses



may or may not be appropriate for the particular study design, and may or may not use validated methods. Therefore, drug developers are reluctant to submit or even generate data that might lead to additional questions from the reviewers, or to contrary conclusions about the efficacy or safety of the compound. This concern has had a dampening effect on the use of these new and powerful methods in drug development.

In November 2003, the United States (US) Food and Drug Administration (FDA) put forward, for consultation, its “Guidance for Industry for Pharmacogenetic Data Submissions” [16]. It is proposed that if a pharmacogenomic test shows promise for enhancing the dose selection, safety, or effectiveness of a drug, a sponsor may wish to fully integrate pharmacogenomic data into the drug development programme. This could occur in two ways:

1. Pharmacogenomic data are intended to be included in the drug label in an informational manner and
2. Dose selection, safety, or efficacy of a drug as described in its label will be contingent upon the performance of a pharmacogenomic test or tests.

It is conceded that most pharmacogenomic data are of an *exploratory* or *research* nature, and FDA regulations do not require either that these data be submitted with an investigational new drug (IND) or that complete reports be submitted with a new drug application (NDA) or biologics license applications (BLA). The FDA is requesting that sponsors conducting such programmes consider providing pharmacogenomic data to the Agency voluntarily, when such data are not otherwise required under IND and NDA or BLA regulations. Under this FDA guidance, *Voluntary Genomic Data Submissions* (VGDS) can be used for the submission of results from pharmacogenomic studies that are not obligatory to be submitted. The FDA intends to establish a cross-center Interdisciplinary Pharmacogenomic Review Group (IPRG) to review VGDS, to work on ongoing policy development, and to advise review divisions dealing with pharmacogenomic data. Under VGDS, data submitted with an IND will not be used for making regulatory decisions. However, after the sponsor submits a VGDS, if additional information becomes available that renders the results obligatory to be submitted under appropriate legislation, the sponsor must submit the data to the IND, NDA, or BLA, respectively, by following an established appropriate procedure.

The regulators in Europe have also shown a great deal of interest in pharmacogenetics with regard to exploring the benefits it can deliver to

the patient in terms of potentially more effective and safer medicines. Over the past few years there have been a number of activities including the announcement of a framework that would facilitate exploration of pharmacogenetic data. In January 2003, the EMEA released a concept paper titled “Concept Paper on Pharmacogenetics – Briefing Meetings” (CPMP/4445/03) [17]. This paper outlines the procedure for individual pharmaceutical companies who wish to discuss informally pharmacogenetic data and strategies with the CPMP Ad-hoc Expert Group on Pharmacogenetics.

### 4.3 Commercial obstacles

Successful pharmaceutical businesses have been built upon product concepts and selling processes that have been carefully developed and time-tested. The idea of targeting a drug at a subgroup of the population defined by a clinical or laboratory test is generally at odds with conventional practices. A process for combining testing with prescribing would have to be developed, sales and marketing staff would require basic training in genetic testing, and reimbursement practices may have to be revised. These would all require significant attention from a staff that is already fully occupied. These concerns could be exacerbated by the potential perception, certainly encouraged by competitors, that a drug that requires prior testing is somehow inferior or incorporates greater risk than the conventional product.

Despite these impediments, it is possible to have a successful drug under these conditions. Trastuzumab, a successful monoclonal antibody treatment for metastatic breast cancer, has been labelled to be used only in patients whose tumours have HER2 protein over expression, as detected with a diagnostic kit. While trastuzumab is an unusual case, in as much as it is for a life-threatening condition and has a very high price, it nevertheless has set an example for success of a targeted drug.

Little stimulus has come from commercialisation of pharmacogenetic tests themselves either as kits or in testing laboratories. Despite the promotion of individualised medicine in the public press and scientific journals, there is little use of genotyping as a means of selecting among prescription drugs. For instance, there are no *in vitro* diagnostic kits for pharmacogenetic markers that have been approved and licensed by the FDA. Most physicians have dealt with patient-to-patient variability in response to antidepressants, warfarin or antiarrhythmic agents without the use of prior testing, and they probably will not see the need for the additional cost and complexity. However, during the clinical use of some thiopurine

drugs, genotyping is becoming the norm. Patients with low or deficient activity of thiopurine S-methyltransferase (TPMT) have a high risk for fatal overdose. As further examples of such associations develop, it is reasonable to believe that pharmacogenetic testing will become a more regular part of medical practice. This is likely to happen in chronic diseases in which drug response tends to be slow in onset, such as depression or schizophrenia, or in therapies with narrow therapeutic range.

## **5. Obstacles in medical practice**

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Most physicians have had little training in genetics since their undergraduate education, and much of what they have learned may be out of date. Therefore, few would have a serious awareness of the role of genetics in drug response, and fewer still would consider this to be an important part in their medical decision making. The prospect of explaining the results of a genetic test to a patient would likely make the average physician uncomfortable. The lack of an effective interface between the basic science and clinical practice only serves to make the situation worse. Scientific jargon and reliance on a large body of technical literature is a significant impediment to the acceptance of genetics as a diagnostic or prescribing tool among physicians. Fortunately, there are a growing number of continuing education courses that bring genetics to the level of a clinician's practical needs. Furthermore, demand from patients and payers may become a significant driver for greater acceptance by the medical community.

## **6. Public perceptions**

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Genetics plays a role in many aspects of our everyday lives, and the public has developed both a respect for and a suspicion of genetic testing. Because of the simplified versions of reports of genetic studies that appear in the press, there is a tendency to believe that genetics is highly predictive of everything from disease to behaviour to appearance to drug responses. This over-acceptance of the role of genetics only serves to amplify any concerns that individuals might have with the possible uses and misuses of genetic testing. These issues, which have been addressed elsewhere in this Report, include:

1. Insurability and consideration of a gene-based condition as pre-existing condition
2. Discrimination in employment
3. Psychological distress
4. Invasion of patient privacy

Many of these issues do not apply to pharmacogenetics, since the patient already has been diagnosed with a disease, and the results of a pharmacogenetic test merely serve to select the most appropriate drug. However, the perception of a problem persists, and is unlikely to go away without significant public education. Nevertheless, the public, especially in the United States, supports the use of genetics in medicine, and one hopes that a reasoned approach from all sides will lead to the use of pharmacogenetics for the benefit of all.

Other public medical policies impact pharmacogenetics more directly. Since allele frequencies differ between racial or ethnic groups [8], would a pharmacogenetic test be restricted to only certain countries or populations, resulting in “race-based” medicine? Also, what about individuals who, due to their genotypes, are not appropriate patients for certain medicines? Will these individuals get adequate care? All in all, the use of genetic testing for drug responses will not change significantly the number of drugs available, but will only help direct the choice among existing drugs. Nevertheless, new choices can lead to new questions.

## **7. Looking forward**

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The use of genetics in the development and use of pharmaceuticals is a new and largely unfamiliar concept. Consequently, there is a need to demonstrate the value of the approach in order to induce researchers, physicians, payers, and patients to change. The contrast between the hype surrounding individualised medicine, and the modest rate at which pharmacogenetics has been applied indicates that acceptance will require tangible benefits rather than promises. How will these tangible benefits come about? First, scientifically, the advances in understanding the human genome organization, cataloguing human polymorphisms and determining gene function will eliminate much of the scientific uncertainty. Second, there must be more examples of the success of targeted medicines. These are likely to come initially from drugs that, because of safety concerns will require special labelling for approval, but which nonetheless provide new solutions for unmet medical needs. Herceptin® is an excellent example, but there will need to be more. Third, education of physicians and others involved directly or indirectly in providing healthcare, regulators, and potential patients will eliminate much of the concern over the unknown aspects of genetic testing and drug use.

Pharmacogenetics offers the possibility of more effective development of new and needed drugs, and the potential for targeting the right drug to the patient. Attaining these goals in the face of the obstacles that face them will require intellect, persistence, and hard work.

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## Annex 1

**Process and Membership of CIOMS Working Group on Pharmacogenetics**

Before establishing the CIOMS Working Group on Pharmacogenetics, two planning meetings were organized in Geneva in January and September 2001. At these two planning meetings, a Core Group agreed on the outline of the project and the topics to be addressed.

CIOMS Working Group on Pharmacogenetics met in a series of five meetings in Europe and the United States from February 2002 to April 2004 as follows:

February 2002	EMEA, London, UK
August 2002	BfArM, Bonn, Germany
February 2003	FDA, Washington DC, USA
September 2003	Warsaw, Poland
April 2004	Windsor, UK

Listed below alphabetically are the senior scientists from drug regulatory authorities, pharmaceutical companies and academia who participated or otherwise contributed to the project (*see note overleaf*).

1. Eric ABADIE AFSSAPS, France
2. Larry ALTSTIEL Schering-Plough
3. Ariel BERESNIAK Serono
4. Celia BRAZELL GlaxoSmithKline
5. Michel EICHELBAUM Dr Margarete Fischer-Bosch-Institut für Klinische Pharmakologie, Germany
6. Csilla FOLDES Aventis
7. Andrew GALAZKA Serono
8. Hiroshi GUSHIMA Yamanouchi
9. Juhana E. IDÄNPÄÄN-HEIKKILÄ CIOMS, Switzerland
10. Agnes V. KLEIN Health Canada
11. Chie KOJIMA MHLW, Japan
12. Gottfried KREUTZ BfArM, Germany
13. David LEPAY FDA, USA
14. Larry LESKO FDA, USA
15. Klaus LINDPAINTNER Roche
16. Duncan McHALE Pfizer
17. Odette MORIN IFPMA, Switzerland
18. Marisa PAPALUCA-AMATI EMEA, London, UK
19. Olavi PELKONEN University of Oulu, Finland

- |                           |  |
|---------------------------|--|
| 20. Mihael POLYMEROPOULOS | Novartis   |
| 21. Lembit RAGO           | WHO, Switzerland                                 |
| 22. Jens S. SCHOU         | University of Copenhagen,<br>Denmark             |
| 23. Rashmi R. SHAH        | MHRA, UK   |
| 24. Brian SPEAR           | Abbott Laboratories                              |
| 25. Jacek SPLAWINSKI      | Narodowy Instytut Zdrowia<br>Publicznego, Poland |
| 26. Noboru TAKAHASHI      | National Institute of Health<br>Sciences, Japan  |
| 27. Mieko TAMAOKI         | Yamanouchi                                       |
| 28. Kiichiro TSUTANI      | University of Tokyo, Japan                       |
| 29. Jan VENULET           | CIOMS, Switzerland                               |
| 30. Mark WATSON           | Merck & Co                                       |
| 31. Thomas R. WEIHRAUCH   | Bayer  |
| 32. Elora J. WERINGER     | Pfizer   |

**Note:**

*Because the affiliation or the responsibility of some members listed above changed during the current tenure of this Working Group, they were unable to continue their full participation and did not have an input in the preparation of the final report*

Non-members who contributed specific sections or items for inclusion in this Report include

1. Dr Leonie Hunt, Director, Drug Safety & Evaluation Branch, Therapeutic Goods Administration, Australia.
2. Prof Hong-Hao Zhou, Pharmacogenetics Research Institute, Central South University, Changshah, Hunan, China.
3. Prof Sang-Goo Shin, Professor of Clinical Pharmacology/Pharmacology, Department of Pharmacology, Seoul National University College of Medicine & Clinical Pharmacology Unit/SNUH, Leader, Korean Pharmacogenomics Research Network/KMHW, Republic of Korea.
4. Dr Kerwin Low, Assistant Director Centre for Drug Administration, Health Sciences Authority, Singapore.
5. Dr Yi-Jin Chiou, Pharmacokinetics Reviewer, Division of Preclinical Sciences, Centre for Drug Evaluation in Taiwan, Chinese Taipei.

The Editorial Board of the report was constituted of Drs. Celia Brazell, Larry Lesko, Rashmi Shah, Brian Spear and Elora Weringer.

Dr Rashmi Shah also acted as the Chief Editor of the final report.



## Annex 2

# Pharmacogenetics and Pharmacogenomics in Australia

Contribution by:

Dr Leonie Hunt, MBBS, FRACGP, BEc, MBA

Director, Drug Safety & Evaluation Branch,

Therapeutic Goods Administration, Australia

## 1. General Guidelines

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The Therapeutic Goods Administration (TGA) is the therapeutic goods regulator for Australia. It has adopted the European Common Technical Document (CTD) for applications lodged in Australia, and most associated guidelines from the Committee for Medicinal Products for Human Use, (CHMP) (formerly the Committee for Proprietary Medicinal Products (CPMP)).

These are listed on the TGA website  
[www.tga.gov.au/pmeds.htm#guidelines](http://www.tga.gov.au/pmeds.htm#guidelines)

## 2. Guidelines on Bioethics

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The Australian Health Ethics Committee (AHEC) is one of four principal committees of Australia's National Health and Medical Research Council (NHMRC). Established under an Act of Parliament, the NHMRC is Australia's national organization for funding health research, promoting the development and maintenance of public health standards through the provision of evidence-based health advice, and providing ethical guidelines and advice in relation to health research and health practice.

Although it forms part of the NHMRC, AHEC has statutory independence and is effectively Australia's 'national bioethics commission'. The membership of 15 people includes categories of persons with expertise, knowledge or experience in philosophy, ethics, medical research, public health, social science research, clinical medical practice, nursing or allied health, law, religion and people with understanding of health consumer issues and of the concerns of people with disabilities. Members are appointed by the federal Minister for Health and Ageing and serve for three years.

The following AHEC publications may be relevant to pharmaceutical regulation and the areas of pharmacoeconomics and pharmacogenomics.

- *The National Statement on Ethical Conduct in Research involving Humans* (1999) is the primary guideline for Australia's Human Research Ethics Committees (HRECs) and for researchers and others on the ethical principles and values, which should govern research activities that involve humans.

Available at <http://www.nhmrc.gov.au.publications/ehome.htm>

- *Essentially Yours: the Protection of Human Genetic Information in Australia* (2003) (joint publication with the Australian Law Reform Commission). This Inquiry was prompted by concerns about privacy and discrimination, especially in the contexts of insurance and employment, and about ethical and other oversight of medical and scientific research, clinical practice, and the use and collection of genetic databases. The final report covers a spectrum of health and related issues including research, privacy, clinical practice, the delivery of health services, and workforce issues. Its two volumes of 1200 pages contain 144 recommendations, which include the establishment of a Human Genetics Commission of Australia, the amendment of discrimination laws to prohibit unlawful discrimination based on a person's real or perceived genetic status, and the strengthening of ethical oversight of genetic research. The report is available at <http://www.alrc.gov.au>.
- *Guidelines for Genetic Registers and Associated Genetic Material* (1999)
- *Ethical Aspects of Human Genetic Testing: an Information Paper* (2000)

Available at <http://www.nhmrc.gov.au.publications/ehome.htm>

A full list of AHEC publications is available at

<http://www.nhmrc.gov.au/publications>

## Annex 3

### **Pharmacogenetics and Pharmacogenomics in Canada**

Health Canada's approach to pharmacogenomics reflects its mandate as the federal department responsible for helping the people of Canada maintain and improve their health. With respect to biotechnology, its primary role is to ensure the prudent use of products and procedures that are derived from biotechnology and consumed by, or applied to, humans.

Pharmacogenomics is a transformative technology that will usher in a new generation of diagnostics and therapies, and could lead to measurable population health impacts. It has the potential to deliver impressive outcomes – better drug safety and efficacy, new tools for evidence-based healthcare decision making and targeted and more effective clinical trials. At the same time, it raises new challenges for Health Canada and the public it serves, from establishing a good clinical evidence base, to regulating the co-marketing of diagnostics and therapeutics, to assessing and addressing economic and ethical issues.

In response to these challenges, the Department, as policy maker and regulator, strives for a balanced and integrated approach that will maximise the potential health and safety benefits of pharmacogenomics, while minimising possible risks. This approach conforms not only to Health Canada's mandate, but also to key priorities in the departmental biotechnology framework, including enhanced regulatory capacity, addressing the social impacts of genetic technology, and robust stewardship pertaining to the impact of biotechnology on Canadians' health and healthcare system.

Canada has been involved closely with the WHO work in genomics and ethics. For example, the University of Toronto's Joint Centre for Bioethics heads a PAHO/WHO Collaborating Centre for Bioethics. The Centre hosted a WHO meeting on Collaboration in Medical Genetics in April 2002 which adopted several recommendations to strengthen the role of WHO in human genetics, to develop comprehensive medical genetics services linked to primary healthcare, to develop ethics capacity and related regulatory systems, to enhance training capacity and to "promote a global public dialogue". In the latter half of 2002, this Centre published an excellent document entitled "Top 10 Biotechnologies for Improving Health in Developing Countries".

The Office of Biotechnology in the Health Products and Food Branch (HPFB) of Health Canada is in charge of coordinating all genetics and related activities within Health Canada. This includes the regulatory activities around pharmacogenomic testing.

The following activities are included in this project:

There exists a Pharmacogenomics Working Group which has developed an analysis and a complete environmental scan in order to provide a basis for developing a Canadian Guidance document that will be a good fit with the Canadian Drug Regulatory Framework. This group has now evolved into a Health Canada-wide group that is developing regulatory guidance on pharmacogenetics/pharmacogenomics and the co-regulation or development of *in-vitro* diagnostics together with the drugs.

This HPFB Pharmacogenomics Working Group had been created in part to support HC participation in the Council of International Organizations of Medical Sciences.

The following activities are going on into which there are regulatory and other inputs:

- Development of commercial testing kits,
- In-house genetic tests;
- Quality assurance; quality control;
- Pharmacogenomics issues – Pharmacogenomics Working Group
- Ethics as part of the regulatory assessment of various products;
- Input from Health Canada into issues around patenting of genetic and related materials
- Canadian Biotechnology Strategy Genetic Information and Privacy Working Group.
- Linkages between the various activities related to genetics, pharmacogenetics and pharmacogenomics with the regulator.

There is still an ongoing need for complete identification of the full range of interested parties and issues and options within the Canadian context. To that end, a series of round table and workshops were organized and continue to be organized. The most recent one was a round table conference on Pharmacogenetics/Pharmacogenomics on November 4, 2004 in Ottawa, while the OECD expert meeting on Pharmacogenetics, held in Paris on 15 October 2004, was co-chaired by Canada.

## Annex 4

# Pharmacogenetics and Pharmacogenomics in China

Contribution by:  
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 Central South University,  
 Changshah,  
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 China.

### 1. Guidelines

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1. Guidelines for Bioethics and Biosafety
2. Clinical Studies and post-marketing surveillance are regulated by the National Pharmaceutical Affairs Law (revised in 2001).

### 2. Projects to establish a foundation for Pharmacogenomic researches

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1. The International Hap Map Project
  - 1.1 Schedule: FY2002-FY2004 (3 years-term)
  - 1.2 Participants: Canada, China, Japan, UK and US
  - 1.3 Aim: clinical application to pharmacogenomics
  - 1.4 Scope: a total of 200-400 blood samples from Mongolian, Caucasian, and African-American donors are to be collected for haplotype mapping. China will bear tenth of the responsibility for analysis. The data will be published in 2004.
2. Chinese Pharmacogenomics Research
  - 2.1 Scheduled: FY1999-FY2005 (7 years-term)
  - 2.2 Budget: 2.2 million RMB
  - 2.3 Aim: Discovery of polymorphisms related to drug safety and efficacy in Chinese population and clinical application of Pharmacogenomics information
  - 2.4 Scope: The research is focused on genetic basis for different response and efficacy of drugs used in patients with hypertension, hyperlipemia, etc.
  - 2.5 Project Leader: Professor Hong-Hao Zhou (Central South University), et al.
3. Project on relationship of genomics and severe diseases
  - 3.1 Schedule: FY2001-2010
  - 3.2 Budget: 10.0 million RMB

- 3.3 Aim: Elucidation of genetic background for susceptibility to various severe diseases.
- 3.4 Scope: Genes that relate to oncogenesis will be elucidated using DNA from approximately 10,000 patients, covering more than a dozen of severe diseases including cancers and diabetes, with the prior informed consent of each patient.
- 3.5 Project leader: Professor Qiang Bo-qing, et al. (Chinese Human Genome Center, CHGC)
4. Bioinformatics on gene functions and drug designing
  - 4.1 Schedule: FY2002-FY2005
  - 4.2 Budget: 5.0 million RMB
  - 4.3 Aim: Development of bioinformatics platforms for studying gene functions and potential targets for drug therapy.
  - 4.4 Scope: Database of genomics and proteomics, bioinformatics methods and softwares.
  - 4.5 Project leader:
5. Xiang-Ya, CSU Demonstrative Lab on Pharmacogenetics
  - 5.1 Schedule: FY2002-FY2007 (6 years-term)
  - 5.2 Budget: 300,000 USD for 6 years
  - 5.3 Aim: Determination of SNP of different drug metabolising enzymes and their phenotype-genotype relationship of clinical drugs.
  - 5.4 Scope: Pharmacogenomics of common diseases
  - 5.5 Project Leader: Professor Hong-Hao Zhou (Central South University)
6. Pharmacogenomics and modernisation of Chinese herbs
  - 6.1 Schedule: FY2001-FY2005
  - 6.2 Budget: 5.0 million RMB
  - 6.3 Aim: Application of pharmacogenomics to modernisation of Chinese herbs
  - 6.4 Scope: Rationalisation of Chinese herbs
  - 6.5 Project leader: Guo De-An (Peking University), et al.
7. Research Center for Medication in Minorities
  - 7.1 Schedule: FY1993-FY2004 (12 years-term)
  - 7.2 Budget: 2.2 million RMB for 12 years
  - 7.3 Aim: Application of pharmacogenomics to clinical practice
  - 7.4 Scope: Ethnic differences of drug metabolism and response in Chinese minorities.
  - 7.5 Project Leader: Professor Hong-Hao Zhou (Central South University)

8. Individualisation of drug therapy for patients with hypertension
  - 8.1 Schedule: FY2001-FY2005
  - 8.2 Budget: 2.0 million RMB
  - 8.3 Aim: Individualisation of treatment for some major antihypertensive drugs
  - 8.4 Scope: Application of gene chips to determine individual's genotype for genes that closely relate to drug response and adverse effect. Types of drugs and their doses will be rationalised according to individual's genotype.
  - 8.5 Project Leader: Professor Hong-Hao Zhou (Central South University)

### **3. Activities**

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1. Ministry of Health and Welfare: funding the disease genomics and Chinese pharmacogenomics research work.
2. Chinese Pharmacology Society (CNPHARMS): the Committee on clinical pharmacology to consider the measure to make use of pharmacogenomics.
3. CHGC and Institute of Environment & Occupational Health (USA): International study meeting concerning Environmental Genomics and Pharmacogenomics to promote pharmacogenomics.
4. Forum of Chinese Pharmacogenomics: Forum held by National Natural Science Foundation of China (NSFC) and Bureau of Science & Technology discussing application of pharmacogenomics to clinical practice.
5. Satellite Meeting on Pharmacogenomics, IUPHARM World Congresses of Pharmacology (2006)

### **4. Pharmaceutical Industry**

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The ethnic differences of drug metabolism and response and relationship of phenotype and genotype of drug metabolising enzymes have been studied and elucidated. A personalised-therapy advice center will be established soon to give more precise prescription for patients, especially those with cardiovascular diseases (including hypertension and heart failure, etc.) and gastrointestinal ulcer, etc. Several pharmaceutical companies will sponsor several clinical trials searching relationship between drug efficacy/adverse effect and specific genotype. More drugs will be administered using a personalised approach.

## Annex 5

# **Pharmacogenetics and Pharmacogenomics in Chinese Taipei**

Contribution by:  
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### **1. Guidelines**

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#### 1. Guidelines on Bioethics

Although life science research has steadily advanced in Taiwan, there are no nation-wide guidelines on bioethics concerning human genome/gene research or genetic testing at present except for some general bioethics guidelines such as “Guideline on Collection and Use of Human Samples for Research Purpose”. Research institutes basically follow individual research guidelines and regulations enforced by in-house boards and/or general guidelines of clinical studies regulated by the Department of Health (DoH). Comprehensive research guidelines for ethical issues related to human genome studies including pharmacogenetics/nomics are currently under discussion at DoH.

#### 2. “Guideline on Ethnic Factors in the Acceptability of Foreign Clinical Data”

This guideline and relevant notifications issued by DoH in 2000 regulating the necessity of conducting bridging studies of a new drug based on evaluation of its potential ethnic sensitivity are considered important and related to pharmacogenetics. Since the evaluation of clinical data package involves determining whether genetically polymorphic enzymes and/or transporters play a significant role in the pharmacokinetics of the drug, the implementation of this guideline is expected to encourage pharmaceutical companies to involve Asians in multinational clinical trials incorporating genetic polymorphism analysis.

### **2. Projects to establish a foundation for pharmacogenomics**

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#### 1. National Research Program for Genomic Medicine

1.1 This is a 5-year nation-wide program starting from 2002 including research projects of four main areas: genomic medicine, bioinformatics, proteomics and structural genomics, and ELSI (Ethics, Legal and Social Implications). It is initiated by the National Science Council



and DoH and involves the most outstanding physicians and scientists from medical centers and research institutes all over the country.

- 1.2 Aims (pharmacogenomics-related): (i) Development of new technologies to identify disease targets and to facilitate therapeutic discovery, which includes gene delivery technology, genomic sequencing, genotyping, microarray and proteomics technology, and drug discovery platform; (ii) Identification of genetic polymorphisms/mutation associated with human diseases such as cancers, metabolic diseases, immune disorders, neurological diseases and mental disorders, cardiovascular diseases and infectious diseases; (iii) Promotion of ELSI-related research projects and transformation of achievements of ELSI projects into concrete reports or recommendations for policy makers in enacting laws and guidelines concerning bioethics of human genome research.
- 1.3 Progress: Many projects derived from this national program have been initiated and making progress in all areas including pharmacogenomics this year.
2. Establishment of “Super Control Genomic Database”
  - 2.1 Aims: Establishment of a control pool that has large enough sample size to serve as multiple controls for various endemic diseases.
  - 2.2 Progress: Normal subjects of Han Chinese origin residing in Taiwan (N= 3312) have been recruited. A pilot study to establish the disease entities, sample size, ELSI concerns, operational methodology and governing body will be done by 2005. A plan to collect several hundred thousand DNA samples with disease information will be prepared afterwards. Single nucleotide polymorphisms (SNPs) of candidate genes potentially involved in drug metabolism and transport mechanisms and adverse drug reactions have been selected for high-throughput genotyping. Allele and haplotype frequencies of SNPs will be determined in the subjects randomly selected from the “Super Control” pool.
3. The Pharmacogenomics Program at Institute of Biomedical Sciences, Academia Sinica
  - 3.1 Aims: (i) Establishment of genetic susceptibility database of adverse drug reactions caused by drugs such as warfarin, azathioprine and carbamazepine; (ii) Identification of genetic determinants underlying individual’s difference in drug efficacy; (iii) Elucidating pharmacokinetics and pharmacodynamics using pharmacogenomics profiling.
  - 3.2 Progress: Patients suffering from moderate to severe adverse drug reactions are being recruited, and genetic variants responsible for the risk of specific adverse drug reactions in clinical patients are being identified, including a severe life-threatening condition (Stevens Johnson Syndrome) caused by carbamazepine.

4. Hepatitis B and C Pharmacogenomic Project
  - 4.1 Aim: Differentiating genetic variant patterns between interferon responders and non-responders by identifying host SNPs that can predict Interferon (IFN) response in new chronic hepatitis C patients contemplating interferon therapy.
  - 4.2 Progress: There are two ongoing studies through collaboration of National Taiwan University Hospital and one of the leading genomics company in Taiwan. In these studies, patients are divided into responder and non-responder groups for an IFN alpha drug regime. More than 10 SNPs on eight genes in the antiviral pathway that may influence IFN response in hepatitis B and C patients have been successfully identified.

### **3. Activities**

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1. Symposium and workshop

A number of scientific meetings in relation with pharmacogenetics/genomics have been held during past years or will be this year. Below are the examples:

  - 1.1 Taipei Science and Technology Law Forum – Legal Reform in Response to the Bio-Tech Revolution in the 21st Century: pharmacogenomics for personalised medicine, the use of genetic testing and protection of personal genetic information were included in the discussion. (August 2002)
  - 1.2 Clinical Research Seminar Series- Pharmacogenomics and Population Pharmacokinetics: The role of pharmacogenomics in drug development and regulatory decision making were addressed. (December 2002)
  - 1.3 Workshop on Biomedicine Research and Bioinformatics: The issues to be discussed are challenges, application and regulations of pharmacogenomics, as well as application of bioinformatics. (March 2004)
2. Center for Drug Evaluation (CDE): internal taskforce meetings to look into current pharmacogenetics/nomics-related research projects and clinical trials and to promote the cooperation between DoH, ELSI and CDE to enactment of pharmacogenomics-related regulations and laws.

### **4. Present situation of pharmacogenomics in academia and industry in Taiwan**

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Research projects investigating pharmacokinetics- and/or pharmacodynamics-related genetic polymorphism are a booming area in academia and major medical centers in Taiwan, mostly through collaboration between the two groups. Although the area of pharmacogenomics has not yet become a focus to the local pharmaceutical companies, a few of genomics companies are making endeavours to understand the genes and pathways involved in major

endemic diseases and the responsiveness of patients to drug therapy using pharmacogenomics approaches and thus to improve the diagnosis, treatment, and eventual cure of the diseases.

1. Major projects by collaboration between industry and clinical research institutes

1.1 Asthma: One study is currently ongoing to look for the naturally occurring genetic variation affecting the function and regulation of genes that are critical for the pathogenesis of asthma, a disease mediated by allergen-specific IgE. This project has identified certain SNPs that are related to the increased IgE levels in paediatric asthma, and the patent application has been filed.

1.2 Diabetes: This ongoing study aims to examine the genetic mechanism underlying the renal complications of diabetics.

1.3 Pharmacogenomics-oriented development of traditional Chinese medicine: This genome-based biomedical research project aims to improve diagnosis of major diseases such as hypertension and hepatitis by identifying their genetic markers and to develop Chinese herbal medicine to better treat such diseases.

2. Clinical Research and Clinical Trials

2.1 Phenytoin: a clinical study was performed in a total of 169 epileptic patients receiving phenytoin treatment for more than one month, and the results indicated that the dosage of phenytoin can be optimised based on the metabolic activities of CYP2C9 and CYP2C19 polymorphisms genotyped by PCR-RFLP analysis.

2.2 A number of multi-national phase III and post-marketing clinical trials including blood sample collection for pharmacogenomics analysis and evaluation of pharmacokinetics-related genetic polymorphism have been started.

3. Development of Diagnostic Kits

3.1 Treatment of hepatitis C: a proprietary DNA-based diagnostic technology was successfully developed using pharmacogenomic approaches to “fish out” patients and carriers who are susceptible to the current single and combination therapies involving IFN drugs. The patent application of this diagnostic technique has been filed.

3.2 More molecular diagnostic related technology and products are being developed through collection and analysis of samples from patients with progressive illnesses and samples from patients being treated with various drugs to help early detection and better treatment of major diseases such as cirrhosis, hepatoma, asthma, breast cancer, diabetes and diabetic nephropathy.

## Annex 6

### **Pharmacogenetics and Pharmacogenomics in the European Union**

The development of pharmacogenetics and pharmacogenomics in the European Union (EU) should be considered in the wider framework of policies for a dynamic knowledge-driven economy, supporting the establishment of a European Area of research and innovation. These policies impact on public health, industrial and social sectors with the objective of enhancing an EU-integrated innovation's performance<sup>1</sup>. In 2000, the European Parliament set up a Temporary Committee on Human Genetics and New Technologies in Modern Medicine to assess the ethical, legal, economic and social implications of human genetics. The draft report from this Committee, dated November 2001, and the European Parliament Report on the Commission communication Life Sciences and Biotechnology – A Strategy for Europe – adopted in November 2002, both indicated the need for policy actions regarding the use of genetic testing for medical and non-medical purposes to lay down a harmonised regulatory framework.

Many initiatives have been undertaken within the European Commission services, in collaboration with other EU Institutions, tackling different aspects of genetic testing and aiming to contributing to i) developing novel or improved genetic tests, ii) improving the quality of genetic services, iii) analysing the ethical, legal and social aspects, iv) providing support for the development of related responsible policies, v) fostering societal dialogue and vi) encouraging international dialogue.

In order to ensure that different services of the European Commission share information, support each others' initiatives and avoid the risk of duplication, an "inter-service" group on genetic testing has been set up. The group meets at regular intervals and provides progress reports to the Biological Steering Committee in preparation of the main policy discussions taking place at the level of the Council of Ministers and the European Parliament. Initiatives have also been undertaken by the European Commission for the establishment of a high level working party with the participation of the representatives of Member States with the objective of exchanging information and coordinating the many important national initiatives taking place in the field of genetics such as the creation of DNA biobanks and the issuance of national guidelines.

The European Medicines Agency (EMA) launched its activities on pharmacogenetics in June 2000 with a facts-finding seminar on pharmacogenetics where experts from the Committee for Proprietary Medicinal Products (CPMP,

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<sup>1</sup> Presidency conclusions Lisbon March 2000

[http://ue.eu.int/ueDocs/cms\\_Data/docs/pressData/en/ec/00100-r1.en0.htm](http://ue.eu.int/ueDocs/cms_Data/docs/pressData/en/ec/00100-r1.en0.htm)

now known as the Committee for Medicinal Products for Human use, CHMP), industry and patients' organisations contributed. A multidisciplinary Ad Hoc Expert Group on Pharmacogenetics was set up by the CPMP in 2001 to address priorities identified during the workshop.

A Position Paper on Terminology on Pharmacogenetics was released by the CPMP in 2002. This is attached herewith. The document addresses the use of key terms applicable to the handling of samples and data generated in pharmacogenetic testing during clinical trials. The document provides the position of CPMP on technical, regulatory and privacy protection aspects. This document has already been accepted as one of the reference documents on terminology in pharmacogenetics at international level. The CPMP document on terminology has also been adapted into lay language in consultation with the CPMP Working Party with Patients Associations. It will be made available in all EU languages for wider use by early 2005.

Since 2002, the EMEA is also contributing as requested to a number of initiatives of the European Commission, especially on technical research aspects and ethical issues specific to pharmacogenetics and pharmacogenomics. The EMEA is also active member of the inter-service co-ordination group on genetic testing.

In 2003, the CPMP implemented a new initiative called Briefing Meetings on Pharmacogenetics which provided for an informal forum for discussion between sponsors and regulators on the main technical issues associated with pharmacogenetics in drug development and scientific and regulatory assessment. As of July 2004, 10 pharmaceutical companies had applied for such informal meetings at the EMEA.

Looking forward to the necessary international dialogue in the field, the EMEA joined the CIOMS Working Group on Pharmacogenetics in late 2001 and also started an exchange of contributions with the FDA in a number of international meetings (Washington May 2002, London October 2003, Washington July 2004).

Further initiatives will be pursued at the EU and international levels to ensure that there will not be significant regulatory differences creating hurdles at a regional or global level to the best exploitation of this new technology in drug development, approval and clinical use.

For additional information the following websites are available for consultation:

<http://europa.eu.int/index.htm>

<http://heads.medagencies.org>

<http://www.emea.eu.int/index/indexh1.htm>

<http://pharmacos.eudra.org/>

**COMMITTEE FOR PROPRIETARY MEDICINAL  
PRODUCTS (CPMP)**

**POSITION PAPER ON TERMINOLOGY  
IN PHARMACOGENETICS**

**1. Introduction**

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Pharmacogenetic research started from the observations that not all subjects respond in the same way to the same medicine and that these differences between individuals may be caused partially by their genetic profile.

Today the drug development programmes consider (usually for practical reasons) the subjects as coming from a rather homogenous population since it is not possible to accommodate fully in the drug development programme the whole range of inter-individual variability observed within a population. When differences in drug response are anticipated, e.g. in subjects with renal or hepatic disease, or with age-related differences, then studies are requested in the specific subgroup identified.

The contribution of genetic influences to variability in drug response often far exceeds that of any other variable and is what the science of pharmacogenetics aims to unravel. The analysis of a broad set of genetic variations may show that a genotypically defined subgroup of subjects may have a higher probability of responding to a certain drug differently from others in the population. The overall genetic profile may vary according to ethnicity.

As a result of the development within the areas of genetics and genomics, changes are likely to occur in the way drug development is currently being conducted and the way medicines will be used.

The use of terms that are harmonised and widely accepted by the stakeholders would contribute greatly to clarity in the dialogue. At present there is not an agreed set of working definitions crucial for pharmacogenetic clinical research. This is urgently required for protocols and guidelines addressing pharmacogenetic testing to ease communication particularly between ethics committees, investigators and subjects.

Following extensive consultation, the CPMP has agreed on a specific set of definitions directly relevant to the current practices in clinical research,

with the understanding that they may have to be revisited in the light of future scientific advance and taking into account emerging legislation. The definitions discussed hereafter are highly relevant to the scenario of individual clinical protocols including pharmacogenetic testing; the principles might however be relevant also for trials involving testing other than pharmacogenetics.

The terms “pharmacogenetics” and “pharmacogenomics” as well as the terms used in the handling of samples and data for pharmacogenetic testing have been defined from the scientific-technical point of view.

The same definitions, following appropriate consultation will then be written in lay-terms and made available in all EU official languages to constitute a useful technical asset for regulatory authorities, ethics committees, health professionals and subjects when confronted with pharmacogenetic testing protocols and consent documents for medicinal product clinical trials.

## **2. Scope**

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This position paper focuses on a specific set of critical terms that are frequently used in protocols for pharmacogenetic testing and that are relevant to define appropriate levels of protection for the privacy of the subjects when describing how the results and samples will be used in clinical trials.

The choice of the level depends on the extent to which it is desired or considered possible to link the data and samples to an identifiable subject and corresponds to the defined category of sample linkage.

The most appropriate level for a particular study depends on the nature of the research, the intended use of the data, the regulatory and legal environment and the specific concerns of the investigator and study sponsor. This choice must respect the needs for the privacy of subjects participating in a clinical study.

Generally, the greater the subject privacy in a study, the less are the opportunities for the subject after sample collection and pharmacogenetic testing have been performed to withdraw the individual samples from further analyses or to receive individual results from the study. Privacy of information, control over the use of samples, and knowledge of study results may all contribute to a subject’s willingness to take part in a study, and as a consequence the choice of process may significantly affect enrolment in a clinical trial in which pharmacogenetic testing is planned.

Sample coding procedures should be documented according to Good Clinical Practices (GCPs) and as provided for by relevant EU directives and accompanying guidance documents. Primary study data and original study-

related records should be accessible to the competent regulatory authority in order to validate the evidence that is reported. While the regulatory authority can accept different levels of documentation, depending on the particulars of the study and the availability of other evidence or records, there may be times when it is necessary to link a clinical outcome to a particular patient. In principle, there is a framework for protecting patients enrolled in clinical trials now, and this framework may be adequate, perhaps with small changes, to apply to clinical pharmacogenetic trials.

Complete anonymity of the subject without any possibility of linking the samples/data to an individual will have great impact on the usefulness of the results and on what aspects might be verified during a GCP inspection from a competent authority or a sponsor audit. The individual subject record is an important component of data for submission to regulatory agencies and so the use of data from a study involving anonymised samples might not be acceptable for the submission of a claim to be included in the label of a drug or clinical diagnostic assay.

In designing clinical trials, investigators and sponsors should attempt, in consultation with competent authorities and ethics committees, to find the optimum balance between achieving the aims of the study and protecting the subject's safety or right to privacy.

It is recognised that DNA data unique to a subject could potentially be used to reconstruct a link between a subject's medical record and genotype information. Procedures should ensure that in order to respect the subject's wishes and privacy, such links are not reconstructed. For the same reasons, it is further recommended that the code should comprise randomly assigned numbers/letters and should not be based on protocol and site number (and perhaps gender) because if a particular site has included only a few subjects, it might be theoretically possible to reconstruct a link to individual subjects.

### **3. Pharmacogenetics and Pharmacogenomics**

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There is at present no consensus in the literature on the definitions of "pharmacogenetics" and "pharmacogenomics". Actually the terms are frequently used interchangeably. The achievement of widely accepted working definitions of the two would be a useful first approach to applying pharmacogenetics and pharmacogenomics in clinical trials. It is important to single out pharmacogenetics and pharmacogenomics from the wider field of genetic testing as the latter encompasses different level of concerns especially in terms of sensitivity of sample handling, data and trial results management.

**Pharmacogenetics** is the study of interindividual variations in DNA sequence related to drug response.



**Pharmacogenomics** is the study of the variability of the expression of the individual genes relevant to disease susceptibility as well as drug response at cellular, tissue, individual or population level. The term is broadly applicable to drug design, discovery, and clinical development.

#### **4. Definitions applicable to DNA samples and data in clinical trials including pharmacogenetic testing**

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Different terminologies relate to the collection of human samples for pharmacogenetic research and the management of the data therefrom. The set of terms described in this paper are a key to correct handling of the samples and the data and to transparency of communication among industry, ethics committees, regulatory authorities and subjects about the pharmacogenetic approach in clinical research, regulatory assessment of medicinal products and clinical practice.

The processes by which samples and data are collected, labelled and stored have a direct effect on how the samples and the results obtained can be used in the future and on the obligations of the investigator and sponsor to the sample subject. This pertains particularly to situations when a subject withdraws his or her consent to further participation in a study and affects the possibility to return information to the subject or his/her physician, the possibility to withdraw a sample from future analyses and verification of data ascribed to a subject in reports and regulatory submissions. Additionally, the readiness and willingness with which a subject would or would not want to take part in a study may be affected by such factors as the uses of the results, the nature of the information the subject might receive, and the perceived risk resulting from disclosure of genetic information to third parties.

Five definitions (See table 1) for the labeling and coding of pharmacogenetic samples and data are proposed describing direct implications for the handling methodology of samples for pharmacogenetic testing and corresponding consequences for the level of privacy protection and use of the information for regulatory purposes. Duration of retention of the sample or its destruction needs to be defined in the protocol and in the consent form. Otherwise, if and when relevant, the timepoint and the procedure for anonymisation of the sample itself should be defined in these documents.

##### **4.1 Identified samples and data**

are those labeled with personal identifiers such as Name or Social Security Number.

Identified samples and data are treated in much the same way as those acquired in everyday medical practice. Because the sample and the data generated from it are directly traced to the subject, it is easy to withdraw the sam-

**Table 1 Summary table of the five terms of sample labelling**

<b>SAMPLE LABELLING CATEGORY</b>	<b>Link Between Subject Identity and Pharmacogenetic Data</b>	<b>Records Identifiable for Clinical Monitoring</b>	<b>Actions Possible if subject withdraws Consent</b>	<b>Return of Individual Results to Subject</b>	<b>Scope of Subject Privacy protection</b>
Identified	Yes, directly	Yes	Sample can be withdrawn with immediate effect for any prospective use	Possible	Similar to general healthcare confidentiality
Single coded	Indirectly, via code key	Yes, via protocol-specified procedures	Sample can be withdrawn with immediate effect for any prospective use	Possible	Standard for clinical research Conforms to principles of GCP
Double coded	Very indirectly, via two sets of code keys	Yes, via protocol-specified procedures	Sample can be withdrawn with immediate effect for any prospective use	Possible	Double code offers added privacy protection over single code
Anonymised	No. Key(s) identifying the link between pharmacogenetic data and the identity of the subject is deleted	No	Sample and data are not identifiable. Sample cannot be withdrawn once key is deleted	Not possible	Pharmacogenetic data not linked to individuals
Anonymous	No	No	None	Not possible	Complete

ple or the data from the study, update subject information, and return results to the subject. Also, at an inspection of the study it will be possible to verify the connection between the subject and the reported results. On the other hand, since a subject's genotyping results are directly linked to the subject's identity, the use of identified samples offers no extra privacy protection in addition to those generally provided.

Identified samples and relevant data might be coded at the given point in time in order to provide for extra long-term privacy protection following the closure of the trial. The protocol should also specify when and whether the samples and data might be destroyed or anonymised.

#### **4.2 Single coded samples and data**

are those to which a single specific code is attributed for protecting individuals. It is recommended that the code should compromise randomly assigned numbers/letters.

The investigator stores the key connecting the code of the sample to the individual's data. This step separates the subject's identity from the results of the pharmacogenetic analysis. The researcher with knowledge of the pharmacogenetic data would not have ready access to the identity of the subject.

Only breaking the code can reveal the subject's identity.

It is possible to withdraw a subject's sample for prospective use or return individual results to the subject or physician if desired.

The maintenance of a link between the subject and the pharmacogenetic information by a single code allows verification of data ascribed to an individual subject. Because the investigator who has coded the sample might also have access to the pharmacogenetic data, the safeguards of the subject's privacy, including doctor-subject confidentiality, are equivalent to those in current clinical trials practice.

#### **4.3 Double-coded samples and data**

have an additional privacy safeguard imposed by the use of a second coding system. Adding an additional code to the samples and data provides further protection.

The investigator who only knows the first code does not know this second code. In this way, anyone with knowledge of the pharmacogenetic results can only trace a subject identity to a coded identifier but no further, unless a key is used to link the codes between the data set with subject identifiers and the data set containing the pharmacogenetic information.

The code key linking the double coded pharmacogenetic samples and information is kept by a third party. This should not be the investigator in possession of the key linking coded sample and/or information to the subject.

The key to the double code might be maintained by the sponsoring organisation, in areas entrusted with maintaining confidential information (e.g. legal, quality assurance, clinical statistics) under strict operating procedures. Alternatively, the key might be held by an external entity, such as governmental agency, legal counsel, or other qualified third party not involved with the research.

The individual can only be linked with the sample or data obtained from it by bringing the two code keys together. Although the samples do not carry any information on the identity of the subject, it is still considered to be possible to identify the subject as long as both code keys exist.

As with single coded samples, the existence of a link between the pharmacogenetic data and the subject's identity makes it possible to withdraw a sample or data (up to the time the results stemming from that data are reported), update subject information, return results and inspect the process. However, the conditions under which the pharmacogenetic information might be linked back to the subject's identity for any purpose are determined strictly by the specifics of the research protocol. These conditions should be explicitly described in each protocol, and included within the subject's informed consent.

#### **4.4 Anonymised samples and data**

are for practical purposes double coded samples where the key linking the first and/or second code is deleted. They may be also previously single coded samples where the single code key is destroyed or even previously identifiable samples where the name/identifier is removed.

Anonymised samples and data do not carry any longer personal identifiers. Once the linking key has been deleted, information related to the subject's identity is no longer linked to data related to the pharmacogenetic results. This offers an additional level of security to the individual's data.

After anonymisation it is not possible to withdraw a subject's sample from analyses, to update subject information for further use, or to return any individual results to the subject or the subject's physician. Similarly, it also is not possible to inspect the study to determine that pharmacogenetic data is accurately correlated to a specific subject.

There will be times when stored samples may provide a regulatory agency additional information related to clinical outcome. The ability to link individual data to a patient will be essential in some circumstances and anonymised samples would be a problem.

In general, anonymised samples are well suited to research studies in which hypotheses are generated, but may be less so for clinical trials on which label claims are based.

#### 4.5 Anonymous samples and data

are those that do not have any link whatsoever between the sample and the individual identity.

Anonymous samples may have population information (e.g., the samples may come from subjects with diabetes) but no individual data that might allow the identity of the subject to be traced. The clinical information is limited to broad categories of data, such as “male, age 50-55, cholesterol > 240mg/dl”. In many instances, the sample has no clinical data at all.

This situation is applicable in cases where the population is large enough and measures are taken in building up the code (see recommendations on page 3 on reconstructing a link).

Anonymous samples are useful in some types of pharmacogenetic studies.

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## Annex 7

# Pharmacogenetics and Pharmacogenomics in Japan

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### 1. Guidelines

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1. Notifications regarding pharmacogenomics from the Ministry of Health, Labor and Welfare (MHLW)
  - 1.1 Clinical Pharmacokinetic Studies of Pharmaceuticals (June 1, 2001)
  - 1.2 Methods of Drug Interaction Studies (June 4, 2001)

Both of these notifications are concerned with genetic polymorphisms. The necessity to accumulate know-how on pharmacogenomic methods and to create an organization for this purpose is also described.

On 8 June 2004, the Ministry of Health, Labour and Welfare published for consultation purposes a guidance note entitled “Submitting information of clinical trials which used pharmacogenomic approaches to the regulatory agency for making the guidance of pharmacogenomic approaches on pharmaceutical developments (Draft)”. They requested that comments be submitted by 9 July 2004.

2. Guidelines on Bioethics

There are one law and six ethical guidelines significant to the promotion of pharmacogenomics in Japan

  - 2.1 Personal Information Protection Law (May 23, 2003)
  - 2.2 Fundamental Principles of Research on The Human Genome (June 2000)  
[http://www.mext.go.jp/a\\_menu/shinkou/seimei/index.htm](http://www.mext.go.jp/a_menu/shinkou/seimei/index.htm)
  - 2.3 Ethics Guidelines for Human Genome/Gene Analysis Research (April 2001) (Currently being translated – draft is now available)
  - 2.4 Ethical Guidelines for Performing Human Genetic Testing Contracted to the Japan Registered Clinical Laboratories Association (April 2001)
  - 2.5 Ethical Guidelines for Epidemiological Research (June 2002)
  - 2.6 Guidelines for Clinical Studies (July 2003)
  - 2.7 Guidelines for Genetic Testing, by The Japan Society of Human Genetics, Council Committee of Ethics (August 2003)

The Personal Information Protection Law was legislated in May 2003. It has been suggested that this law does not apply to fields of scientific research or matters concerning public health and hygiene. Therefore, at present, the necessity of a separate law or guideline is being considered.

Among the guidelines listed above, “Ethical Guidelines for Human Genome and Gene Analysis Research” enforced in April 2001 is the most important. This guideline is under review, as the Personal Information Protection Law shall take effect as of April 1, 2005. This guideline, regulating human genome/gene analysis, demands the compliance of researchers in these fields. The basic policies are as follows: 1) respect for human dignity, 2) adequate prior explanation, and consent by one’s own free will (informed consent), 3) complete protection of personal information, 4) the research conducted shall be useful to society and shall contribute to human intellectual advancement, health and welfare, 5) priority shall be placed on the protection of individual human rights rather than social/scientific benefits, 6) assurance of study adequacy by preparation of and compliance with study protocols based on the guideline, after their review and approval by an independent ethical review board, 7) assurance of study transparency by third-party monitoring of study performance at each site and by publishing study results. Clinical studies and post-marketing surveillance are regulated by the Pharmaceutical Affairs Law, and are thus excluded from the guideline.

## **2. Projects to establish a foundation for pharmacogenomics**

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1. The International Hap Map Project
  - 1.1 Schedule: FY2002- FY2004 (3-year term)
  - 1.2 Participant: U.S., U.K., Japan, Canada, and China
  - 1.3 Aim: clinical application of pharmacogenomics
  - 1.4 Scope: a total of 200–400 blood samples from Mongolian, Caucasian, and African-American donors are to be collected for haplotype mapping. Japan will bear one-quarter of the responsibility for analysis. The data will be published in 2004.
  - 1.5 Project Leader in Japan: Nakamura, Yushuke (The University of Tokyo Institute of Medical Science)
2. Project on Realization of a Medical Care System in Accordance with Genetic Information
  - 2.1 Schedule: FY2003- FY 2007 (5-year term)
  - 2.2 Budget: 20 billion yen
  - 2.3 Aim: optimising drug therapy based on elucidating a patient’s genetic constitution
  - 2.4 Scope: SNPs that are related to drug efficacy, onset of adverse reactions, and diseases will be elucidated using DNA and serum obtained from approximately 300,000 patients, covering 40 diseases, including cancer and diabetes, with the prior informed consent of each patient.

2.5 Project Leader: Nakamura, Yushuke

3. Cancer Epidemiology Research

Full-scale cancer epidemiology research is scheduled to be initiated from 2005 with a programme for the collection of gene samples from 100,000 people nationwide.

4. Pharma SNP Consortium (PSC)

4.1 Period: FY2000- FY 2002 (3-year term)

4.2 Budget: 1 billion yen

4.3 Aim: promotion of research on pharmacokinetic-related Japanese genetic polymorphisms, especially frequency analysis, in an ordinary Japanese population, the formation of a pharmaceutical research and development base, and contributions to healthcare in Japan via promotion of genome research

4.4 Results: frequency analysis results were obtained for 4,272 SNPs in 202 pharmacokinetic-related genes. These will be published internationally in December 2003. The Human Science Research Resources Bank (HSRRB) has had 996 cell lines established and deposited so far. The methods for functional analysis of CYP and transporter mutant proteins have been standardised.

4.5 Participants: forty-three JPMA (Japan Pharmaceutical Manufacturers Association) member companies

### **3. Activities**

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1. MHLW: Internal study meeting consisting of the MHLW and the Pharmaceuticals and Medical Devices Agency (PMDA) to consider the measures for making use of pharmacogenetics

2. Japan Health Sciences Foundation (HS): A working group investigation on genomics; several reports were issued and a symposium was held to promote pharmacogenomics.

3. Japan Medical Association: Discussion by the Committee on the Handling of Human Genetic Information on the enactment of an individual law to protect individual patient information to be used for medical research, etc.

4. JPMA

4.1 A symposium to promote pharmacogenomics (June, 2004 in Kyoto)

4.2 Drug Evaluation Committee: internal study meeting

4.3 Research & Development Committee: internal study meeting

### **4. Present situation of pharmacogenomics by the industry in Japan**

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According to the HS report entitled “Toward Clinical Application of Pharmacogenomics”, the present status of the clinical development of com-



pounds using genome information in Japan is as follows. With reference to compounds currently under development or slated for development, 16 companies are investigating or are scheduled to investigate the effect of genetic polymorphism clinically. With regard to drug metabolising enzymes, 4 clinical studies are already underway, and 6 studies are expected to begin in the near future. With regard to drug reactions, 3 clinical studies are already underway, and 7 studies are expected to begin in the near future. These results suggest the possibility that clinical studies incorporating genetic polymorphism will increase rapidly in the next 1 or 2 years. Five companies plan prospective studies for their commercially available drugs. The objective is to identify responders and non-responders and to identify an association with the development of specific adverse reactions. The reason why most other members are not planning such studies is that they have, as yet, no appropriate candidates.

### 1. Examples of Clinical Usage

- 1.1 Trastuzumab: IHC and FISH tests, used to select patients to whom trastuzumab should be administered, are covered by health insurance and have already been used in clinical practice.

### 2. Clinical Research

- 2.1 Troglitazone: Troglitazone, a drug for the treatment of type II diabetes, was forced to be withdrawn from the market in March 2000, due to liver toxicity. Sixty-eight SNPs in 51 candidate genes gathered from the blood samples of 110 patients were analysed and the results indicated that SNPs in the metabolic enzymes GSTT1 and GSTM1 might play a role in the development of this liver toxicity.
- 2.2 Imatinib mesilate: A method for predicting the therapeutic effects of imatinib mesilate by gene expression in each subject has been developed.
- 2.3 Gefitinib: Clinical trials to investigate therapeutic effects based on changes in gene expression have been performed since 2001, and projects to identify SNPs related to acute lung injury have just started.
- 2.4 Pioglitazone: Projects to identify SNPs related to the effectiveness and adverse reactions of pioglitazone, a member of the thiazolidinedione class of insulin-sensitizing agents, has started. The discovery should allow for tailor-made medicines as well as new drug development.

### 3. Clinical Trial

- 3.1 Post-marketing clinical trial: omeprazole, lansoprazole (*H. pylori* eradication therapy, CYP2C19)

### 4. Development of Diagnostic Kits

- 4.1 Interferon (hepatitis C treatment): prediction of therapeutic effect
- 4.2 Irinotecan (anticancer drug): prediction of severe toxicity.

## Annex 8

# Pharmacogenetics and Pharmacogenomics in the Republic of Korea

Contribution by:

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Republic of Korea.

### 1. Guidelines

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1. Bioethics and Biosafety Law (to be effective in January 2005)
  - 1.1 A National Bioethics and Biosafety Review Committee will be established under direct control of President by the law. The guideline will request institutional bioethics review board be established in each institution dealing with embryo, gene bank and gene therapy, etc. (article 6 and article 10)
  - 1.2 Facilities testing genetic information should receive quality accreditation by minister of Ministry of Health and Welfare. Genetic tests of scientific ambiguity that may mislead test subjects are prohibited. Genetic testing of embryo or foetus is allowed only for the diagnosis of hereditary disease that Presidential decree decides. (Article 24 and article 25)
  - 1.3 Genetic information must not be used to differentiate individual in social activities such as education, employment, promotion, or insurance. The genetic test or the submission of the test result must not be forced. The director or employee of facilities performing genetic test must not release the genetic information of a person to another without proper justification or must not use the information for improper purpose. (Article 31 and article 35).
2. Research Guideline for Functional Analysis of Human Genome  
<http://www.elsikorea.org/>, <http://www.koreabioethics.net/> (June 2002)  
The essential contents of the guideline are focused on several issues.
  - (1) Specimens from human beings can be used in human genome research.
  - (2) Another issue is autonomy or the right of self-determination of the potential subjects. When researchers select the human subject, they must respect his/her autonomy. To protect the potential subject's autonomy, researchers must get the informed consent.
  - (3) The third issue is to protect the individual's genetic privacy. To protect the individual's genetic privacy, the genetic information must not be linked with the individual's medical record. And the disclosure of individual's genetic information must be banned.
  - (4) The IRB (Institutional Review Board) can be a responsible

body to control the scientific quality of research and the ethical and/or legal problems of research. (5) And researchers can use the genetic counsellor system to assist in getting informed consent, resolving the conflicts between researchers and subjects, and so on.

3. Korean Association of Institutional Review Boards (KAIRB's): comprehensive guideline for IRB Standard Operating Procedures (February 2003) was published as a monograph by KAIRB.

## **2. Projects to establish a foundation for Pharmacogenomic research**

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1. Korean Pharmacogenomics Research Network (KPRN)
  - 1.1 Schedule: FY2003- FY2011 (9-year term)
  - 1.2 Budget: 21 million USD for 9 years
  - 1.3 Aim: Discovery of polymorphisms related to drug safety and efficacy in Korean population and clinical application of pharmacogenomics information.
  - 1.4 Scope: 5 specific pharmacogenomic research centers focused on adverse drug reaction, drug metabolism, drug transporter, respiratory drug, and CNS drug pharmacogenomics.
  - 1.5 Project Leader: Professor Sang-Goo Shin (Seoul National University)
2. National Research Laboratory for Pharmacogenomics
  - 2.1 Schedule: FY2003- FY2007 (5-year term)
  - 2.2 Budget: 3.3 million USD for 5 years
  - 2.3 Aim: Application of pharmacogenomics to clinical practice.
  - 2.4 Scope: Relations of pharmacokinetics and pharmacogenomics.
  - 2.5 Project Leaders: Professor Jae-Gook Shin (Inje University) and Hyong Doo Shin (SNP Genetics Inc.)
3. Hap Map Project
  - 3.1 Schedule: FY2003-2008 (5-year term)
  - 3.2 Budget: 9 million USD for 5 years
  - 3.3 Participant: JE Lee (DNA Link, Inc.), JJ Hwang (Samsung), KY Song (Ulsan Univ), JM Yang (Seongkyunkwan Univ.), and CB Kim (NIH bioinformatics)
  - 3.4 Aim: Haplotype and LD mapping (Chromosome based + gene based approach) of Korean genome
  - 3.5 Scope: As a start, chromosome 22 is targeted (about one million genotyping/year, about 10,000 SNP/year)
  - 3.6 Project Leader: Kyuyoung Song (Ulsan University)
4. The Center for Functional Analysis of Human Genome
  - 4.1 Schedule: FY1999-FY2009 (10-year term)
  - 4.2 Budget: 90 million USD for 10 years
  - 4.3 Aim: Large-scale isolation of genes and proteins associated with diseases most characteristic of Korean populations. Identification of candidate target genes from in-depth functional analysis. Development of novel, genome-based diagnostics and therapeutics. Establishment of tech-

nological basis on which to build the national competitiveness in bio-industry and by which to contribute to the improvement of human welfare

- 4.4 Scope: genomic research on gastric and liver cancers, etc.
- 4.5 Project leader: Hyang-Sook Yoo (KRIBB)
- 5. Disease and Pathogenic Microbe Genomics
  - 5.1 Schedule: FY2001 – FY2011 (10-year term)
  - 5.2 Budget: 62 million USD for 10 years
  - 5.3 Aim: Disease and pathogen related functional genomics
  - 5.4 Scope: 11 disease specific genomics centers and 3 pathogenic microbe specific genomic centers
  - 5.5 Project management: Ministry of Health and Welfare, National Institute of Health
  - 5.6 Project coordinator: Professor Yangsoo Jang (Yonsei University)

### **3. Activities**

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- 1. Ministry of Health and Welfare; funding the Korean pharmacogenomics research network, disease genomics, pathogenic microbe genomics, proteomics research center.
- 2. KFDA (Korean Food and Drug Administration); preparing guideline for application of pharmacogenomics in drug regulation
- 3. Ministry of Science and Technology; funding National Research Laboratory for Pharmacogenomics, planning to fund the research in the toxicogenomics in non-clinical field
- 4. Academia
  - 4.1 Pharmacogenomics Research Study Group was established in June 2001 with over 100 members working at universities and drug industries. Regular research seminar and symposia are arranged by the network.
  - 4.2. PharmacoGenomics Research Center (PGRC) was established in January 2003 in Inje University, Busan.
  - 4.3 International symposia:
    - 4.2.1 Yonsei Biomedical Symposium: February, 2003, Seoul
    - 4.2.2 Pharmacogenomics: Impact on clinical trial – October, 2003, Seoul
    - 4.2.3 Pharmacogenomics: A step toward personalised pharmacotherapy – February 2004, Busan, organized by KPRN and PGRC.

### **4. Pharmaceutical Industry**

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Many drug discovery and genotyping bio-ventures are investing in this field. Several bio-ventures are applying the genotype to clinical practice. Multinational pharmaceutical companies are sponsoring several clinical trials searching any relation between drug efficacy/adverse effect and specific genotypes. A global pharmaceutical company sponsored a genotype-phenotype association study of CYP enzymes using probe drugs as cocktail administration. The study was done in Caucasian, Japanese and Korean, simultaneously. Pharmacogenetics/genomics is becoming an important issue in new drug approval especially related to the ethnic sensitivity of a drug by ICH E5 foreign clinical data acceptance guidance.

## Annex 9

# Pharmacogenetics and Pharmacogenomics in Singapore

Contribution by:  
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### 1. Relevant laws and regulations

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1. No specific laws on pharmacogenetics research
2. Regulations governing clinical trials of medicinal products:  
<http://www.hsa.gov.sg/html/business/00000000000000001901.html>
  - 2.1 Medicines Act
  - 2.2 Medicines (Clinical Trials) Regulations
  - 2.3 Singapore Guideline for Good Clinical Practice

### 2. Guidelines on bioethics

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1. No specific guidelines on pharmacogenetics.
2. Other relevant guidelines and reports:
  - 2.1 National Medical Ethics Committee (NMEC) Ethical Guidelines for Gene Technology (2001)  
<http://app.moh.gov.sg/pub/pub03.asp>
    - 2.1.1 Provides guidelines for introduction of genetic testing into clinical practice, reviewing research protocols involving gene technology and on gene therapy.
    - 2.1.2 For genetic testing, guidelines recommend 1) genetic counseling for patient and/or family; 2) informed consent; 3) determination of any objection to use test material for research purposes; 4) respect for wishes of key relative in regard to pedigree analysis; 5) determination of whether subject wishes to know test results; 6) guidelines for disclosure of genetic test results; 7) gene examined is associated with disease in question, test is validated and useful test results obtained; 8) advertising and marketing of predictive gene test strongly discouraged.

- 2.2 NMEC Ethical Guidelines on Research Involving Human Subjects (1997)  
[http://www.moh.gov.sg/nmec/NMEC94\\_97.pdf](http://www.moh.gov.sg/nmec/NMEC94_97.pdf) (Annex IV/D)  
Provides guidelines for ethics committees in the review of research proposals in order to ensure rights and welfare of subjects are protected. Accepted by the Ministry of Health and sent out to all hospital ethics committees.
- 2.3 Bioethics Advisory Committee (BAC) Report on Human Tissue Research (2002)  
<http://www.bioethics-singapore.org/resources/reports.html>  
Provides recommendations on tissue research that includes 1) adopt the ethical principles of primacy of the welfare of donor, informed consent, respect for human body, donations to be outright gifts, ethical review of research proposals and access requests and confidentiality; 2) conduct of research in approved institutions; 3) statutory regulations and authority for research tissue banking; 4) continuing professional and public dialogue.
- 2.4 BAC Consultation Paper on Research Involving Human Subjects (released for consultation in 2003)  
Proposes a national framework for the ethical review by statutorily formalised ethics committees of all human clinical research proposals in Singapore.

### **3. Advisory boards**

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1. National Medical Ethics Committee  
<http://www.moh.gov.sg/nmec/nmec.html>  
Set up in 1994 by the Ministry of Health (MOH) to provide advice to MOH on ethical issues in medical practice.
2. Bioethics Advisory Committee  
<http://www.bioethics-singapore.org/>  
Appointed by the Singapore Cabinet in 2000 to examine and make recommendations to the Ministerial Committee for Life Sciences on potential ethical, legal and social issues arising from research in biomedical sciences in Singapore.

### **4. Projects & Activities**

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Some government initiatives include the set up of a national DNA and tissue repository, i.e. the Singapore Tissue Network, in 2002 to advance Singapore's genomics initiative through the collaboration between the Agency for Science, Technology and Research (A\*STAR), the Genome Institute of Singapore (GIS) and Genomics Collaborative, Inc. This network has links to 5 national disease registries covering cardiology, oncology, myopia, stroke

and nephrology. Other tissue repositories to provide researchers with samples of RNA and DNA include the National Cancer Centre (NCC) and National University Hospital/National University of Singapore (NUH/NUS) tissue repositories.

The Genome Institute of Singapore, set up with the support of A\*STAR in 2000, is the national flagship programme in the genomic sciences in Singapore and is involved in looking for novel gene targets through SNP analyses and disease associations. Other institutes involved in genomic research include the Institute of Cell and Molecular Biology, Bioinformatics Institute as well as academic institutions, e.g. National University of Singapore.

Because of the ethnic diversity in Singapore, a significant portion of the pharmacogenetic research focuses on elucidating genetic differences influencing drug response and disease susceptibility among different ethnic groups, i.e. Chinese, Caucasians, Indians and Malays.

1. Singapore Tissue Network <http://www.stn.org.sg/>
2. National Cancer Centre tissue repository and research projects  
[http://www.nccs.com.sg/Rsch/DMS\\_tissue.htm](http://www.nccs.com.sg/Rsch/DMS_tissue.htm)  
[http://www.nccs.com.sg/rsch/rsch\\_therapy.htm](http://www.nccs.com.sg/rsch/rsch_therapy.htm)
3. National University Hospital/ National University of Singapore (NUH/NUS) tissue repository  
<http://www.med.nus.edu.sg/path/tissues/welcome.htm>
4. Genome Institute of Singapore  
<http://www.gis.a-star.edu.sg/homepage/gistechnology-intro.jsp>
5. Institute of Cell and Molecular Biology  
[http://www.imcb.a-star.edu.sg/research/research\\_group/index.html](http://www.imcb.a-star.edu.sg/research/research_group/index.html)
6. National University Hospital pharmacogenetic research
  - 6.1 Projects include pharmacogenetic research with respect to optimising anticancer drug utilization, with particular interest in differences in drug behaviour among Asian ethnic representations.
  - 6.2 Current approach is to have phenotype for all subjects genotyped, and to fully sequence key candidate genes, including promoter, exons and exon-intron junctions, 3'UTR.
  - 6.3 Recent data on CYP2C9, which is the 3rd most important drug metabolising enzyme after CYP3A and CYP2D6, has been submitted. Many novel variants were found, and the gene patterns were different between the Indians (who are similar to the Caucasians), and the Chinese and Malays.

- 6.4 Project collaborations with the US-based Pharmacogenetics Anticancer Agents Research (PAAR) Group, who are sponsored by the National Institute of General Medical Sciences (NIGMS), National Institutes of Health.
7. National University of Singapore  
[http://www.med.nus.edu.sg/phar/dept/staff/academic/Lee\\_EJD/homepage.htm](http://www.med.nus.edu.sg/phar/dept/staff/academic/Lee_EJD/homepage.htm)  
[http://www.med.nus.edu.sg/research/progrsch/hum\\_mol\\_genetics.shtml](http://www.med.nus.edu.sg/research/progrsch/hum_mol_genetics.shtml)  
 Some examples of research projects carried out in the Pharmacogenetics Lab, NUS include:
- 7.1 target gene approach, identifying and characterising polymorphisms affecting genes regulating drug metabolism, drug transporters and ion channels involved in long QTc syndrome
  - 7.2 systematic characterisation of novel genetic variants in Chinese, Malays and Indians
  - 7.3 functional characterisation of variant transporters and ion channels through cultured cell systems and patch clamp electrophysiology
  - 7.4 establishing Hapmap for MDR1 and MRP1 and 2 genes through collaboration with the National Cancer Centre

## **5. Present situation in Singapore – Clinical Trials**

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1. 20 clinical trials incorporating pharmacogenetic research have been received from both pharma industry (16) as well as hospitals/institutions (4) during the period of 2003 to 1st quarter of 2004. This constitutes about 15% of all trials reviewed by HSA in the same period.
2. Of the 20 clinical trials, 10 are phase I trials, 4 are phase II trials and 6 are phase III trials. 16 of the studies are currently ongoing with 3 studies pending regulatory approval. One study has been withdrawn by sponsor.
3. The trials can be broadly categorised into the following types of studies:
  - 3.1 Genotyping e.g., CYP2D6, to exclude low responders (n=1)
  - 3.2 Genotyping of specified candidate genes, e.g. drug metabolising enzymes, transport proteins, target protein, to determine influence on drug pharmacokinetics or for interpretation of trial results (n=9)
  - 3.3 Exploratory analysis (candidate genes not specified) including possible whole genome scans to identify genetic biomarkers that can predict drug pharmacokinetics, clinical safety, drug response, clinical outcome, prognosis (n=10)